



Trinity
College
Dublin

The University of Dublin

Development of Audio-Based Signal Processing Methods to Objectively Assess Patient Adherence in Respiratory Medicine

Terence E. Taylor, B.E., M.E.

Under the supervision of Prof. Richard B. Reilly

A dissertation submitted to the
University of Dublin, Trinity College

In fulfilment of the requirements for the degree of
Doctor of Philosophy

May, 2018



Department of Electronic and Electrical Engineering
University of Dublin, Trinity College

Declaration

I, Terence Taylor, confirm that this thesis has not been submitted as an exercise for a degree at this or any other university and is entirely my own work.

I agree to deposit this thesis in the University's open access institutional repository or allow the Library to do so on my behalf, subject to Irish Copyright Legislation and Trinity College Library conditions of use and acknowledgement.

Signed,

Terence E. Taylor

May 31st, 2018

Summary

Over four million people die every year from chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). There is no cure currently available for these diseases; however, they may be controlled using inhaled medication which directly targets the airways to relieve symptoms. Medication is usually administered to asthma and COPD patients using inhaler devices. Patients are required to inhale through the inhaler device in order to deliver medication to the airways. Despite the proven clinical efficacy of inhaler devices, up to 80% of patients make critical user technique errors which significantly reduce the amount of medication delivered to the patient. Poor adherence to correct user technique is associated with increased hospitalisations and healthcare costs. Inhaler user technique is currently assessed using checklists from healthcare professionals during treatment. However, they are subjective and have been reported to generate inaccurate assessments of patient inhaler user technique. Therefore, there is an urgent clinical need for objective methods to assess patients' inhaler user technique during clinical consultation and remotely over the course of treatment.

In this thesis, audio-based signal processing methods were developed to objectively assess patient inhaler user technique. Audio recordings of patients using inhaler devices were obtained using microphones attached and distant to different inhalers to simulate attachable and wearable monitoring devices. A range of temporal and spectral features were extracted from the inhaler audio recordings to automatically assess critical events of inhaler use. A new novel method of objectively assessing patient inhaler user technique is introduced for the first time. Furthermore, this thesis also investigates the potential of employing audio-based methods to monitor patients' clinical response to treatment, providing promising insights into new potential clinical measures in respiratory medicine. The central aim of this research was to investigate the clinical applicability of audio-based signal processing methods to assess critical steps of patient inhaler use.

The main findings of the studies detailed in this thesis suggest that temporal and spectral audio-based features of inhaler inhalation sounds can be used to objectively estimate pertinent clinical measures of inhalation technique such as the peak inspiratory flow rate (PIFR), inspiratory capacity and ramp time of inhalation. Furthermore, there exists a relationship between audio-based measures of the PIFR of inhaler inhalations and lung function. This may allow healthcare professionals to intervene before the onset of an exacerbation. Moreover, these audio-based signal processing methods can accurately detect the release of medication during inhaler use. It was shown that the audio-based methods presented in this thesis provide more accurate assessment of patient inhaler user technique than standard subjective clinical checklists. This highlights the need to implement these new audio-based objective measures of user technique assessment into clinical practice.

In conclusion, the original contribution to knowledge in this thesis lies in the development of audio-based signal processing methods to provide objective assessment of patient inhaler user technique. This thesis builds on previous research by advancing signal processing methods to assess user technique in a range of different inhalers and providing new clinical measures in the treatment of chronic respiratory diseases. The main findings of this thesis establish the acoustic properties of inhaler sounds and provide significant value for future research in the field of audio-based inhaler monitoring systems. The audio-based methods described in the studies in this thesis can provide healthcare professionals with more accurate objective information regarding patient inhaler user technique. This information can be used to give patients feedback regarding their inhaler user technique which can improve the clinical efficacy of inhaler medication, reduce healthcare costs and enhance precision medicine in the treatment of chronic respiratory diseases.

Acknowledgements

I would like to give a special mention to a number of people without whom this thesis would not have been possible.

Prof. Richard Reilly for giving me the opportunity to join his lab and to undertake a PhD. Your academic guidance and enthusiasm for research is so inspiring and I cannot thank you enough for all of your support over the last four years. Although, next time we go to a Toto concert together, let's catch the early train!

Prof. Richard Costello for his guidance and advice over the last number of years. Your clinical expertise and your love for what you do is so inspirational and it was a pleasure to work with you. All of the INCA team at Beaumont Hospital are a credit to your work ethic and leadership in spearheading such an amazing project.

Mr. Frank Keane and Vitalograph Ltd. for giving me the opportunity to work in a research area that I have grown to be very passionate about and for part funding this research.

Dr. Yaniv Zigel for his academic guidance over the last year. It was an absolute pleasure to work with you. Your guidance has improved my skills as a researcher greatly and I very much enjoyed discussing music and countless ideas for new research projects with you for hours upon end. Any researcher would be lucky to have such an incredible mentor like you. I will always remember to "keep it simple"!

Dr. Martin Holmes for helping me settle in to my PhD when I first joined the lab and for reviewing this thesis and the publications. It was great to work with you and I wish you the very best of luck in the future.

Mrs. Elaine MacHale, Dr. Imran Sulaiman, Ms. Aoife Sartini Bhreathnach, Ms. Philippa MacHale, Ms. Clarice Egan, Dr. Breda Cushen and all of the INCA team at Beaumont Hospital, Dublin, Ireland. You are an amazing group of people and it was an absolute pleasure to be a part of such a great project.

Mr. Denis Drennan for his advice and friendship over the last number of years. You're a true friend, thanks for everything man!

Dr. Céline De Looze for reviewing this thesis along with her academic advice and support over the past few years. Your dedication to research and determination is so motivating and it was a pleasure sitting beside you in the lab. Special thanks for the PhD survival kit, this thesis would not have been possible without it!

All patients and participants who gave their time to participate in the studies reported in this thesis. I am extremely grateful to you all.

The Irish Research Council and Enterprise Ireland who kindly part funded this research.

Students whom I had the pleasure of working with; Helena Lacalle Muls, Tom McCartan, Fintan Hughes, Johnny McNulty and Isadora De Melo Oliveira. Thank you for your hard work and dedication in assisting with this research.

Everyone in the Neural Lab at the Trinity Centre for Bioengineering (Gio, Niamh, Alejandro, Brendan, Saskia, Mick, Isabelle, Jim, Ciara, Shruti, Clodagh, Michael and Eugene). It was great to be among such a friendly group of people and I wish you all the best in the future.

My fellow musicians, thank you for your support also. Playing music helped me to be creative and keep motivated over the last number of years.

A special mention to Mam, Eliz, Eugene, Lisa, Adam, Catherine, David, Aaron, Ella, Grandad and all of my family and friends, thank you for everything. This thesis would not have been possible without your love and support. This thesis is dedicated to you all.

Finally, I'd like to give a special mention to my Dad. You gave me the guidance and strength to achieve everything I have in life. You are my hero and always will be.

TERENCE TAYLOR, MAY 2018

Publications Arising from this Thesis

Peer Reviewed Journal Articles

- **Taylor T E**, Zigel Y, Egan C, Hughes F, Costello R W and Reilly R B 2018 Objective Assessment of Patient Inhaler User Technique Using an Audio-Based Classification Approach. *Scientific Reports* 8 2164.
- **Taylor T E**, Lacalle Muls H, Costello R W and Reilly R B 2018 Estimation of Inhalation Flow Profile Using Audio-Based Methods to Assess Inhaler Medication Adherence. *PLoS One* 13 e0191330.
- **Taylor T E**, Zigel Y, De Looze Céline, Sulaiman I, Costello R W and Reilly R B 2018 Advances in Audio-Based Systems to Monitor Patient Adherence and Inhaler Drug Delivery. *Chest* 153 710-722.
- **Taylor T E**, De Looze C, MacHale P, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2016 Characterization of Patient Inhaler Inhalation Sounds Using Non-Contact and Tracheal Microphones. *Biomedical Physics & Engineering Express* 2(5):055021.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2016 Monitoring Inhaler Inhalations Using an Acoustic Sensor Proximal to Inhaler Devices. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 29 439-46.

Peer Reviewed Conference Papers

- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2015 Influence of gender and anthropometric features on inspiratory inhaler acoustics and peak inspiratory flow rate. *37th Annual International Conference of the IEEE EMBS*, Milan, Italy. 25th– 29th August 2015.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2014 An acoustic method to automatically detect pressurized metered dose inhaler actuations. *36th Annual International Conference of the IEEE EMBS*, Chicago, USA. 26th – 30th August 2014.
- McCartan T, **Taylor T E**, Sulaiman I, Costello R W and Reilly R B 2016 Changes in inhaler inhalation acoustic features during induced bronchoconstriction: A Pilot Study. *38th Annual International Conference of the IEEE EMBS*, Orlando, USA. 16th – 20th August 2016.
- Lacalle Muls H, **Taylor T E**, Costello R W and Reilly R B 2016 Objective measurement of inhaler inhalation flow profile using acoustic methods. In: *The Annual Congress of the Spanish Society of Biomedical Engineering (CASEIB)*, Valencia, Spain. 23rd-25th November 2016.

Conference Poster Presentations

- **Taylor T E**, Lacalle Muls H, Costello R W and Reilly R B 2016 Remote monitoring of Ellipta inhalation profile using an acoustic recording device. *Irish Thoracic Society Meeting 2016*, Dublin, Ireland. 18th-19th November 2016.
- **Taylor T E**, Egan C, Costello R W and Reilly R B 2016 Remote monitoring of peak inspiratory flow rate in the pressurized metered dose inhaler using an acoustic recording device. *Irish Thoracic Society Meeting 2016*, Dublin, Ireland. 18th-19th November 2016.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2016 Effects of lung function and anthropometric features on inhaler inhalation sounds: a step towards personalizing acoustic monitoring of inhalation technique. *American Thoracic Society International Conference 2016*, San Francisco, California, USA. 13th-18th May 2016.

- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2015 Acoustic features of inhaler inhalation sounds are repeatable across a range of peak inspiratory flow rates: An opportunity to monitor respiratory health longitudinally. *20th International Congress on Aerosols in Medicine and Pulmonary Drug Delivery*, Munich, Germany. 30th May – 3rd June 2015.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2015 Objective measurement of peak inspiratory flow rate (PIFR) in the Diskus, Turbuhaler and Evohaler using non-contact acoustic methods. *20th International Congress on Aerosols in Medicine and Pulmonary Drug Delivery*, Munich, Germany. 30th May – 3rd June 2015.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2014 An acoustic method to automatically detect pressurized metered dose inhaler actuations. *36th Annual International Conference of the IEEE EMBS*, Chicago, USA. 26th – 30th August 2014.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2014 Identification of pressurized metered dose inhaler drug actuations using the continuous wavelet transform. *20th Annual Bioengineering in Ireland (BINI) Conference*, Castletroy, Co. Limerick, Ireland. 24th – 25th January 2014.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2014 An acoustic method to automatically detect pressurized metered dose inhaler actuations. *Trinity Centre for Bioengineering (TCBE) Winter Symposium*, Dublin, Ireland. December 2014.

Table of Contents

Declaration	ii
Summary	iii
Acknowledgements	v
Publications Arising from this Thesis	vii
Table of Contents	x
List of Figures	xvi
List of Tables.....	xix
Glossary of Abbreviations.....	xxi
Chapter 1. Introduction	1
1.1 Asthma.....	1
1.2 Chronic Obstructive Pulmonary Disease (COPD)	3
1.2.1 Spirometry	4
1.3 Inhaled Therapy.....	5
1.3.1 Pressurised metered dose inhaler (pMDI)	6
1.3.2 Dry powder inhaler (DPI)	7
1.4 Adherence	9
1.5 Research Goal and Collaborations	11
1.6 Thesis Outline.....	12
Chapter 2. Literature Review	14
2.1 Patient Adherence to Pressurised Metered Dose Inhaler User Technique	14

2.2	Patient Adherence to Dry Powder Inhaler User Technique	17
2.3	Factors Associated with Poor Inhaler Adherence	22
2.3.1	Patient factors	22
2.3.2	Treatment factors	23
2.3.3	Healthcare professional factors.....	24
2.4	Current Methods of Monitoring Inhaler Adherence	24
2.4.1	Monitoring temporal adherence.....	24
2.4.2	Monitoring user technique adherence.....	26
2.4.3	Electronic monitoring devices (EMDs)	29
2.5	Audio-Based Systems to Objectively Monitor Inhaler Adherence.....	31
2.5.1	Inhaler Compliance Assessment (INCA) device	33
2.5.2	Inhaler audio recording overview	35
2.6	Acoustic Properties of Breath Sounds.....	37
2.6.1	Generation of breath sounds	38
2.6.2	Normal chest wall breath sounds	40
2.6.3	Normal tracheal breath sounds	42
2.6.4	Acoustic sensors used to record breath sounds.....	43
2.6.5	Audio analysis of asthma breath sounds.....	45
2.6.6	Audio analysis of COPD breath sounds	47
2.7	Automatic Classification of Breath Sounds	48
2.7.1	Pre-processing.....	50
2.7.2	Feature extraction	50
2.7.3	Classification methods.....	53
2.7.4	Performance measures	53
2.8	Automatic Detection and Classification of Inhaler Sounds	58
2.9	Estimation of Respiratory Flow Parameters	60
2.10	Respiratory Flow Estimation Using Audio-Based Methods	62

2.10.1	Inhaler inhalation flow estimation using audio-based methods	72
2.11	Quantification of Inhaler Drug Delivery Using Audio-Based Methods	74
2.12	Audio-Based Adherence Measures	76
2.12.1	Comparing audio-based adherence measures to current clinical standard of assessment	78
2.13	Providing Objective Feedback on Patient Inhaler Adherence	78
2.14	Chapter Conclusion.....	81
Chapter 3.	Research Questions and Hypothesis	83
3.1	Employing Non-Contact Audio-Based Methods to Monitor Inhalation Technique in Inhaler Devices.....	84
3.2	Audio-Based Objective Measurement of Peak Inspiratory Flow Rate during Patient Inhaler Use and its Application to Detecting Changes in Lung Function.....	85
3.3	Estimation of Inhalation Flow Profile from a Dry Powder Inhaler Using Audio-Based Methods	85
3.4	Development and Validation of an Audio-Based Algorithm to Objectively Assess Patient Pressurised Metered Dose Inhaler User Technique	86
Chapter 4.	Employing Non-Contact Audio-Based Methods to Monitor Inhalation Technique in Inhaler Devices.....	88
4.1	Investigation into the Relationship between Inhalation Audio-Based Features and Peak Inspiratory Flow Rate	89
4.1.1	Introduction	89
4.1.2	Methods	90
4.1.3	Results	96
4.1.4	Discussion	101
4.2	Quantifying the Effects of the User and the Inhaler Device on Inhaler Inhalation Audio-Based Features	103
4.2.1	Introduction	103
4.2.2	Methods	104
4.2.3	Results	106

4.2.4	Discussion.....	108
4.3	Chapter Conclusion.....	110
Chapter 5. Audio-Based Objective Measurement of Peak Inspiratory Flow Rate during Patient Inhaler Use and its Application to Detecting Changes in Lung Function 112		
5.1	Characterisation of Patient Inhaler Inhalation Sounds Using Non-Contact and Tracheal Microphones	113
5.1.1	Introduction.....	113
5.1.2	Methods	114
5.1.3	Results.....	121
5.1.4	Discussion.....	125
5.2	Investigation into the Relationship between Audio-Based Features of Inhaler Inhalation Sounds and Lung Function During and After Bronchoconstriction.....	128
5.2.1	Introduction.....	128
5.2.2	Methods	129
5.2.3	Results.....	133
5.2.4	Discussion.....	135
5.3	Chapter Conclusion.....	137
Chapter 6. Estimation of Inhalation Flow Profile from a Dry Powder Inhaler Using Audio-Based Methods 139		
6.1	Introduction.....	140
6.2	Methods.....	141
6.2.1	Participants.....	141
6.2.2	Inhaler audio recording setup	142
6.2.3	Participant recording protocol	143
6.2.4	Audio and flow signal pre-processing	143
6.2.5	Audio-based feature extraction.....	144
6.2.6	Flow-sound regression model.....	145
6.2.7	Effect of noise on audio-based flow estimation.....	147

6.3	Results	147
6.4	Discussion.....	153
6.5	Chapter Conclusion	155
Chapter 7. Development and Validation of an Audio-Based Algorithm to Objectively Assess Patient Pressurised Metered Dose Inhaler User Technique		156
7.1	Investigating the Use of Time-Frequency Audio-Based Features to Automatically Detect Pressurised Metered Dose Inhaler Actuations	157
7.1.1	Introduction	157
7.1.2	Methods.....	158
7.1.3	Results	163
7.1.4	Discussion	165
7.2	An Audio-Based Signal Processing Algorithm to Objectively Assess Patient Pressurised Metered Dose Inhaler User Technique	166
7.2.1	Introduction	166
7.2.2	Methods.....	168
7.2.3	Results	180
7.2.4	Discussion	187
7.3	Chapter Conclusion	190
Chapter 8. General Discussion.....		192
8.1	Thesis Summary	192
8.2	Main Findings of the Thesis	193
8.3	Limitations of Research.....	202
8.4	Clinical Impact of Research	206
8.5	Future Research Directions	207
8.6	Final Conclusion.....	213
References		214
Appendices		231
Appendix A: Chapter 4 Supplementary Material.....		231

Appendix B: Chapter 6 Supplementary Material	232
Appendix C: Chapter 7 Supplementary Material	235
Appendix D: Chapter 8 Supplementary Material	247

List of Figures

Figure 1.1. Illustration of the pathophysiology of asthma (A.D.A.M, 2007).	2
Figure 1.2. Illustration of the pathophysiology of COPD (Houghton, 2013).	4
Figure 1.3. Pressurised metered dose inhaler (pMDI).	6
Figure 1.4. Examples of dry powder inhalers (DPIs).	9
Figure 2.1. Illustration of a DPI inhalation flow profile.	19
Figure 2.2. DPI inhalation flow profiles from two different inhalation manoeuvres.....	20
Figure 2.3. Examples of inhaler electronic monitoring devices.....	31
Figure 2.4. Block diagram of an audio-based inhaler monitoring system.	32
Figure 2.5. Inhaler Compliance Assessment (INCA) device.	33
Figure 2.6. Example of a typical Diskus DPI INCA recording audio time domain signal (linear representation of sound pressure) and corresponding spectrogram.....	34
Figure 2.7. Anatomy of the upper and lower respiratory tract (Teva Respiratory, 2014).	39
Figure 2.8. Block diagram of audio-based classification.	50
Figure 2.9. Block diagram of automatic inhaler sound detection algorithm (Holmes <i>et al.</i> , 2014a).....	59
Figure 2.10. Area of semi-ellipse from which the volume or IC of an inhaler inhalation can be estimated.	73
Figure 2.11. NGI cascade impactor used for <i>in-vitro</i> inhaler drug delivery testing [Copley Scientific Limited, Nottingham, UK].....	75
Figure 4.1. Inhaler Recording Experimental Setup.....	91
Figure 4.2. Averaged power spectral density estimates of inhaler inhalation sounds from one participant.	94
Figure 4.3. PIFR versus P_{ave} regression plots.	98
Figure 4.4. Average CoV of inhalation audio-based features.	99

Figure 4.5. Boxplot of R^2 highlighting repeatability of peak frequencies of inhaler inhalation power spectral density.	100
Figure 4.6. Average P_{ave} values ($\pm$ std. error) of inhaler inhalations for male and female groups.....	108
Figure 5.1. Pictures of patient inhaler recording experimental setup.	115
Figure 5.2. Audio time domain signals and spectrograms of inhaler inhalation sounds.	117
Figure 5.3. Linear relationship between PIFR and the Shannon entropy (H) of non-contact inhalation sounds from patient cohort.	123
Figure 5.4. Power spectral density estimates of three inhalations across and within patients.	124
Figure 5.5. Median ($\pm$ standard error) of Pearson's linear correlation coefficient r values of intra and inter-patient PSD profile correlations in the non-contact and tracheal inhalation audio signals.	125
Figure 5.6. Changes in lung function, inhaler PIFR and audio-based features of inhaler inhalations during bronchial challenge test for responsive and non-responsive patients.	134
Figure 6.1. Inhaler recording setup.	142
Figure 6.2. Example of inhaler inhalation audio and flow signals.	145
Figure 6.3. Examples of actual and estimated inhaler inhalation flow profiles.....	149
Figure 6.4. Average audio-based flow estimation errors.	150
Figure 6.5. Average flow estimation accuracy ($\pm$ standard error) averaged across all flow ranges for each participant.	151
Figure 6.6. Boxplots representing the median, interquartile range and $1.5 \times$ interquartile range of regression coefficients.	152
Figure 6.7. Average accuracy (%) $\pm$ standard error (shaded region) of inhalation flow profile parameter estimation across all flow rates at different SNR levels.	152
Figure 7.1. pMDI recording setup.	158
Figure 7.2. Audio signal of a patient using a pMDI.	159
Figure 7.3. The continuous wavelet transform of a pMDI audio signal.	162
Figure 7.4. Flow chart of actuation sound event detection algorithm.	163
Figure 7.5. Example of a patient pMDI recording highlighting the detected actuation event.....	164

Figure 7.6. Inhaler audio recording setup. Evohaler pMDI with the Flo-Tone attached to the mouthpiece.	169
Figure 7.7. Overview of audio-based classification of inhaler sound events from patient audio recording.....	171
Figure 7.8. Feature projection visualisation and feature selection results.	176
Figure 7.9. The relationship between PIFR and $P_{f_{ofl}}$	182
Figure 7.10. Audio-based inhaler inhalation flow estimation performance within different SNR levels.....	183
Figure 7.11. Bland Altman plot showing the relationship between the reference and estimated PIFR and volume measures.	184
Figure 7.12. Example of patient inhaler audio signals before and after tuition regarding user technique from a clinical reviewer.	186
Figure 8.1. Power spectral density estimates of inhalation sounds at low, medium and high flow rates in (A) Ellipta DPI and (B) Evohaler pMDI.	203
Figure 8.2. Typical examples of inhaler audio signals using attachable and non-contact microphone setups.....	205
Figure 8.3. Current and future inhaler audio recording devices.....	208
Figure 8.4. Monthly INCA patient adherence summary reports that have been used in clinical practice.	210

List of Tables

Table 2.1. Steps required to correctly use a pressurised metered dose inhaler (pMDI).	15
Table 2.2. Studies reporting common user technique errors associated with the pMDI.	16
Table 2.3. Steps required to correctly use a dry powder inhaler (DPI).	18
Table 2.4. Studies reporting common user technique errors associated with the DPI.	21
Table 2.5. List of studies involving automatic classification of respiratory sounds.	55
Table 2.6. List of studies involving respiratory flow estimation using audio-based signal processing methods.	64
Table 2.7. Summary of advantages and disadvantages of current methods of monitoring patient inhaler adherence.	80
Table 4.1. Summary of participant demographics and baseline lung function data.	97
Table 4.2. Correlation scores (R^2) between PIFR and audio-based features.	97
Table 4.3. Participant anthropometric information (mean $\pm$ standard deviation).	104
Table 4.4. Statistical analyses of non-contact and tracheal inspiratory inhaler sounds with gender, height, weight and BMI.	107
Table 5.1. Patient demographics and baseline spirometric measurements.	122
Table 5.2. Adjusted R^2 correlation values between audio-based features and PIFR of inhaler inhalations.	122
Table 5.3. Patient information (n=8) and baseline lung function (mean $\pm$ standard deviation).	130
Table 5.4. Regression results (R^2 values) detailing the correlation between changes in lung function ($\Delta FEV1\%$) and audio features ($\Delta AF\%$) for responsive patients (n=4).	133
Table 5.5. Regression results (R^2 values) detailing the correlation between changes in lung function ($\Delta FEV1\%$) and audio features ($\Delta AF\%$) for non-responsive patients (n=4).	134
Table 6.1. Participant information and baseline lung function (mean $\pm$ standard deviation).	148

Table 6.2. Mean ($\pm$ standard deviation) of flow parameter values from recorded inhalation flow signals averaged across all participants.	148
Table 7.1. Actuation sound event detection algorithm performance results.	164
Table 7.2. Performance measures of quadratic discriminant analysis and artificial neural network classification on patient inhaler audio testing dataset.	181
Table 7.3. Cohen’s kappa statistic (κ) measuring level of agreement between the inhaler user technique checklist, labelled inhaler audio events and detected inhaler audio events according to the audio-based algorithm.	185

Glossary of Abbreviations

ACT	Asthma Control Test
ANN	Artificial Neural Network
AQLQ	Asthma Quality of Life Questionnaire
ATS	American Thoracic Society
a.u.	Arbitrary Units
BA	Bronchoconstrictor Agent
BCT	Bronchial Challenge Test
BMI	Body Mass Index
CFC	Chlorofluorocarbon
COPD	Chronic Obstructive Pulmonary Disease
CORSA	Computerised Respiratory Sound Analysis
CoV	Coefficient of Variation
CWT	Continuous Wavelet Transform
d	Diameter
dB	Decibel
dba	Decibel (A-weighted)
DCT	Discrete Cosine Transform
DPI	Dry Powder Inhaler
$\hat{F}$	Estimated Flow Rate
f_0	Fundamental Frequency
F₂₅	Frequency below which 25% of total spectral power lies
F₅₀	Frequency below which 50% of total spectral power lies
F₇₅	Frequency below which 75% of total spectral power lies
F₉₉	Frequency below which 99% of total spectral power lies
F_s	Sampling Frequency

FEF50	Forced Expiratory Flow at 50% Vital Capacity
FEV1	Forced Expiratory Volume in 1 Second
FIVC	Forced Inspiratory Vital Capacity
FFT	Fast Fourier Transform
F_{max}	Frequency of Maximum Power
FPF	Fine Particle Fraction
FSR	Force Sensitive Resistor
FVC	Forced Vital Capacity
GLS	Generalised Least Squares
GMM	Gaussian Mixture Model
H	Shannon entropy
HFA	Hydrofluoroalkane
HFI	Highest Frequency during Inspiratory breath phase
HMM	Hidden Markov Model
IC	Inspiratory Capacity
IFR	Inspiratory Flow Rate
INCA	Inhaler Compliance Assessment
J	Performance Measure
κ	Cohen's Kappa Statistic
KFD	Katz Fractal Dimension
LABA	Long-Acting Beta-Agonist
LPC	Linear Predictive Coding
MAD	Mean Absolute Deviation
MEMS	Microelectromechanical System
MFCC	Mel Frequency Cepstral Coefficient
NC	Non-Contact microphone
NGI	Next Generation Cascade Impactor
NPV	Negative Predictive Value
P	Pressure change inside of a dry powder inhaler during inhalation
P_{ave}	Average Power
P_{f0f1}	Summation of power of fundamental frequency and first harmonic
P^A	Positive predictive value of Actuation sound event detection
P^E	Positive predictive value of Exhalation sound event detection
P^I	Positive predictive value of Inhalation sound event detection

P_{xx}	Welch Power Spectral Density
pdf	Probability Density Function
PEFR	Peak Expiratory Flow Rate
PET	Polyethylene Terephthalate
PIFR	Peak Inspiratory Flow Rate
PIFR_{sim}	Peak Inspiratory Flow Rate of inhalation (not at maximum effort)
$\widehat{\text{PIFR}}$	Estimated Peak Inspiratory Flow Rate
pMDI	Pressurised Metered Dose Inhaler
PPV	Positive Predictive Value
PSD	Power Spectral Density
QDA	Quadratic Discriminant Analysis
r	Pearson's Linear Correlation Coefficient
R	Airflow resistance of inhaler
R²	Coefficient of Determination
RCSI	The Royal College of Surgeons in Ireland
RIP	Respiratory Inductance Plethysmography
RMS	Root Mean Square of amplitude
SABA	Short-Acting Beta-Agonist
s	Seconds
S^A	Sensitivity of Actuation sound event detection
S^E	Sensitivity of Exhalation sound event detection
S^I	Sensitivity of Inhalation sound event detection
SNR	Signal to Noise Ratio
STFT	Short Time Fourier Transform
SVM	Support Vector Machine
T	Tracheal microphone
TED	Total Emitted Dose
V	Volts
WAV	Waveform Audio File Format
WHO	World Health Organisation
Z	Zero Crossing Rate

Chapter 1. Introduction

Chronic respiratory diseases affect the airways and involve airflow obstruction and the destruction of lung parenchyma (Houghton, 2013). These diseases include asthma, chronic obstructive pulmonary disease (COPD), sleep apnoea and pulmonary hypertension. Chronic respiratory disease places a significant burden on a person's quality of life. Hundreds of millions of people are affected by these diseases worldwide causing over four million deaths per annum (Cruz *et al.*, 2007). In the European Union (E.U), over 600,000 people die from respiratory diseases every year (van Boven *et al.*, 2017). As well as this, a significant economic burden is caused from chronic respiratory diseases in terms of direct medical costs (e.g. hospital admissions) and indirect medical costs (e.g. lost time at work) (Masoli *et al.*, 2004). Two of the most prevalent chronic respiratory diseases are asthma and COPD. There is currently no cure for these diseases but they may be controlled using inhaler devices to administer medication to patients. Inhalers can improve symptom control and prevent exacerbations (sudden worsening of symptoms) from occurring (Bosnic-Anticevich *et al.*, 2017). However, the initiation, implementation and persistence of prescribed inhaled medication is imperative for the long term treatment of asthma and COPD (Vrijens *et al.*, 2016).

1.1 Asthma

Asthma is characterised by chronic inflammation of the airways. The small airways can become narrow, constricted and inflamed causing symptoms such as shortness of breath, chest tightness, cough and wheeze which can vary over time (Normansell and Kew, 2016). The airway obstruction caused by chronic inflammation is mostly reversible in asthma patients. If not treated effectively, symptoms can increase in severity causing

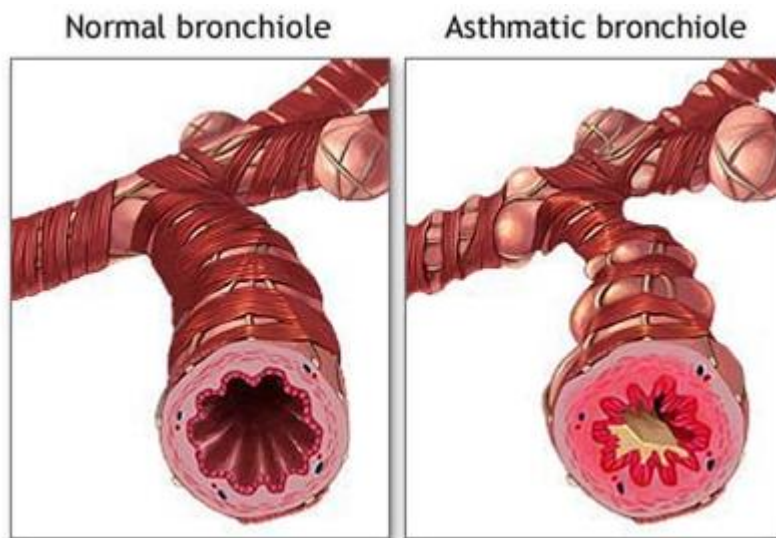


Figure 1.1. Illustration of the pathophysiology of asthma (A.D.A.M, 2007).

an “attack” or exacerbation which can be potentially life threatening to patients. Figure 1.1 illustrates the basic pathophysiology of asthma (A.D.A.M, 2007).

Over 300 million people are affected by asthma worldwide and it is estimated that a further 100 million will be affected by 2025 (Normansell and Kew, 2016; Zeki, 2014). It is the most common chronic disease suffered by children with over 6.8 million children affected in the United States (U.S) alone. It is the most common chronic respiratory disease in adults with over 250,000 people affected in Ireland (Asthma Society of Ireland, 2017; Health Service Executive, 2017a). Over 250,000 people die from asthma every year (Bateman *et al.*, 2008). Ireland has the fourth highest prevalence of asthma worldwide (Health Service Executive, 2017a).

The causes of asthma are not fully understood. Some of the risk factors associated with asthma include (Ferkol and Schraufnagel, 2014);

- Genetic predisposition
- Environmental allergens
- Air pollutants
- Dietary factors
- Abnormal immunological responses

Asthma causes a significant economic burden making up 1-2% of health care budgets in developed countries (Masoli *et al.*, 2004). More than 80% of healthcare resources are used by 20% of asthma patients (Szeffler *et al.*, 2011). The total cost of asthma to the U.S

economy is reported to be over \$50 billion per annum between direct and indirect costs associated with the disease (Szeffler *et al.*, 2011). In Europe, the estimated average cost for a child with asthma ranges from €883 to €2,202 per annum with costs of €632 to €2,745 per annum for adults (Price *et al.*, 2013). Costs can be significantly higher in uncontrolled patients (Accordini *et al.*, 2013). Much of this economic burden is associated with patients not taking their inhaler or using their inhaler with incorrect user technique (Normansell and Kew, 2016).

1.2 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a preventable, progressive disease that is characterised by airflow limitation that is not fully reversible and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases (Pauwels and Rabe, 2004; Bateman *et al.*, 2008). The main site of obstruction is reported to be in the smaller airways. The airways become inflamed in response to noxious particles or gases such as tobacco smoke (Hanania and Sharafkhaneh, 2011). The most common symptoms include shortness of breath, cough and sputum production (GOLD, 2017). COPD is an umbrella term that is used to describe a number of chronic respiratory diseases such as emphysema and chronic bronchitis that cause limitations in lung airflow (WHO, 2015). Emphysema involves gradual destruction of the alveoli in the lungs while chronic bronchitis involves inflammation of the bronchioles and can result in chronic cough (Cruz *et al.*, 2007). Differentiating between asthma and COPD can sometimes be challenging in clinical practice as symptoms may overlap, change or exist in parallel (Toy *et al.*, 2011). Figure 1.2 illustrates the pathophysiology of COPD differentiating between emphysema and chronic bronchitis (Houghton, 2013).

COPD affects 210 million people worldwide (Cruz *et al.*, 2007). It is the fourth leading cause of death worldwide and is predicted to be the third leading cause of death by 2020 (WHO, 2015; Decramer *et al.*, 2012). The prevalence of COPD in Europe is estimated to be 4-10% with 110,000 people affected in Ireland alone (Miravitlles *et al.*, 2016; Health Service Executive, 2017b). Exacerbations are common among COPD patients, particularly in more severe patients, which involve rapid impairment of lung function, disease progression and decreased quality of life (Price *et al.*, 2011).

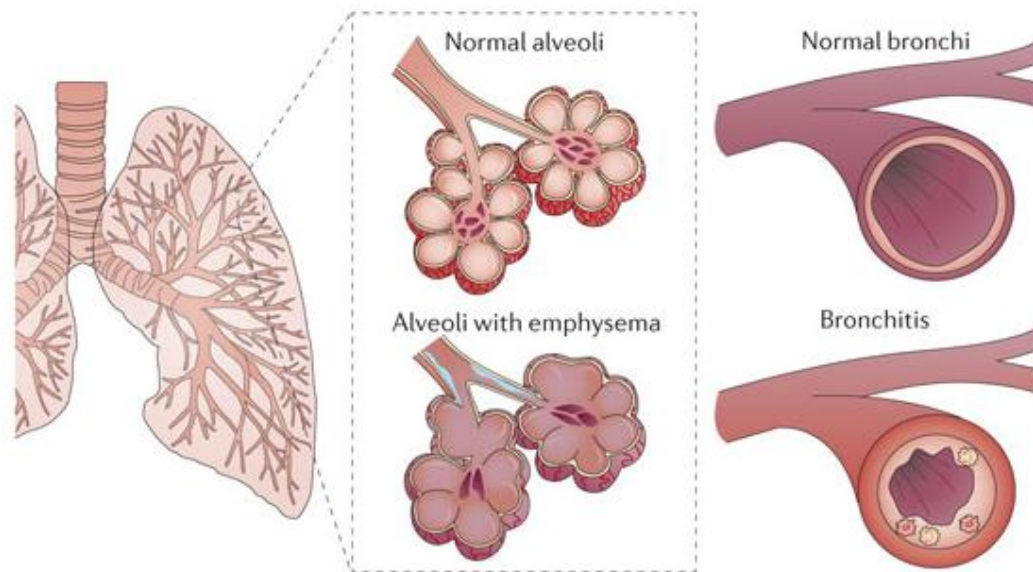


Figure 1.2. Illustration of the pathophysiology of COPD (Houghton, 2013).

Smoking is responsible for 75% of COPD cases and is the number one risk factor associated with the disease (Aït-Khaled *et al.*, 2001). It has been reported that 15-25% of smokers will be affected by COPD at some point in their life (Houghton, 2013). Other main risk factors associated with COPD include (Ferkol and Schraufnagel, 2014);

- Indoor smoke
- Occupational gasses and particles
- Outdoor pollutants
- Asthma

As with asthma, COPD causes a significant economic burden. In the U.S, COPD is the fourth leading cause of death and accounts for 1.5 million emergency room visits. There are 636,000 hospitalisations every year costing a total of \$42.6 billion, \$11.3 billion of which is directly associated with hospital care (Dalal *et al.*, 2011). Direct costs of COPD are estimated to be \$1,500 per patient per annum. In, Europe, annual healthcare costs associated with COPD are reported to be €48.4 billion with costs projected to continually increase to 2020 (Ford *et al.*, 2014; European Respiratory Society, 2017).

1.2.1 Spirometry

Many patients may go undiagnosed, particularly in COPD, until the disease progresses into advanced stages (Price *et al.*, 2011). Spirometry is the preferred clinical

test to diagnose chronic respiratory diseases such as asthma and COPD. Spirometry is defined as “a physiological test that measures how an individual inhales or exhales volumes of air as a function of time” (Miller *et al.*, 2005). Patients are instructed to perform tidal breathing through a pneumotachograph mouthpiece before performing forced inhalation and exhalation manoeuvres. The forced expiratory volume in one second (FEV1), forced vital capacity (FVC), the ratio between FEV1 and FVC and the percentage of predicted FEV1 (FEV1%) are used to characterise airflow limitation in patients. Predicted values are based on the patient’s age, BMI, sex and race. Patients with moderate COPD tend to have FEV1% values of between 50%-80% with severe COPD values between 30%-50% (GOLD, 2017). FEV1/FVC values less than 0.7, particularly after the administration of a bronchodilator, can signify the presence of COPD (Pauwels and Rabe, 2004; Celli, 2000). Reversible airflow obstruction can be diagnosed by assessing lung function measurements before and after the administration of a bronchodilator. This can assist in the diagnosis of asthma (Horak *et al.*, 2016).

1.3 Inhaled Therapy

Asthma and COPD are usually treated with medication administered through inhalation. Inhalation therapy is the preferred choice over other forms of therapy, such as oral or nasal administration, for a number of reasons. Inhaled medications directly target the airways which is critical for relieving symptoms of asthma and COPD. The speed of onset is significantly quicker than oral administration and the therapeutic effect may last longer also (Hajian *et al.*, 2016; Lavorini, 2013; Everard, 2003). Adverse side-effects are limited with inhaled therapy as they require significantly smaller doses to relieve symptoms in comparison to oral medication (Rodriguez-Martinez *et al.*, 2016; Hajian *et al.*, 2016).

There are a range of inhaled medications available which can be categorised into bronchodilators and corticosteroids. They are also sometimes referred to rescue/reliever (bronchodilators) and preventative/controller (corticosteroids) medications. Bronchodilators usually come in the form of short-acting beta-agonists (SABA) such as salbutamol and long-acting beta-agonists (LABA) such as salmeterol. These medications are used to relieve symptoms of respiratory disease by opening or dilating the airways. The LABA medications are also used in combination with corticosteroids (such as fluticasone propionate/salmeterol) to dilate the airways and reduce inflammation over a

longer period of time (Normansell and Kew, 2016). A range of specific combinations of medication are available for asthma and COPD patients depending on the severity of the disease.

Inhaled medication is administered to patients using inhaler devices of which there are three main types; pressurised metered dose inhaler (pMDI), dry powder inhaler (DPI), soft mist nebulizers (Backman *et al.*, 2014). The most common inhaler devices used in clinical practice are pMDIs and DPIs and so will be the primary focus of this research.

1.3.1 Pressurised metered dose inhaler (pMDI)

The pMDI is the most commonly used inhaler worldwide with total worldwide sales in excess of \$2 billion per annum (Lavorini, 2013; Virchow *et al.*, 2008). It is a handheld, cheap, multi-dose, portable device that is available for a number of medications (Lavorini, 2013). Approximately 40% of the aerosol particles in pMDIs are in the respirable range (Lavorini, 2013). The pMDI consists of a pressurised canister which contains the medication, a metering valve and support casing as shown in Figure 1.3.



Figure 1.3. Pressurised metered dose inhaler (pMDI).

Adapted from (MPR, 2017; A.D.A.M., 2017).

The medication is suspended or dissolved in a propellant within the pressurised canister. Propellants are volatile substances that are gaseous at ambient temperature and pressure but liquify when cooled. Originally, chlorofluorocarbon (CFC) propellants were used in pMDIs but have been phased out in recent years due to the consensus that they damage the o-zone layer. For this reason, hydrofluoroalkane (HFA) propellants have been introduced as a replacement for CFCs (Rau, 2006).

When the user actuates (presses down) the canister, the propellant/medication solution/suspension is fired from the inhaler where the propellant then evaporates

immediately leaving only the medication to be inhaled by the patient. The metering valve ensures a known consistent volume of propellant/medication is dispensed from the inhaler (Roche and Dekhuijzen, 2016). The HFA pMDIs contain ethanol so they tend to generate a warmer temperature aerosol plume (approximately 8°C) (Lavorini *et al.*, 2014). The aerosol plume generated from HFA pMDIs generate slower velocity upon actuation also compared to CFCs. This reduces the cold freon effect sometimes experienced by patients whereby patients cease their inhalation prematurely due to the cold sensation exhibited from the aerosol plume hitting the back of the throat during actuation (Crompton, 1982; Gabrio *et al.*, 1999).

As with all inhalers, pMDI requires a number of specific steps in order for the patient to receive maximum therapeutic effect from the inhaler. The most critical step when using any inhaler is the inhalation event. When using a pMDI, patients are instructed to actuate the canister of the pMDI as they begin a “slow” and “deep” inhalation (Chrystyn and Price, 2009). Patients are required to inhale steadily below 90 L/min in order to ensure the medication reaches the lower airways (Al-Showair *et al.*, 2007a; Ammari and Chrystyn, 2013). The flow rate of inhalation directly affects the velocity of the aerosol particles. Inhaling too fast may increase the probability of the aerosol particles being deposited in the oropharynx and larynx rather than the lower airways (Laube *et al.*, 2011).

1.3.2 Dry powder inhaler (DPI)

The DPI is also a handheld, multi-dose device that delivers medication to the airways via an inhalation. DPIs are also available for a range of medications. As the name suggests, the medication is in dry powder form and, therefore, they do not require any propellant gases to deliver medication. DPIs are breath-actuated devices meaning that they do not require the patient to physically actuate the inhaler during inhalation. This highlights a major advantage of DPIs over pMDIs. It has been reported that patients make fewer user technique errors that prohibit maximum drug delivery when using DPIs in comparison to pMDIs. For this reason, DPIs are becoming more and more popular in clinical practice (Melzer *et al.*, 2017).

The medication in DPIs is usually formulated with a carrier such as lactose (Plaza Moral and Giner Donaire, 2016). In order to remove the powder from the mouthpiece and to deliver the medication efficiently to the lower airways, the patient must inhale “fast”, “hard and as deep as possible” (Chrystyn and Price, 2009). A fast and hard inhalation is

required to generate sufficient turbulent energy to break up and de-agglomerate the powder into an aerosol of suitable particle size to reach the lower airways (<5 µm). The turbulent energy within the DPI is caused from the pressure drop associated with the patient's inhalation flow rate and the DPI's internal resistance to airflow. This relationship can be represented as follows;

$$\sqrt{P} = F \times R \quad (1.1)$$

where P is the pressure change inside the DPI, F is the inhalation flow rate and R is the DPI resistance to airflow (Chrystyn and Price, 2009; Azouz and Chrystyn, 2012).

DPI resistance to airflow varies across different DPI designs, therefore, it is not suitable to compare patient inhalation flow rate across DPI devices. The turbulent energy generated within the device during inhalation is of more significance. Patients may be able to achieve significantly higher inhalation flow rate in certain DPIs compared to others.

Figure 1.4 presents the main components of a range of DPIs including the Diskus, Ellipta and Turbuhaler. DPIs also require a number of specific steps in order for patients to receive maximum clinical benefit from the inhaler. There are many different designs and brands of DPI devices, all with different airflow resistance levels and different mechanisms to prepare the medication dose for inhalation. According to the literature, the “optimal” inhalation flow rate of inhalation may change across different DPI device designs, therefore, the minimum inhalation flow rate required to generate sufficient turbulent energy within the device can be considered. The recommended minimum peak inspiratory flow rate (PIFR) of inhalation for DPIs is reported to be 30 L/min (Azouz and Chrystyn, 2012). However, total lung dose from DPIs is not only dependent on inhalation flow rate, it is also dependent on the inspiratory capacity (IC) and acceleration (ramp or rise time) of inhalation (Haughney *et al.*, 2010; Dorosz *et al.*, 2016). Failure to generate the rapid, forceful and deep inhalation required to de-aggregate the dose particles can lead to medication being deposited in the oropharynx from where it may be swallowed by the patient and have little therapeutic effect (Haughney *et al.*, 2010).

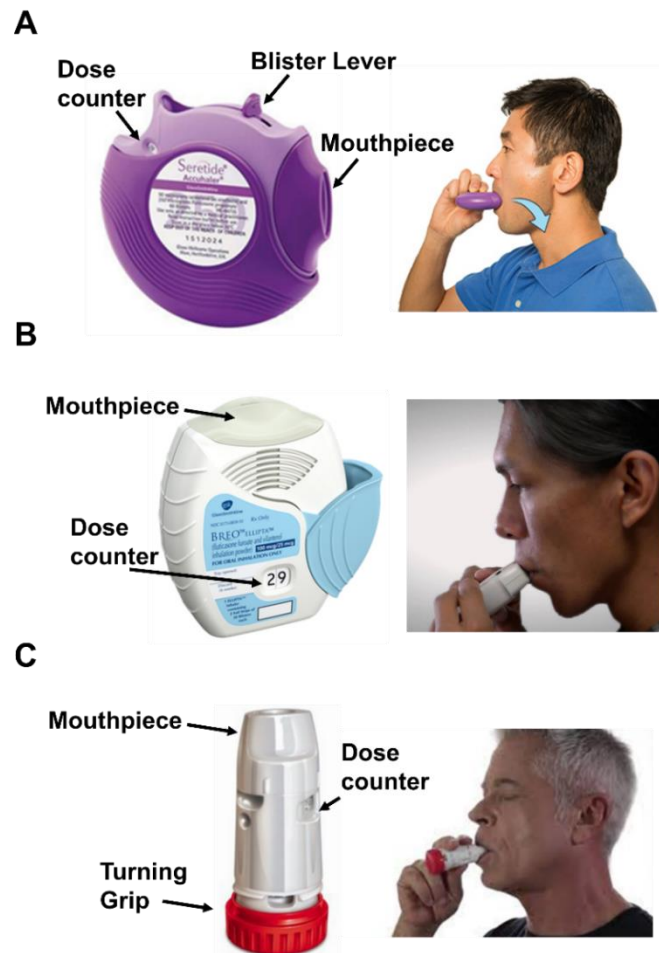


Figure 1.4. Examples of dry powder inhalers (DPIs).
 (A) Diskus [GlaxoSmithKline, London, UK], (B) Ellipta [GlaxoSmithKline, London, UK] and
 (C) Turbuhaler [AstraZeneca, Södertälje, Sweden].

1.4 Adherence

Adherence is a term used to describe “the extent to which a person’s behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider” (WHO, 2003). Adherence is also referred to as “compliance”, “persistence” or “concordance” in the literature (Pritchard and Nicholls, 2015; Blaschke *et al.*, 2012). In terms of inhaler use, adherence is composed of temporal adherence (when the patient used their inhaler) and user technique adherence (how the patient used their inhaler). Adherence to inhaler medication is imperative for the long term management of chronic respiratory diseases (Toy *et al.*, 2011).

Poor adherence to inhaled medication is a complex problem and is a major clinical concern in the treatment of chronic respiratory diseases. Adherence in asthma and COPD is poorer compared to other diseases such as diabetes, depression, hypertension and

osteoporosis (Sanduzzi *et al.*, 2014). According to a Cochrane review, up to 80% of asthma patients do not use their inhaler with correct user technique (Normansell and Kew, 2016). COPD adherence has not improved in the last 40 years, with studies reporting over 50% of COPD patients having poor inhaler adherence (Sanchis *et al.*, 2016; Molimard *et al.*, 2016). In terms of inhaler user technique adherence, patients often make critical errors while using their inhaler which prohibits them from receiving the maximum available medication dose. Critical errors can be defined as those resulting in little or no medication reaching the lungs and resulting in poor disease outcomes (Batterink *et al.*, 2012; Price *et al.*, 2017). It is important to understand what critical errors are most common amongst patients, what are the consequences of these critical errors in terms of clinical outcomes and how can they be objectively monitored to improve patients' inhaler user technique.

Poor inhaler adherence leads to poor disease control in asthma patients, particularly with uncontrolled asthma (Price *et al.*, 2017; Horak *et al.*, 2016; Giraud *et al.*, 2011). It is also associated with poor disease control in COPD patients (Lee *et al.*, 2014). It was previously reported that COPD patients are twice as likely to be hospitalised if they do not use their inhaler correctly (Molimard *et al.*, 2016). Mortality rates have been reported to double in COPD when patients are non-adherent to their inhaler medication (Vestbo *et al.*, 2009). Another previous study reported that COPD patients tend to have poor pMDI user technique during an exacerbation (Broeders *et al.*, 2004). This highlights that some patients may not be able to use their inhaler correctly when they need it the most. Poor inhalation technique in DPIs is associated with increased rate of exacerbations in asthma patients (with 32%-38% making this critical error) (Price *et al.*, 2017). Furthermore, patients may not feel an improvement in their respiratory health if they are non-adherent to their inhaler medication. Healthcare professionals may increase the dose of inhaler medications as they may attribute poor disease control with the pharmacological properties of the medication rather than adherence (Bonini and Usmani, 2015; Bateman *et al.*, 2008). This can increase healthcare costs even though it may not be completely necessary.

A substantial economic burden which affects patients, providers and the healthcare system is caused due to poor adherence. In the U.S, over \$50 billion is spent on inhalers every year with \$7-15 billion wasted due to poor adherence (Fink and Rubin, 2005; Normansell and Kew, 2016). Poor adherence increases healthcare costs from increasing the number of hospitalisations. Approximately 275 million medical visits are wasted each year due to poor patient adherence (Schappert and Rechtsteiner, 2008). Poor inhalation

technique is associated with increased healthcare costs in Europe also. It was reported that poor inhalation technique in inhalers was associated with costs of €782 million across Spain, Sweden and the UK (Lewis *et al.*, 2016). The estimated revenue loss to the pharmaceutical industry is an estimated \$637 billion due to poor adherence (Capgemini Consulting, 2016).

Improving patient inhaler adherence can reduce the risk of exacerbations and improve respiratory health. Therefore, there is an urgent clinical need to provide healthcare professionals with objective information regarding patient inhaler adherence (both temporal and user technique) (Davis *et al.*, 2017). Sensor-based inhaler monitoring technologies have shown promising opportunities to collect pertinent data regarding when (temporal adherence) and where patients use their inhalers (Kikidis *et al.*, 2016; Chan *et al.*, 2013; Su *et al.*, 2017). The global market for “smart” inhalers and sensor-enabled monitoring technologies is on the rise and it is estimated that it will be a \$3.56 billion industry by 2024 (Grand View Research, 2016). However, many of the monitoring devices available cannot objectively assess patient user technique adherence (how patients use their inhaler). In previous research, the Inhaler Compliance Assessment (INCA) system highlighted the potential in employing audio-based methods to obtain objective information regarding both temporal and user technique adherence as well as quantifying the amount of drug delivered to patients using the Diskus DPI (Holmes *et al.*, 2014a; Sulaiman *et al.*, 2017). The system employed audio-based signal processing methods to automatically classify inhaler events such as inhalation, drug preparation and exhalation sounds. By assessing the timing and the order of these inhaler sound events, objective assessment of patient user technique is possible. This allows healthcare professionals to personalise treatment to the patients’ needs with the goal of improving their adherence and their beliefs towards their medication. However, little is known regarding the use of audio-based methods to objectively assess patient user technique in pMDIs and other DPIs such as the Ellipta and Turbuhaler. Furthermore, there is lack of research to date on how audio-based methods of inhaler use can be used to observe patients’ clinical response to treatment.

1.5 Research Goal and Collaborations

The research goal of this thesis was to develop audio-based signal processing methods to allow investigation into patient adherence to correct inhaler user technique. In order

for new adherence measures to be introduced into respiratory medicine, new signal processing methods are needed to extract pertinent clinical information of patient inhaler use. Based on the existing literature, previous audio-based methods of objectively assessing patient inhaler user technique were examined in significant detail. The specific aims and hypothesis are presented in further detail in Chapter 3. Studies to further improve the scientific depth and applicability of these methods to a range of different inhaler devices were conducted as part of this thesis.

This research involved a close collaboration between the Trinity Centre for Bioengineering in Trinity College Dublin and healthcare professionals in the Royal College of Surgeons in Ireland (RCSI), Beaumont Hospital, Dublin, Ireland and in the Bon Secours Hospital, Dublin, Ireland. This collaboration enabled the collection of clinical data from patients with chronic respiratory diseases, enhanced the design of patient-focused experiments and ensured that studies were performed in line with current ethical guidelines. This research also involved collaboration with the engineering team at Vitalograph Ireland Ltd., Ennis, Co. Clare, Ireland who manufactured and provided spirometers and INCA audio recording devices for acquiring inhaler flow and audio data.

1.6 Thesis Outline

This thesis is organised into a series of studies. Chapter 2 reviews the literature associated with the prevalence and consequences of poor adherence to correct pMDI and DPI user technique amongst asthma and COPD patients. It also focuses on the existing literature on audio-based methods of detecting and classifying respiratory sounds and estimating respiratory flow rate. Chapter 2 reviews the literature on audio-based methods of monitoring inhaler adherence and the clinical impact it has on the treatment of asthma and COPD. Chapter 3 introduces the main aim and hypothesis of this thesis and the specific research questions that were addressed.

The studies described in Chapter 4 investigate the use of audio-based methods to estimate PIFR in pMDIs and DPIs as well as investigating the acoustic properties of inhaler inhalation sounds and how they may significantly differ across inhaler devices. The first study described in Chapter 5 focuses on employing audio-based methods to estimate PIFR in asthma and COPD patients. It also investigates the spectral properties of inhalation sounds across patients which may assist future audio-based algorithmic development for monitoring patient inhaler adherence. The second study reported in

Chapter 5 investigates the relationship between audio-based features of inhaler inhalation sounds and patient lung function during and after an induced exacerbation with the aim of remotely monitoring lung function during treatment through audio analysis of inhaler inhalation sounds. The study described in Chapter 6 focuses on the development of a method to estimate the inhalation flow profile (which allows for measuring PIFR, IC and other flow parameters that directly influence inhaler drug delivery) from the Ellipta DPI using audio-based features from just one inhalation audio signal for calibration. The final two studies of the thesis described in Chapter 7 focus on the development of an audio-based signal processing algorithm to automatically objectively assess pMDI user technique in asthma and COPD patients. The second study in Chapter 7 also compares the performance of the developed audio-based methods of assessing inhaler user technique with a subjective clinical checklist method.

Finally, Chapter 8 presents a discussion of the main findings reported in this thesis along with a discussion of the clinical impact of this research. In addition, the limitations of this research, followed by recommendations for future studies in this research area are also discussed in order to further enhance audio-based inhaler monitoring systems.

Chapter 2. Literature Review

2.1 Patient Adherence to Pressurised Metered Dose Inhaler User Technique

Although the pMDI is the most commonly used inhaler device worldwide and generates high dose consistency, there are some major disadvantages in terms of using pMDIs in clinical practice. The main disadvantage with pMDIs is that many patients do not use them with correct user technique which greatly impairs clinical outcomes for patients (Crompton, 2004). The specific user technique steps regarding how to correctly use a pMDI are given in Table 2.1 (Laube *et al.*, 2011). The device requires the patient to physically actuate the inhaler canister to receive medication; therefore, they are not breath-actuated. Good coordination between actuation and inhalation (also referred to as actuation coordination) is critical (see step 8 in Table 2.1) in ensuring maximum drug deposition in the lower airways which makes it challenging to use for many patients (Sanchis *et al.*, 2016). Moreover, the pMDI propellant fires the medication from the inhaler rapidly, therefore the patient is only required to guide the medication with a low flow rate inhalation (Murphy, 2016). The pMDI has minimal resistance to air flow which may allow patients to inhale too fast in relation to the recommended flow rate of 90 L/min (Azouz *et al.*, 2014). This causes high oropharyngeal deposition which reduces therapeutic effect (Lavorini, 2013). Also, many pMDIs do not have dose counters, making it very challenging for patients to keep a record of the number of doses administered (Chrystyn and Price, 2009).

Many studies have reported on patient pMDI user technique and they all lead to the same consensus that many asthma and COPD patients cannot use pMDIs with correct

Table 2.1. Steps required to correctly use a pressurised metered dose inhaler (pMDI).

Step Number	Instruction
1	Shake four or five times (if suspension formulation)
2	Take the cap off
3	Prime the inhaler (refer to the patient information leaflet)
4	Exhale slowly, as far as comfortable (to empty the lungs)
5	Hold the inhaler in an upright position
6	Immediately place the inhaler in the mouth between the teeth, with the tongue flat under the mouthpiece
7	Ensure that the lips have formed a good seal with the mouthpiece
8	Start to inhale slowly, through the mouth and at the same time press the canister to actuate a dose
9	Maintain a slow and deep inhalation, through the mouth, until the lungs are full of air. This should take an adult 4–5 seconds
10	At the end of the inhalation, take the inhaler out of the mouth and close the lips
11	Continue to hold the breath for as long as possible, or up to 10 seconds before breathing out
12	Breathe normally
13	If another dose is required, repeat steps 4–12

user technique. As there are a number of critical steps to perform, patients are prone to make at least one mistake during inhaler use. According to Restrepo *et al.* (2008), 90% of patients use their pMDI with poor user technique (Restrepo *et al.*, 2008). However, some errors are more critical than others in terms of impeding drug delivery to the patient. Studies have reported that 43.8% of patients made critical errors that impeded drug delivery (Molimard *et al.*, 2016). This is quite alarming as it suggests that these patients did not receive the full clinical benefit from their inhaler medication. Also, patients are more likely to make critical errors when using the pMDI as opposed to any other inhaler device (Batterink *et al.*, 2012; Sanchis *et al.*, 2016; Melzer *et al.*, 2017). Table 2.2 lists a number of studies that reported several critical errors associated with pMDIs. The top

Table 2.2. Studies reporting common user technique errors associated with the pMDI.

Author	No. Patients	Most Common Errors (% of patients making error)
(Price <i>et al.</i>, 2017)	760	• Inhalation too fast (47.2%) • Poor actuation coordination (34.7%) • Head not tilted upward (34.1%)
(Jha <i>et al.</i>, 2017)	105	• Inhalation too fast (100%) • Poor actuation coordination (100%) • Insufficient breath hold (90%)
(Sanchis <i>et al.</i>, 2016)	23,296	• Insufficient breath hold (46%) • Poor actuation coordination (45%) • Inhalation too fast (44%)
(Melani <i>et al.</i>, 2011)	1,633	• Insufficient breath hold (53%) • Inhalation too fast (52%) • No exhalation before inhalation (50%)
(Molimard, 2005)	3,811	• Inhalation too fast (37%) • Didn't shake inhaler (33.5%) • No exhalation before inhalation (28.9%)
(Giraud and Roche, 2002)	3,955	• Insufficient breath hold (44%) • Inhalation too fast (34%) • Not inhaling to total inspiratory capacity (23%)
(McFadden Jr, 1995)	955	• Poor actuation coordination (27%) • Insufficient breath hold (26%) • Inhalation too fast (19%)
(Crompton, 1982)	1,038	• Poor actuation coordination (73%) • Multiple actuations (17%) • Inhaled through nose (12%)

three most common critical errors observed in each study are listed also. It is clear from Table 2.2 that inhaling too fast and poor actuation coordination are both very common critical errors patients make when using a pMDI. A fast inhalation (PIFR over 90 L/min) increases the velocity of the aerosol particles and increases the impaction of particles where the airflow changes direction (such as at the back of the throat). Therefore, the amount of drug penetrating the lower airways is significantly reduced (Murphy, 2016;

Haughney *et al.*, 2010; Pirozynski and Sosnowski, 2016). Poor coordination leads to excess deposition in the oropharynx (Giraud and Roche, 2002). More specifically, even actuating towards the end of an inhalation can reduce the penetration of drug to the lower airways due to the reduced volume of inhalation (Pirozynski and Sosnowski, 2016). Actuating the inhaler multiple times can reduce the delivered dose per actuation also (Murphy, 2016). Reduced volume of inhalation can also come as a consequence of not exhaling to empty the lungs before inhaling. Consequently, there was a clinical need to introduce new inhaler device designs such as DPIs to address these issues. However, DPIs have their own clinical disadvantages.

2.2 Patient Adherence to Dry Powder Inhaler User Technique

Although DPIs eliminate the issue of actuation coordination observed in pMDIs and are breath-actuated, there are still some concerns regarding DPI use in clinical practice also. The clinical efficacy of DPIs is heavily reliant on the patient's inhalation manoeuvre. The specific steps regarding how to correctly use a DPI are listed in Table 2.3 (Laube *et al.*, 2011). The patient's inhalation flow profile (how the inhalation flow rate changes over time) affects the clinical performance of DPIs (Dorosz *et al.*, 2016). There are a number of flow parameters that can be computed from the inhalation flow profile from DPIs. Figure 2.1 presents an illustration of an inhalation flow profile from a DPI. The PIFR corresponds to the maximum point on the flow profile curve. The IC corresponds to the volume of air inhaled in litres which is computed as the area under the flow profile curve. The ramp time (or rise time) refers to the time taken to reach the PIFR. In DPIs, the medication leaves the inhaler mouthpiece almost instantly at the onset of an inhalation. Therefore, it is essential for the patient to inhale as fast and as hard as possible (with sufficiently high PIFR and IC values with short ramp time) to receive the maximum dose available.

Table 2.3. Steps required to correctly use a dry powder inhaler (DPI).

Step Number	Instruction
1	Take the cap off (some do not have a cap)
2	Follow the dose preparation instructions in the patient information leaflet
3	Do not point the mouthpiece downwards once a dose has been prepared for inhalation because the dose could fall out
4	Exhale slowly, as far as comfortable (to empty the lungs). Do not exhale into the DPI
5	Start to inhale forcefully through the mouth from the very beginning. Do not gradually build up the speed of inhalation
6	Continue inhaling until the lungs are full
7	At the end of the inhalation take the inhaler out of the mouth and close the lips. Continue to hold the breath for as long as possible, or up to 10 seconds
8	Breathe normally
9	If another dose is required, repeat steps 1–8

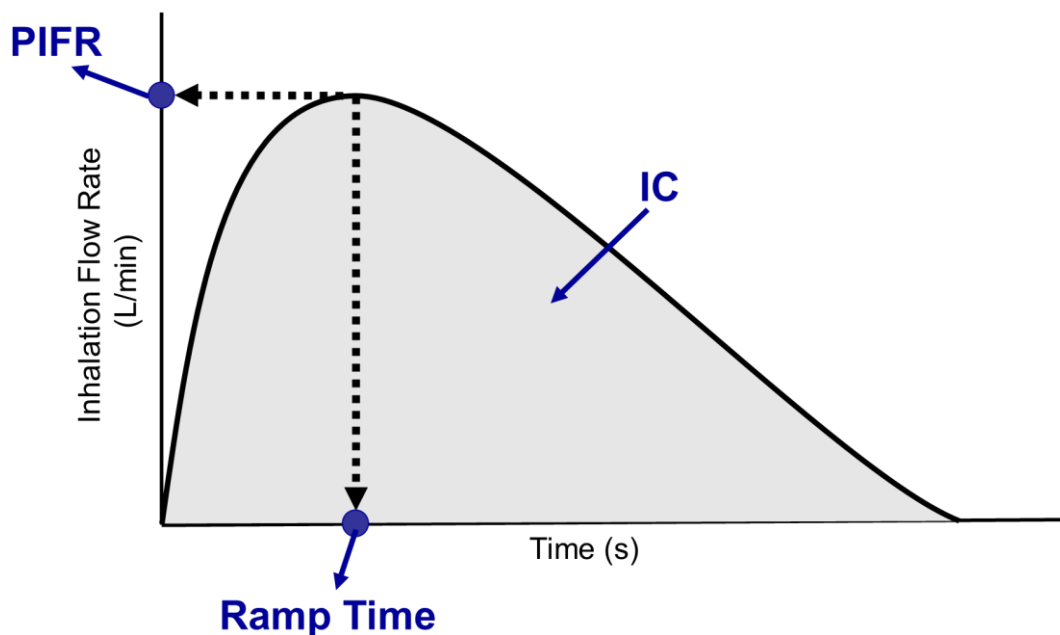


Figure 2.1. Illustration of a DPI inhalation flow profile.

The plot demonstrates flow parameters including peak inspiratory flow rate (PIFR) which corresponds to the peak flow rate of the flow profile curve, the inspiratory capacity (IC) which corresponds to the area under the curve (shaded region) and the ramp time which corresponds to the time at which PIFR is achieved.

Figure 2.2 presents examples of two inhalation flow profiles through a DPI (Chrystyn and Price, 2009; Haughney *et al.*, 2010). In Figure 2.2, both inhalation profiles generate the same PIFR, however, it is clear that the inhalation demonstrated by Profile 2 is more ideal due to a more rapid onset (short ramp time) and, therefore, will deliver more of the available dose to the patient. Improper inhalation technique in DPIs can lead to over 50% of the drug being deposited in the throat (de Boer *et al.*, 2016). Some patients may not be physically able to achieve the required inhalation flow parameters, particularly children under the age of 5 years and COPD patients with impaired lung function (Bonini and Usmani, 2015; Fink and Rubin, 2005). DPIs can be challenging to administer to non-cooperating patients. Also, the drug output is reported to be less accurate and reproducible compared to other devices (Melani, 2007). Exhaling into the mouthpiece of the DPI may significantly reduce the dose available to the patient (Holmes *et al.*, 2014b; Fink and Rubin, 2005). This issue is non-existent in pMDIs.

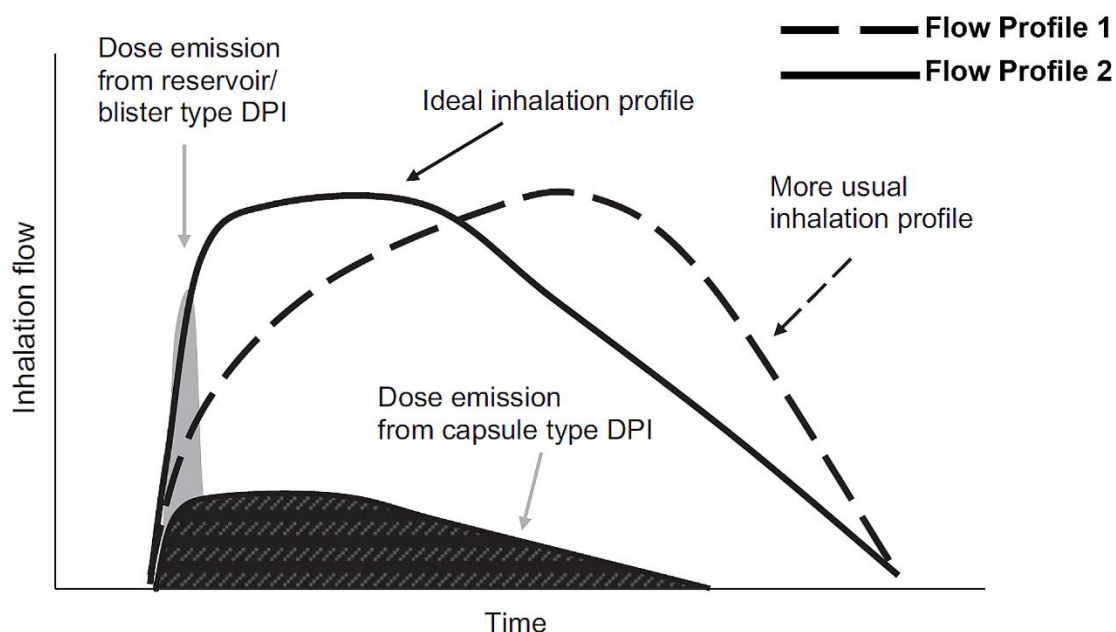


Figure 2.2. DPI inhalation flow profiles from two different inhalation manoeuvres.
The plot presents patient inhalation profiles that are usual (Flow Profile 1) vs. ideal (Flow Profile 2) for DPI dose emission. Actual shape will vary with the device used (adapted from (Chrystyn and Price, 2009; Haughney *et al.*, 2010)).

New DPI devices are being developed regularly as the medication market for DPIs continues to rise (Chrystyn and Niederlaender, 2012). However, new medication formulations have to be optimised to the inhaler design. Certain formulations may be tailored to high resistance or low resistance DPIs depending on the properties of the drug carrier agglomerate and mixtures. Therefore, using the same formulation of medication in different DPIs may generate different clinical outcomes (Lavorini *et al.*, 2014).

Many patients make critical errors when using DPIs also. A study by Melani *et al.* (2011) reported that patients made more critical errors using DPIs than pMDIs (Melani *et al.*, 2011). Table 2.4 lists a number of studies that reported several critical errors associated with DPIs. The top three most common critical errors observed in each study are listed also.

It is clear from Table 2.4 that there exists a significant clinical problem with DPIs in that patients cannot generate sufficient inhalation effort to receive the available dose. Insufficient inspiratory effort increases the size of the emitted particles (which reduces lower airway deposition) and can lead to a build-up of medication at the mouthpiece of the inhaler where the medication is wasted (Sulaiman *et al.*, 2017; Virchow *et al.*, 2008). Not only do patients find it challenging to generate the required inhalation flow rate, they also struggle to generate sufficient inspiratory volume also. Insufficient inspiratory volume can be a result from not emptying the lungs by exhaling to residual capacity

Table 2.4. Studies reporting common user technique errors associated with the DPI.

Author	DPI Used	No. Patients	Most Common Errors (% of patients making error)
(Price <i>et al.</i>, 2017)	Diskus	826	• Insufficient inhalation flow rate (38.4%) • Head not tilted upward (34.6%) • No exhalation before inhalation (32.4%)
(Price <i>et al.</i>, 2017)	Turbuhaler	2,074	• Insufficient drug preparation (48.8%) • Head not tilted upward (34.3%) • Insufficient inhalation flow rate (32.1%)
(Jha <i>et al.</i>, 2017)	DPI (General)	105	• No exhalation before inhalation (87.7%) • Insufficient breath hold (82.2%) • Insufficient inhalation flow rate (79.5%)
(Sanchis <i>et al.</i>, 2016)	DPI (General)	27,040	• No exhalation before inhalation (46%) • Insufficient breath hold (37%) • Incorrect drug preparation (29%)
(Melani <i>et al.</i>, 2011)	Diskus	1,633	• Insufficient breath hold (32%) • Not inhaling to total inspiratory capacity (29%) • Exhaling into the mouthpiece (22%)
(Melani <i>et al.</i>, 2011)	Turbuhaler	1,633	• Insufficient breath hold (28%) • Insufficient inhalation flow rate (22%) • Not inhaling to total inspiratory capacity (22%)

before inhalation. Moreover, patients with severe COPD may not be able to generate the required inhalation manoeuvre due to the obstructive pathophysiology of their disease. It has been reported that exhalation before inhalation in DPIs is associated with an increase in PIFR and may also improve drug delivery as a result (Kondo *et al.*, 2015). Insufficient breath hold is also a common critical user technique error amongst patients. A recent

study by Horváth *et al.* (2017) reported that a breath hold of even just five seconds during DPI use can increase drug deposition in the airways by 11.3-26.5% (Horváth *et al.*, 2017).

2.3 Factors Associated with Poor Inhaler Adherence

There are a range of factors associated as to why poor adherence is so prevalent amongst patients. These factors can be divided into a number of categories; patient, treatment and healthcare professional factors (Bourbeau and Bartlett, 2008; Ari, 2015).

2.3.1 Patient factors

As previously mentioned, patient satisfaction with their device influences inhaler adherence and clinical outcomes of inhaled therapy (Small *et al.*, 2011; Mäkelä *et al.*, 2013). However, it has been reported that patients may be still prone to incorrect user technique even if they are satisfied with their device (Jahedi *et al.*, 2016). Patients' beliefs in their medication can play a significant role in adherence (Conn *et al.*, 2007). This may relate to the patient not believing the medication has any clinical effect, or that they do not have confidence in their healthcare professional. Some patients believe that they use their inhaler with correct user technique when in reality they do not (Jahedi *et al.*, 2016). In a study by Giraud and Roche (2002), it was reported that 85% of patients with poor user technique using a pMDI believed they had correct user technique (Giraud and Roche, 2002). A patient's memory of the correct steps to use an inhaler device may diminish over time also (Crompton *et al.*, 2006; Ammari *et al.*, 2017). Cognitive ability may influence patients becoming non-adherent (Moran *et al.*, 2017; Baird *et al.*, 2017). Studies have reported that performance in the minimental test (MMT) was significantly correlated with inhalation technique ($r=0.48$, $p=0.032$) (Allen and Ragab, 2002). This is also likely linked with age, as age has also been reported to be a significant influence on inhaler adherence in several studies (Jarvis *et al.*, 2007; Giraud and Roche, 2002; Melani *et al.*, 2011; Lurslurchachai *et al.*, 2014). Comorbidities such as visual and hearing loss are also associated with poor inhaler adherence (Ammari *et al.*, 2017).

Patient's health literacy levels influence adherence in both pMDIs and DPIs (O'Connor *et al.*, 2015). Health literacy can be defined as the "degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions" (Kindig *et al.*, 2004). It has been previously

reported that elderly patients tend to have low levels of knowledge regarding their respiratory disease (Ozturk *et al.*, 2015). Education/literacy levels have shown to be a significant factor on inhaler user technique with illiterate patients making more errors than postgraduate/professionally qualified patients (Arora *et al.*, 2014).

2.3.2 Treatment factors

There exists almost 200 different designs of inhalers across pMDIs ,DPIs and soft mist nebulizers, each with their own different specific steps required to deliver the medication efficiently (Braido *et al.*, 2016a). Selecting a suitable inhaler device is a critical step in treating asthma and COPD. However, there is a lack of consensus on the standards for selecting appropriate inhaler devices for patients (Bonini and Usmani, 2015; Haughney *et al.*, 2010). Factors that should be considered include the patient's preference of device, the availability and cost of the device and the medication, the age of the patient and their ability to use the device as well as the healthcare professional's preference on what should be administered (Dolovich *et al.*, 2005; Hajian *et al.*, 2016; Restrepo *et al.*, 2008). As previously discussed, there are advantages and disadvantages to using either a pMDI or a DPI in the treatment of asthma and COPD. The patient's ability to use the inhaler with correct user technique is critical when selecting an inhaler device as it has been previously reported that the choice of inhaler can be a predictor of poor adherence in patients (Jha *et al.*, 2017).

Patients are rarely prescribed just one inhaler (Fink and Rubin, 2005). Usually multiple different inhalers are prescribed for different medications which influences adherence (Bonini and Usmani, 2015; Chrystyn *et al.*, 2014). However, combination medication inhalers are becoming more popular which should decrease the number of inhalers prescribed to patients. If patients are prescribed multiple inhalers, the devices should require similar inhalation techniques. It has been reported that patients using multiple inhalers with similar inhalation techniques are less likely to have an exacerbation (Bosnic-Anticevich *et al.*, 2017). The dosing regimen a patient is put on by their healthcare professional is important also. Increasing the dosage per day can have an adverse effect on adherence (Sanduzzi *et al.*, 2014; Toy *et al.*, 2011), with the majority of patients preferring a single dose per day system (Tamura and Ohta, 2007).

2.3.3 Healthcare professional factors

How healthcare professionals educate patients on correct inhaler user technique is crucial in ensuring patients understand how to use their inhaler device (Chrystyn and Price, 2009). It has been reported that it takes three clear step-by-step demonstrations for patients to understand how to use an inhaler device (Rottier and Rubin, 2013; Takaku *et al.*, 2017). However, in some cases, patients are not given sufficient information by their healthcare professional (Sanduzzi *et al.*, 2014). It has been widely reported that many healthcare professionals cannot perform all steps of inhaler use correctly themselves. As many as 33-67% of healthcare professionals are unable to adequately perform all critical inhaler steps (Fink and Rubin, 2005; Broeders *et al.*, 2009). Also, many patients visit more than one healthcare professional so opinion on inhaler use may change accordingly and become confusing for patients (Bender *et al.*, 1997). Therefore, by standardising adherence assessment using objective methods, it may improve treatment for respiratory disease by educating patients as well as healthcare professionals on inhaler adherence.

2.4 Current Methods of Monitoring Inhaler Adherence

As previously mentioned, adherence consists of temporal adherence and user technique adherence. There are a range of subjective and objective methods of monitoring inhaler temporal and user technique adherence.

2.4.1 Monitoring temporal adherence

2.4.1.1 Subjective methods

Monitoring temporal adherence heavily relies on self-reported diaries from patients. This is a simple and low cost method however they can be widely inaccurate. Patients may intentionally or unintentionally report better adherence than their true adherence and so this will impede healthcare professionals from obtaining reliable data (Pritchard and Nicholls, 2015; Micallef *et al.*, 2014). The dose counters on the inhalers can give an indication of temporal adherence i.e. was the inhaler used or not. However, they cannot give exact time stamps of when the inhaler was used nor can they distinguish trends in patient temporal adherence.

2.4.1.2 Objective methods

Objective methods of monitoring temporal adherence include **canister weighing** for pMDIs. The weight of the pMDI canister is measured upon prescribing the inhaler to the patient. The canister is then weighed when the patient returns at a later date and the difference in weight can give a measure of temporal adherence (Howard *et al.*, 2014). Although this method is relatively simple to implement, it still requires a professional and it is not capable of detecting canister dumping (also referred to as dose dumping) (Pritchard and Nicholls, 2015). Dose dumping refers to a patient emptying or dumping the medication before they visit their healthcare professional.

Pharmacy records on medication refills, the type of medication and the amount of medication prescribed can give a measure of temporal adherence. However, this also cannot detect dose dumping and it may not be useful for certain inhalers if certain inhalers are available over the counter (Pritchard and Nicholls, 2015).

Biochemical monitoring involves analysing blood, urine or secretions to measure drug level (Ari, 2015). However, this method is invasive, expensive and is not available for all medications (Vitolins *et al.*, 2000). It also cannot distinguish trends in patient adherence. The method may overestimate adherence due to the “toothbrush effect” which involves patients improving their adherence just prior to a scheduled healthcare visit (Pritchard and Nicholls, 2015).

Electronic monitoring devices (EMDs) have been developed for inhalers in recent years to obtain more objective data regarding patient temporal adherence. There are a range of EMDs available to monitor temporal adherence.

The **Doser**¹ is an attachable device [Meditrack Inc., Massachusetts, USA] that records time stamps of when pMDI actuations occurred (i.e. when the inhaler was used). As many pMDIs do not have dose counters, the Doser can remind patients to take their inhaler and inform them when the canister is nearly empty. However a disadvantage of the Doser is that it does not allow for the data to be transferred to a computer and so healthcare professionals cannot monitor trends over time in patient adherence (Howard *et al.*, 2014).

More advanced EMDs have been introduced for pMDIs such as the **Smart Inhaler Tracker**² [Nexus 6, Auckland, New Zealand] which is shaped similar to a pMDI and records time stamps of when actuations occurred. The device can also set reminders for

¹ <https://www.doser.com/>

² <http://www.smartinhaler.com/>

patients to use the inhaler. Other generations of this device were developed including the **SmartTrack** and **SmartTouch AV** which provide better display screens and allow for smartphone interaction. They can also detect if the canister was inserted or removed from the inhaler (Howard *et al.*, 2014). Data can be transferred from the device for post-analyses.

Other devices such as the **Spiroscout**³ [Propeller Health, Wisconsin, USA] also include additional GPS sensors to allow healthcare professionals analyse when and where patients used their inhalers. This may be clinically beneficial to know if there are high risk locations that may trigger an asthma attack in a patient (Pritchard and Nicholls, 2015). Data can be transferred from the device for post-analyses also.

In terms of DPIs, EMDs such as the **Diskus Adherence Logger** (DAL) [University of Pennsylvania, Pennsylvania, USA] and **SmartDisk**⁴ [Adherium Ltd., Auckland, New Zealand] are attachable devices that record drug preparation in the Diskus DPI (The DAL uses a magnetic sensor and the SmartDisk uses a switch when the inhaler is blistered or activated to record drug preparation). Data can be transferred from the device for post-analyses. However, none of the above mentioned EMDs record any information on inhalation technique and other critical steps of inhaler user technique.

2.4.2 Monitoring user technique adherence

2.4.2.1 Subjective methods

Checklists are the clinical standard for assessing user technique based on visual assessment from a healthcare professional in clinical practice. They are used to calculate a “score” of patient user technique based on a healthcare professional visual assessing each critical step of inhaler use. Newly refined checklists have reported promising results in training patients on user technique (Mac Hale *et al.*, 2014). However, checklists only consider adherence at one point in time and give equal rating to all errors (Sulaiman *et al.*, 2017). Patients tend to perform better when being monitored in a clinical setting, therefore, this visual assessment does not give a clear indication of how patients use their inhalers in real life outside of the clinical setting. Furthermore, given that some healthcare professionals do not have sufficient knowledge of the correct critical steps during inhaler

³ <https://www.propellerhealth.com/>

⁴ <http://www.smartinhaler.com/portfolio/smartdisk/>

use (Broeders *et al.*, 2009), this method of assessment is prone to error and over estimation of adherence. Opinion on inhaler technique will change from person to person so this will generate variability and uncertainty regarding standard clinical assessment of inhaler user technique. Many studies have used checklists to measure user technique (Batterink *et al.*, 2012; Ozturk *et al.*, 2015). Checklists based on visual assessment are heavily subjective and it may be challenging to measure specific critical errors using this method. For example, determining whether a patient inhaled at the correct flow rate in any inhaler may be quite challenging for healthcare professionals based on visual assessment. There is a clinical need for more objective methods to monitor inhaler user technique remotely in the treatment of chronic respiratory diseases.

Training devices have been developed to help patients improve their user technique. These devices are generally cheap and can give patients feedback on some aspects of their technique. The Clement Clarke In-Check **Flo-Tone**⁵ [Clement Clarke International Ltd, Harlow, UK] is an add-on mouthpiece for pMDIs. A plastic reed is situated on top of the Flo-Tone which generates an audible sound once the patient inhales at approximately 30-60 L/min (clinically optimal flow rate for pMDIs) (Ammari *et al.*, 2017). Patients are instructed to inhale slowly and steadily until they hear the whistle from the Flo-Tone. When the whistle becomes audible, patients are to actuate their inhaler while keeping the inhalation whistle sound constant and steady. Although the Flo-Tone gives the user an audible signal upon inhalation, it may be difficult to interpret if the patient inhales too fast. The device does not give feedback on actuation coordination. However, studies have reported an improvement in patient pMDI inhalation technique using the Flo-Tone (Ammari *et al.*, 2017). The Flo-Tone does not record any data so it does not allow for remote monitoring of pMDI user technique. The Flo-Tone devices were originally developed for training use only on placebo inhalers but the company have recently introduced Flo-Tone CR which can be used with real active pMDIs.

The **2Tone Trainer**⁶ [Canday Medical, Newmarket, UK] is a device that is shaped similar to a pMDI but does not attach to a real placebo or active inhaler (Lavorini *et al.*, 2010). The device contains two reeds which generate audible sounds giving the patient audible feedback on their inhalation technique (correct or too fast inhalation) (Al-Showair *et al.*, 2007b). As with the Flo-Tone, the 2Tone Trainer does not record any data and does not give objective feedback on actuation coordination.

⁵ <http://www.flo-tone.com/>

⁶ <http://www.2tonetrainer.net/>

2.4.2.2 Objective methods

Other training devices are available that offer more objective measurements of user technique for both pMDIs and DPIs.

The **Mag-Flo**⁷ [Fyne Dynamics Ltd., Harlow, UK] can be used with both pMDIs and DPIs. The device consists of a magnetic flow sensor to measure inhalation flow rate. When the patient inhales at a correct flow rate it switches on a battery powered green light to give patients visual feedback on their inhalation technique (Lavorini *et al.*, 2010). Data cannot be transferred from the device for post-analyses.

The Clement Clarke **In-Check Dial**⁸ [Clement Clarke International Ltd, Harlow, UK] is a device that is used to objectively measure PIFR of inhaler inhalations. The In-Check Dial can simulate the airflow resistance of a number of different pMDI and DPI devices which assists healthcare professionals in choosing a suitable inhaler device for patients (Chrystyn, 2003). The In-Check Dial was employed in a study which showed that elderly patients generate lower inhalation flow rate in the Turbuhaler DPI (Kawamatawong *et al.*, 2017). However, the device cannot be used with real inhalers, it can only measure PIFR and cannot be used to remotely record data on real life inhaler use. Data cannot be transferred from the device for post-analyses.

The **Turbutest** [Astra Draco, Lund, Sweden] is a training device used to train patients on inhalation technique for the Turbuhaler DPI. The device consists of a replica Turbuhaler connected to an electronic sensor that measures PIFR. The patient receives visual feedback through a number of lights that indicate if they inhaled at a clinically acceptable flow range. The device also detects if the patient prepared the drug correctly (Lavorini *et al.*, 2010). Data cannot be transferred from the device for post-analyses.

The Vitalograph **Aerosol Inhalation Monitor (AIM)**⁹ [Vitalograph Ltd., Co. Clare, Ireland] monitors inhalation flow rate, actuation coordination and breath hold for pMDIs. It is an electronic desktop device that gives patients visual feedback regarding their inhalation technique. When using the AIM device, the patient is required to keep a needle gauge within a certain flow range. The AIM device cannot be used with real pMDIs remotely and data cannot be transferred from the device for post-analyses.

A recent study introduced an image processing method of assessing inhalation technique in DPIs such as the Turbuhaler and the Handihaler (Liang *et al.*, 2016). The

⁷ <http://www.fyne-dynamics.com/>

⁸ <https://www.haag-streit.com/clement-clarke/>

⁹ <https://vitalograph.ie/>

method consisted of placing a dark cloth over the air inlets of the inhalers and quantifying the efficiency of inhalation based on the resulting image of the dry powder on the cloth after inhalation. However, there is currently no device that can employ this method to remotely monitor inhalation technique.

The main disadvantage with all of the previously discussed devices is that they cannot monitor both temporal and user technique adherence outside of the clinical setting. As previously discussed, patient user technique differs in real life environments in comparison to clinical settings. There is a clinical need for attachable EMDs that can monitor real life inhaler use remotely. This would allow healthcare professionals to longitudinally monitor patient adherence and perhaps intervene if adherence declines over time. Unfortunately, there are limited devices available that can monitor both temporal and user technique adherence.

2.4.3 Electronic monitoring devices (EMDs)

There has been a surge in popularity in EMDs that can monitor adherence remotely (Kikidis *et al.*, 2016; Pritchard and Nicholls, 2015; Howard *et al.*, 2014). EMDs offer much more in-depth pertinent information on patient behaviours outside of the clinical setting in terms of when, how and where patients use their inhaler.

The **MDILog**¹⁰ [Westmed, Colorado, USA] is an attachable device for the pMDI. It can record time stamps of actuations by using a mechanical beam with a strain gauge. Inhalations through a pMDI are recorded using a heated thermistor which allows for monitoring actuation coordination. The device can also record if a patient shakes the inhaler through a movable magnet within the device. The device was previously used in studies to monitor adherence in children (Spaulding *et al.*, 2012; McQuaid *et al.*, 2003). However, it does not record inhalation flow rate and does not give feedback on overall inhalation technique (inhalation flow rate and actuation coordination) (Howard *et al.*, 2014). Data can be transferred from the device for post-analyses. However, the device is no longer available for clinical use.

The **SmartMist** [Aradigm Corporation, California, USA] is a device which encompasses nearly all of the pMDI. The device actuates the inhaler automatically once an inhalation flow rate of approximately 25-60 L/min is generated by the user. The device

¹⁰ <http://westmedinc.com/>

actuates the pMDI canister using a small plunger upon inhalation. It records time stamps of actuations and inhalations also. Data can be transferred from the device for post-analyses. It can also provide feedback to the patient informing them if their user technique was sufficient or not (Howard *et al.*, 2014). However, the size of the device is a major disadvantage and it was also discontinued (Pritchard and Nicholls, 2015).

The pMDI Datalogger is small attachable device for pMDIs that can record time stamps of actuations and inhalations. It consists of an ultrasonic sensor to detect actuations, a flow sensor to detect inhalations and an accelerometer to detect if the inhaler was shaken (Kikidis *et al.*, 2016). It can give feedback on inhalation flow rate and actuation coordination. However, the device does not contain on-board memory and needs to be connected to a computer to operate.

The **Amiko**¹¹ [Amiko, Milan, Italy] device was recently developed as an attachable device and was tested on a range of DPIs. The device can detect drug preparation, estimate inhalation PIFR and volume, and measure the orientation of the DPI (Braidó *et al.*, 2016b). The device cannot record inhalation flow profile. No information has been reported on whether the Amiko device is compatible with pMDIs. Also, no information regarding the sensors within the device is reported from the study. Details were not given also on whether the data can be transferred from the device to a computer for post-analyses. Based on the literature, the device has yet to be tested on real asthma and COPD patients.

Figure 2.3 displays some examples of inhaler electronic monitoring devices. There is a need for more clinically available monitoring systems with integrated sensing capabilities to monitor user technique in pMDIs and DPIs. Having the capability to obtain data on real life inhaler use can help healthcare professionals personalise respiratory treatment to the patient. This may help patients change their attitude towards their medication and grow more confident in their inhaler use. However, there remains a clear lack of portable and attachable devices to record when and how patients use their pMDIs and DPIs.

¹¹ <http://amiko.io/>

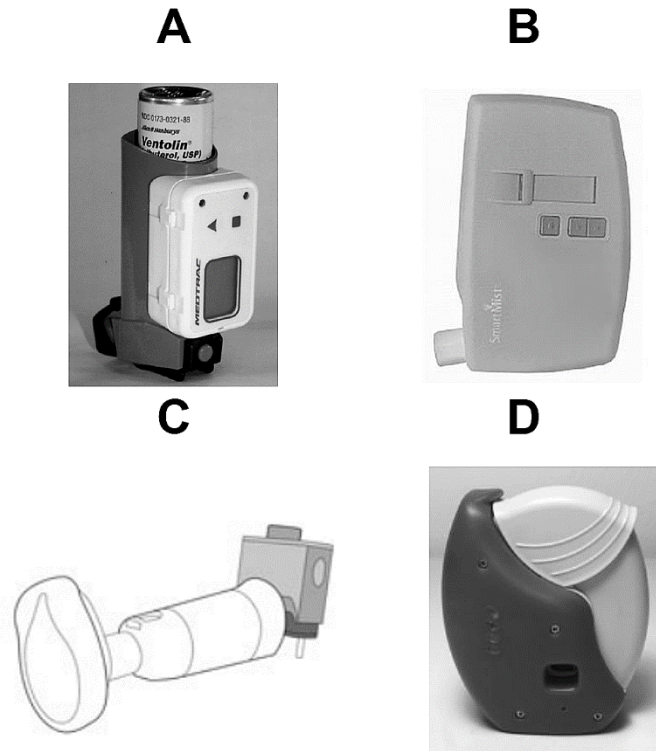


Figure 2.3. Examples of inhaler electronic monitoring devices.

(A) MDILog (Apter *et al.*, 2001), (B) SmartMist (Muchão and Silva Filho, 2010), (C) pMDI Datalogger (Ditcham *et al.*, 2014), (D) Amiko (Braido *et al.*, 2016b).

2.5 Audio-Based Systems to Objectively Monitor Inhaler Adherence

Recent advances in the development of audio-based systems have shown promising opportunities to monitor patient adherence (both time of use and user technique) (D'Arcy *et al.*, 2014; Holmes *et al.*, 2014a; Sulaiman *et al.*, 2016e). A major clinical advantage that audio-based inhaler monitoring systems have over other sensor-based inhaler monitoring technologies is the capability of objectively assessing patient user technique remotely. By applying signal processing methods to audio recordings of patients using their inhaler, it is possible to detect inhaler sound events (inhalation, drug preparation and exhalation sounds) which can be used to objectively assess patient user technique. This allows patients to receive personalised objective feedback regarding their adherence from healthcare professionals to help improve the efficacy of treatment.

Audio-based inhaler monitoring systems can be divided into three main sections;

1. Audio data acquisition system
2. Signal processing of audio data
3. Calculation and presentation of objective adherence measures

The **audio data acquisition system** refers to how the audio recordings of inhaler use are obtained. This is through the use of an inhaler audio recording device. The **signal processing** methods applied to inhaler audio recordings can be divided into three stages; i) automatic detection and classification of inhaler sounds (inhalation, exhalation and drug preparation sounds), ii) estimation of inhalation flow parameters and iii) estimation of pulmonary drug delivery. The **calculation and presentation of objective adherence measures** section can be divided into two stages; i) calculation of adherence measures and ii) presentation of adherence measures to the patient. This can be visually illustrated in the block diagram presented in Figure 2.4 (Taylor *et al.*, 2018b).

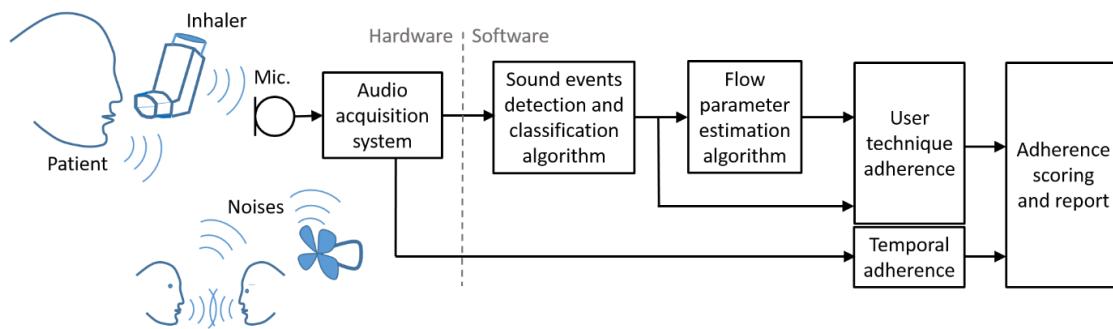


Figure 2.4. Block diagram of an audio-based inhaler monitoring system.

The first section of audio-based inhaler monitoring systems is the audio data acquisition system. The main audio-based inhaler monitoring system that will be discussed in this section will be the Inhaler Compliance Assessment (INCA) system which, according to the literature, is the only audio-based inhaler monitoring system currently employed in clinical practice to measure both temporal and user technique adherence. The INCA system applies signal processing methods to inhaler audio recordings in order to calculate an objective measure of adherence that accounts for both temporal adherence and user technique adherence. It has been used to introduce new standards of adherence assessment and has proven to improve inhaler adherence by providing patients with objective feedback (Sulaiman *et al.*, 2016c; Sulaiman *et al.*, 2018). The system is currently being implemented in multi-centre clinical trials across

Ireland, recruiting over 1,000 patients in six major hospitals and 77 pharmacies (D'Arcy *et al.*, 2014; O'Dwyer *et al.*, 2016; Sulaiman *et al.*, 2016a; Sulaiman *et al.*, 2016d; Mokoka *et al.*, 2017).

2.5.1 Inhaler Compliance Assessment (INCA) device

The INCA audio-based monitoring system acquires data using an audio recording device (referred to as the INCA device in this thesis). The INCA device (Figure 2.5) is a non-invasive attachable device designed specifically for the Diskus DPI. Figure 2.5 illustrates the location of the device when attached to a Diskus DPI. The device was originally designed and developed at the Trinity Centre for Bioengineering, Trinity College Dublin, Ireland and was licensed in 2011 to Vitalograph Ltd. to manufacture. The device consists of a microelectromechanical systems (MEMS) microphone, on-board memory, an LED to indicate device activation and a battery to power the components. The device is activated using a magnetic reed switch within the device which aligns with a magnet situated inside the inhaler casing when the inhaler is opened. The INCA device begins to record audio when the Diskus DPI is fully opened and ceases recording when the inhaler is closed or left open for 90 seconds. Recordings are then each saved onto the device from where they can be transferred to a computer via USB for further analysis.

Audio signals are sampled at 8 kHz with 8 bits per sample resolution and are stored as mono WAV files. The device also records a time stamp of each audio recording which allows for accurate measurement of temporal adherence. Usually patients are prescribed

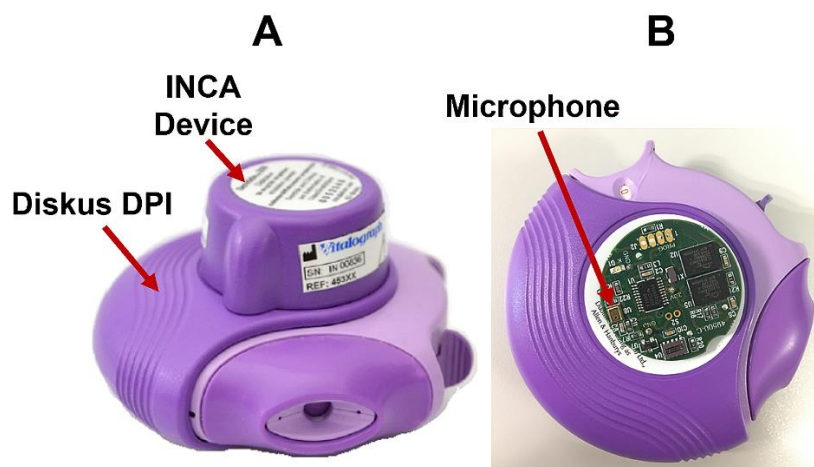


Figure 2.5. Inhaler Compliance Assessment (INCA) device.
(A) INCA device attached to a Diskus DPI and (B) the INCA device opened without casing and the battery removed ((A) adapted from (Seheult *et al.*, 2014b)).

to use the Seretide (preventative medication) Diskus inhaler twice a day for one month before returning for a clinical consultation. As a result, the INCA device was designed to store up to 60 recordings (two uses per day for 30 days), each of 90 second duration. Figure 2.6 presents an example of a typical audio recording of an asthma patient using a Diskus DPI recorded from the INCA device. It illustrates the patient preparing the drug (blister), then exhaling to empty the lungs followed by an inhalation. It is evident from Figure 2.6 that INCA audio recordings of inhaler use may contain important information regarding inhaler user technique. However, for each patient there may be up to 90 minutes of inhaler audio recordings at each clinical visit (60 recordings $\times$ 90 second duration). This makes it very challenging and time-consuming for healthcare professionals to aurally review or over-read each audio recording in order to assess inhaler user technique. Consequently, there is a need for automatic detection and classification algorithms to determine what events occurred in each inhaler audio recording and to interpret these inhaler events to assess patient user technique.

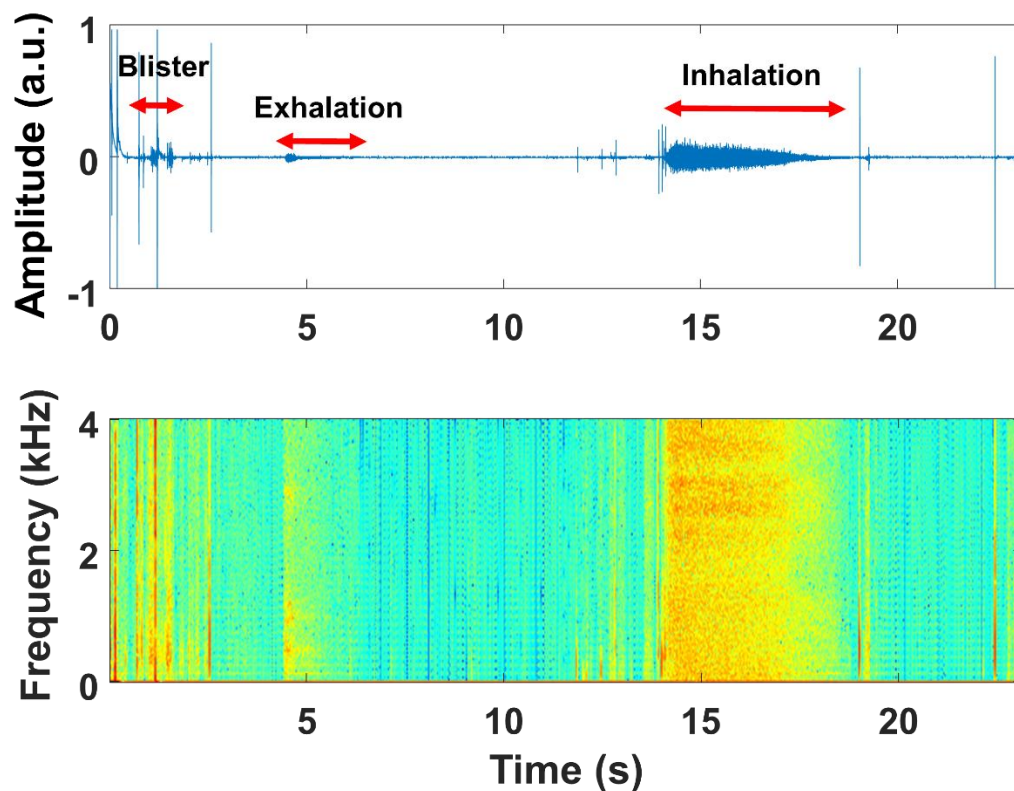


Figure 2.6. Example of a typical Diskus DPI INCA recording audio time domain signal (linear representation of sound pressure) and corresponding spectrogram.

2.5.2 Inhaler audio recording overview

The recorded inhaler audio signal, $x(t)$, is composed of three main sound source types: the inhaler device, $s(t)$, the human breathing, $b(t)$, and added noise, $n(t)$. Therefore, the inhaler audio signal may be represented as;

$$x(t) = s(t) + b(t) + n(t) \quad (2.1)$$

2.5.2.1 Inhaler drug preparation sounds (blister/actuation)

Drug preparation sounds are associated with the medication being prepared or released from the inhaler. In DPIs (Diskus, Turbuhaler and Ellipta), this is usually interpreted as a "click" sound. In relation to the Diskus DPI, it is sometimes referred to as a "blister" sound. In terms of pMDIs, the drug preparation sound is associated with medication being dispensed from the pressurised canister (also referred to as actuation). This is usually interpreted as a short "spray-like" sound. Drug preparation sounds are generated from the inhaler sound source, are usually short in duration (100-150 ms) and generate high power across a range of frequencies.

2.5.2.2 Inhaler inhalation sounds

Inhaler inhalation sounds are associated with the patient attempting to inhale the medication from the inhaler. These sounds are generated from both inhaler device and human breathing sound sources simultaneously. Inhaler inhalations consist of both inhaler-based sounds (turbulence within the device) and human breathing sounds (physiological inhalation sound of human breathing without the influence of the inhaler). As a patient inhales, air passes through the device, causing turbulent energy that produces sound. The turbulent energy arises from the unsteady air interacting with different sharp edges or boundaries within the inhaler causing an edge effect (Howe, 1978). Acoustic power is proportional to the eighth-power of flow velocity, and this reduces to a sixth-power relationship in the presence of solid boundaries (Lighthill, 1952; Curle, 1955). Because of the different mechanical shape and functioning of each inhaler device, it is hypothesised that the acoustic properties of inhaler inhalation sounds may differ in temporal and spectral domains. In DPIs, the inhaler inhalation sound may be more prominent than the human breathing sound due to higher airflow resistance which results in increased turbulence within the inhaler device. It may be hypothesised from Figure 2.6

that DPI inhalation sounds contain power over a broad range of frequencies. In pMDIs, one may hypothesise that inhalation sounds are much quieter than in DPIs, because of lower air-flow resistance, causing the human breathing sound to be more prominent. There is a correlation between the inhaler-based sounds and the human breathing sounds during inhalation, because these two sound sources are acoustically connected together (patient having their mouth/lips sealed around the inhaler mouthpiece). Therefore, even though inhaler inhalation sounds may be influenced by the inhaler design, the patient's physiological breath sound and also their interaction with the device may influence the acoustic properties of the inhalation sound.

2.5.2.3 Inhaler exhalation sounds

During inhaler use, an exhalation sound is expected before and after inhalation. An exhalation sound before inhalation signifies the patient emptying their lungs before inhaling the medication. An exhalation sound after inhalation signifies the patient exhaling after holding their breath. Exhalations should be directed away from the inhaler device. Exhalation sounds are not influenced by the inhaler device and are generated solely from the human breathing source. Consequently, the spectral and temporal properties of exhalation sounds may vary across patients.

2.5.2.4 Inhaler background/interference noises

Noise within an inhaler audio recording can be divided into two main types: background noise and interferences. The background noise contains continuous sounds such as air-conditioning or fan sounds. In a relatively short recording session (10-90 sec), and under the assumption that the user (patient) is in one place (environment) during inhaler use, the background noise can be assumed to be stationary (statistical properties are constant in time). The interferences are transient noises such as speech, the user fumbling with the inhaler (unwanted inhaler sounds) and other short-time noises. These noises contain irrelevant information regarding inhaler usage, and should be neglected or filtered out.

The second section of audio-based inhaler monitoring systems is the signal processing of audio data. The automatic detection and classification of inhaler events is the first stage of this section. This involves extracting pertinent features from the audio signal that may characterise each inhaler event (inhalation, exhalation and drug preparation) and applying

different detection and classification methods to these features to identify how the patient used their inhaler.

As it is of significant importance to analyse and classify inhalation and exhalation sounds during inhaler use, it is important to review the acoustic properties of breath sounds (inhalation and exhalation). Section 2.6 reviews how breath sounds are generated and what types of audio-based features of breath sounds have been reported in the literature to objectively analyse breath sounds of asthma and COPD patients. Section 2.7 reviews the literature on automatically detecting and classifying breath sounds and how these methods may be applied to automatically analysing inhaler sounds to assess patient adherence.

2.6 Acoustic Properties of Breath Sounds

The primary purpose of analysing breath sounds using audio signal processing methods is to extract pertinent features that can be used to detect and classify breath sounds in different applications and to quantify physiological changes occurring in the lungs. This offers more objective assessment of breath sounds as opposed to the use of the stethoscope which can be quite subjective. Although the analytical methods of signal processing are developed primarily independent of their application, interpretation of their results in relation to biological data, such as breath sounds, requires a thorough understanding of the physiological system involved (Moussavi, 2006). Therefore, the following sections discuss how breath sounds are generated in the airways and how such sounds relate to the audio-based features obtained using signal processing methodology.

Another key aspect in the objective analysis of breath sounds is the choice and placement position of acoustic sensor employed to obtain the sounds. In order to detect breath sounds and to quantify physiological changes occurring in the upper and lower airways using audio-based methods, the most appropriate acoustic sensor must be selected and positioned in an appropriate anatomical site. The majority of literature on the acoustic properties of breath sounds has reported use of contact acoustic sensors. Non-contact microphones are also becoming more popular for other clinical applications such as assessing sleep patterns and monitoring inhaler inhalation technique (Dafna *et al.*, 2015, 2013; Holmes *et al.*, 2013c). However, little is known on the acoustic properties of non-contact inhaler sounds. It is important to understand the fundamental properties of

contact breath sounds and how they may relate to inhaler sounds using non-contact sensors.

The choice of audio-based features is also of vital importance when automatically classifying and analysing breath sounds. Changes in audio-based features during chronic respiratory diseases such as asthma and COPD can provide empirical objective evidence of physiological variations in the lungs, allowing clinicians to monitor disease progression and investigate treatment outcomes. Normal breath sounds can be defined as the sounds generated during respiration that are free from adventitious (abnormal) components (i.e. crackles, wheezes etc.). As inhaler inhalation and exhalation sounds (recorded using non-contact microphones) generally do not contain continuous adventitious sounds and can be categorised as normal breath sounds, this review will only focus on normal breath sounds. However, a brief explanation of continuous adventitious sounds will be reported.

The primary objectives of this review in Section 2.6 are

1. To investigate how normal breath sounds are generated and what the acoustic properties of these respiratory sounds are.
2. To review the most popular types of acoustic sensors employed in the literature to record breath sounds and the most popular location for recording breath sounds.
3. To review what audio-based features have been previously employed to objectively quantify physiological changes occurring due to chronic respiratory diseases, primarily in normal breath sounds.

2.6.1 Generation of breath sounds

Breath sounds are generated by air flowing through the airways during breathing. There are two types of airflow; laminar and turbulent. Laminar flow usually occurs when the airflow has low velocity and passes through narrow tubes or airways. Here the flow is orderly and in smooth parallel layers (Batchelor, 2000). This is dependent on the resistance of the tube which is associated with the diameter. As the diameter of the tube (or airway) increases, the resistance drops accordingly. Turbulent flow occurs when the airflow is at higher velocities and passes through tubes with higher resistance (through airways with irregular walls or lower diameter) (Moussavi, 2006). Airflow patterns can be measured using a dimensionless quantity known as the Reynolds number which is the

ratio of inertial forces to the ratio viscous forces. It can be calculated using the following equation for fluid passing through a straight pipe;

$$Reynolds\ number = \frac{\rho u d}{\mu} \quad (2.2)$$

where ρ is the density of the fluid,

u is the velocity of the fluid,

d is the diameter of the tube,

μ is the viscosity of the fluid.

A Reynolds number below 2000 represents laminar flow where a value above 4000 indicates turbulent flow. A value between 2000-4000 represents transitional flow (between laminar and turbulent).

The acoustic energy of breath sounds increases with turbulent energy. Figure 2.7 illustrates the anatomy of the upper and lower respiratory tract (Teva Respiratory, 2014).

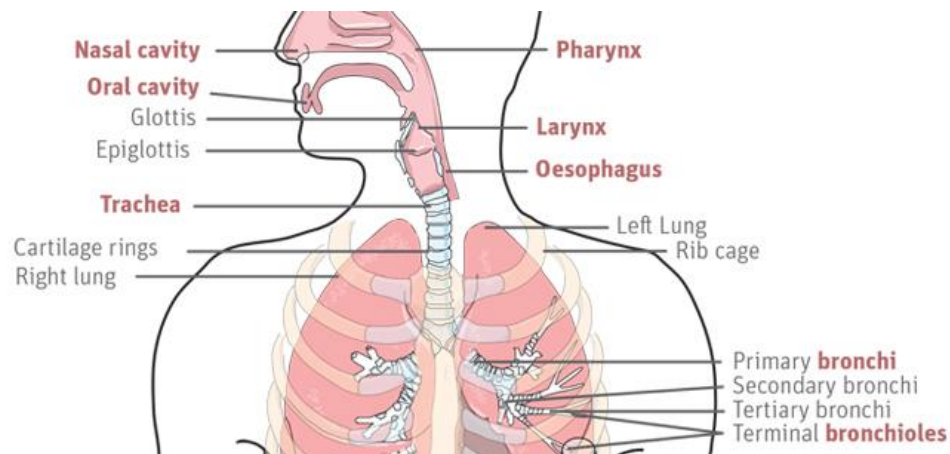


Figure 2.7. Anatomy of the upper and lower respiratory tract (Teva Respiratory, 2014).

It may seem from Figure 2.7 that the resistance of the trachea is much lower than that of the lower airway bronchi as the diameter is significantly larger, therefore generates less acoustic energy. However, the resistance of the lower airways acts in parallel, therefore the net lower airway resistance is much lower to that of the trachea (Moussavi, 2006). Furthermore, there is less of a low pass filtering effect on the trachea due to less tissue

filtering the breath sounds. Hence, breath sounds recorded over the trachea are generally louder than chest wall sounds due to higher turbulent energy in normal breath sounds.

2.6.2 Normal chest wall breath sounds

Chest wall or lung sounds are those which originate in the lungs and are heard through the chest wall. They arise from turbulence generated in the lower airways. However, turbulence is a density-dependent phenomenon which may alter the acoustic properties of normal lung sounds (Pasterkamp and Sanchez, 1996; Pasterkamp *et al.*, 1997; Austrheim and Kraman, 1985). They are soft low frequency murmurs that can be heard as air enters and leaves the airways. Chest wall sounds can be recorded from locations on both the anterior and posterior chest wall. In comparison to tracheal sounds, chest wall sounds have a lower signal-to-noise ratio and are susceptible to heart and muscle sounds. Nonetheless, researchers have investigated the possibility of using chest wall sounds as a diagnostic tool in demarcating normal and abnormal breath sounds.

Inspiratory lung sounds are hypothesised to originate in the lobar and segmental airways, while the expiratory lung sounds are generated in more proximal larger central airway locations (Pasterkamp *et al.*, 1997; Malmberg *et al.*, 1995). Inhalations have been reported as having a higher pitch, longer duration and greater intensity in comparison with exhalations (Gavriely *et al.*, 1995; Pasterkamp *et al.*, 1997).

Chest wall sound energy peaks below 100 Hz and then drops off significantly between 100-200 Hz (Gavriely *et al.*, 1995). However, it can still be detected at or above 1,000 Hz in quiet recording environments (Pasterkamp *et al.*, 1996). Unlike bronchial sounds, chest wall sounds have a relatively flat spectral profile without any discrete peaks (Pasterkamp *et al.*, 1997). Chest wall sound intensity is dependent on a number of factors such as the individual subject and the location of recording on the chest wall. Chest wall sounds are also highly dependent and closely correlated with airflow rate which will be discussed more thoroughly in Section 2.10.

A number of factors may have the potential to influence chest wall breath sounds. Pasterkamp *et al.* (1996) investigated differences in lung sound spectra in 10 new-born infants, nine children between 6 to 8 years old and 10 adults between 25 to 37 years old. They reported that the new-born infant breath sounds contained less power below 300 Hz in comparison with the other two groups. This resulted in higher frequencies at which 25%, 50% and 75% of the spectral power lies (F_{25} , F_{50} , F_{75} and F_{99}) in the infant group

(Pasterkamp *et al.*, 1996). Other studies have reported that infants have higher median frequencies (F_{50}) while breathing in comparison with older children and adults (Kanga and Kraman, 1986; Hidalgo *et al.*, 1991). Reasons for this may lie in the fact that infants have a thinner chest wall which may result in less filtering of high frequency lung breath sounds. Smaller sized lungs and narrower airways may also contribute to high frequency components of the acoustic signal, and as previously mentioned, subject height is also a factor. Gross *et al.* (2000) recorded lung sounds from 162 subjects and computed a ratio (Q) of relative power in two frequency bands, 330 to 600 Hz and 60 to 330 Hz (Gross *et al.*, 2000). Using linear regression methods, they reported a small but significant correlation ($R^2=0.1$, $p<0.05$) between Q and age. For both men and women, an increase in the relative power was observed with a corresponding increase in age in the 330-600 Hz frequency band (Gross *et al.*, 2000). Importantly however, they concluded that the percentage changes observed in Q (5%) were too small to be clinically relevant.

Differences in the frequency spectra of chest wall breath sounds have been observed between healthy males and females (Gavriely *et al.*, 1995). It was reported that females had higher maximal frequencies (F_{max}) in comparison with males. Inspiratory F_{max} values were 12-19% higher in females in comparison with males (767 ± 246 Hz versus 667 ± 246 Hz, $p<0.001$) at all chest wall recording locations. Expiratory F_{max} values were 32% higher in females only at the right anterior chest in the mid clavicular line in the second intercostal space. The results of this study therefore suggest that healthy females generate more power at higher frequencies during breathing in comparison to healthy males. Moreover, it suggests that the position of peak frequencies in the spectral profile of breath sounds is different across individuals. Another study also found significant differences in the normal chest wall breath sounds of healthy people, with a larger proportion of higher frequencies observed in females in comparison with males (Gross *et al.*, 2000).

The results of the aforementioned studies would indicate that although normal chest wall breath sounds are consistent among individuals, height, gender and age are important factors that influence the frequency content of the sounds. Such considerations must be taken into account when applying audio signal processing methods to analyse breath sounds recorded from the chest wall.

2.6.3 Normal tracheal breath sounds

Tracheal sounds are a subset of bronchial sounds that attract a lot of interest in the field of respiratory audio-based monitoring. They can easily be recorded and are known to contain important information regarding upper airway obstructions. Tracheal sounds are typically recorded from locations on the suprasternal notch or the lateral neck. Sounds recorded from these locations are considered “pure” and less filtered, as the quantity of lung tissue that the sounds pass through before reaching an acoustic sensor is small, in comparison with other chest based respiratory sounds (Pasterkamp *et al.*, 1997). Therefore, they generate a higher signal-to-noise-ratio than chest wall sounds.

The generation of tracheal breath sounds is related to the flow of turbulent air in the upper airways, including pharynx, glottis and subglottic regions (Pasterkamp *et al.*, 1997). An early study on bronchial sounds reported that they were produced in airways with diameters of 4 mm or larger, and that the glottis also plays a role in generating these sounds (Fahr, 1927). Beck *et al.* (2005) explains that it is vibration of the tracheal wall that is detected when a surface sensor is used. The tracheal wall vibrates due to pressure forces acting on the inside surface. The quantity of tracheal wall motion is determined by the magnitude and frequency content of the pressure force, but also by the mass, elasticity and resistance of the wall (Beck *et al.*, 2005).

A strong relationship exists between airflow rate and tracheal sound audio features which will be discussed more thoroughly in Section 2.10. An important point to note however, is that although airflow rate will affect sound intensity, Beck *et al.* (2005) reported that the airflow rate does not affect the pattern and position of resonance peaks in the tracheal spectral curve.

Tracheal sounds cover a broad energy spectrum, starting from below 100 Hz and going up to more than 1,500 Hz in some cases (Pasterkamp *et al.*, 1997). A drop off in power has been reported to occur above 850 Hz (Gavriely *et al.*, 1981). The spectral profile of tracheal sounds has many peaks and troughs, and these are known to be related to subject height and gas density (Sanchez and Pasterkamp, 1993; Pasterkamp and Sanchez, 1996). The implications for this are that the peaks and troughs seen in the spectral profile of tracheal breath sounds are dependent on resonances created in the airways. In a study on tracheal breath sounds at standardised airflow rates, it was reported that children, having short tracheal lengths, had significantly louder sounds and higher quartile and spectral edge frequencies in comparison to adults with longer tracheas

(Sanchez and Pasterkamp, 1993). These significant differences in loudness and frequency may imply that the length of the trachea is involved in the generation of tracheal sounds.

Tracheal sounds have been studied in great detail in relation to upper airway obstruction. The main hypothesis adopted by researchers is that the narrowing of the upper airways may cause alterations in the acoustic signal and that this may be quantified using acoustic features. Greater sound power at high frequencies is frequently associated with upper airway obstructions (Pasterkamp and Sanchez, 1992). Inversely, it has been reported that a decrease in power in low frequencies may highlight upper airway obstruction (Pasterkamp *et al.*, 1997). Tracheal sound intensity has been related to physiological changes in the trachea, the principal bronchi and their lobal segmental branches. The degree of narrowing in the central bronchi can be closely related to the loudness and pitch of abnormal inspiratory sounds (Forgacs, 1971). This has been employed previously to distinguish changes in the spectral profile due to airway obstruction (Malmberg *et al.*, 1995). The clinical implications for this are that acoustics may be employed as a tool to objectively study airway obstruction.

Use of tracheal sounds for clinical applications is dependent on their intra-subject repeatability. Sanchez and Vizcaya (2003) investigated the repeatability of tracheal breath sounds in seven healthy subjects over a period of 30 days. They reported that F_{25} , F_{50} , F_{75} F_{99} between 100 and 200 Hz were not statistically significantly different, and that all these features had variations below 20% (Sanchez and Vizcaya, 2003). This implies that the within subject variation of tracheal sounds are relatively repeatable over time. Sanchez and Vizcaya (2003) also reported a significant variation between subjects and postulated that such variations could be as a result of gender, height and anatomical characteristics. Mahagnah and Gavriely (1994) reported that tracheal breath sounds were significantly repeatable in a cohort of five healthy adult males. Since the variability of the spectral features during normal breathing has been reported as being low, this would suggest that spectral features may be employed to study changes in breathing during periods of illness, or to monitor patients' respiratory function longitudinally.

2.6.4 Acoustic sensors used to record breath sounds

The selection of a suitable acoustic sensor and its placement position are of vital importance in recording breath sounds. There have been two popular choices of contact

sensors employed in the audio analysis of breath sounds; electret condenser microphones and piezoelectric contact sensors.

2.6.4.1 Electret condenser microphone

The electret condenser records acoustic signals from sound waves displacing an electret diaphragm which converts a varying capacitance into an electrical signal (Paajanen, 1996). The sensor is usually mounted in a chamber. Conically shaped chambers are popular and are more sensitive to higher frequencies (Pasterkamp *et al.*, 1997). The electret condenser microphone accompanied with a coupling chamber has been a popular choice of acoustic sensor for chest wall and tracheal sound analysis due to their low weight and sensitivity in several studies (Murphy, 2008; Kraman *et al.*, 2006; Malmberg *et al.*, 1995). Due to their light weight, low cost and practicality, researchers have also previously employed miniature electret sensors in a sensor array placed on the posterior chest wall surface to analyse lung sounds (Murphy, 2008). These acoustic sensors tend to have a flat frequency response within the frequency ranges of chest wall and tracheal sounds. This means that the sensor does not attenuate or amplify specific frequencies. The main disadvantage of electret condenser microphones is that there are additional components required, such as a mounting chamber, which may alter the frequency characteristics depending on the chamber shape. One must have prior knowledge of the frequency range of interest in order to design the electret sensor set-up efficiently.

2.6.4.2 Piezoelectric contact accelerometer

Piezoelectric contact accelerometers capture surface vibrations and convert them into electrical signals, while they also have the advantage of being insensitive to air vibrations. They are typically mounted on the skin, on the trachea (tracheal sounds) or on the posterior and/or anterior chest wall surface (chest wall sounds). They are usually attached to the chest wall with rubber belts and/or adhesive rings (Earis and Cheetham, 2000). Unlike electret condenser microphones piezoelectric sensors generally do not need an air-coupled chamber (Vannuccini *et al.*, 2000). It has been reported that piezoelectric sensors are robust to ambient background noise and also have a high sensitivity in ambient environments (Kraman *et al.*, 1998). Piezoelectric contact accelerometers are sensitive at high frequencies and this makes them an appealing choice of sensor when recording respiratory sounds (Sanchez and Vizcaya, 2003; Pasterkamp *et al.*, 1993). However, it

has been reported that contact piezoelectric accelerometers tend to be heavy and fragile sensors (Earis and Cheetham, 2000; Vannuccini *et al.*, 2000). They can also resonate at frequencies close to those of lung sounds which may introduce noise into the recorded signal (Vannuccini *et al.*, 2000; Pasterkamp *et al.*, 1997).

2.6.5 Audio analysis of asthma breath sounds

Automated respiratory sound analysis approaches have frequently been postulated as methods to objectively diagnose asthma, make more accurate anatomical diagnoses and to guide asthma management. Asthma can result in narrowing of the airways and it is this narrowing that may cause variations in time and/or frequency features of respiratory sounds during breathing. In addition to identifying the presence of adventitious respiratory sounds, it has also been hypothesised that asthma can be detected and monitored from normal breath sounds. Regarding normal breath sounds, researchers have primarily attempted three main things using acoustic analysis methods:

- (i) Discriminate asthmatic individuals from healthy individuals and those with other variations of chronic respiratory illnesses.
- (ii) Estimate the degree of airflow limitation.
- (iii) Investigate regional variations caused by asthma.

A study by Malmberg *et al.* (1995) employed both chest wall and tracheal inspiratory breath sounds to investigate differences between asthma participants ($n=10$), COPD participants ($n=17$) and healthy participants ($n=11$). It was reported that breath sound recordings at the chest wall (10 cm below the margin of the scapula and 15 cm to the right of the spine) of individuals with stable asthma had a median frequency (F_{50}) higher to that of the COPD and healthy subjects ($p<0.001$). The F_{50} feature from the normal breath sound spectra was 239 ± 19 Hz for asthma subjects, while it was 201 ± 21 Hz for COPD subjects and 206 ± 14 Hz for healthy subjects. They also reported that the root mean square (RMS) of the normal breath sounds recorded at the chest, was higher in stable asthmatics than in subjects with COPD.

Regarding estimating the degree of airflow limitation, Malmberg *et al.* (1994) observed a significant correlation between F_{50} and FEV_1 from both normal tracheal and chest wall recordings during a histamine challenge test. Twelve asthmatic subjects and six healthy subjects participated in the study. It was reported that the normal tracheal

expiratory sounds F_{50} feature had the best correlation with FEV_1 ($r=-0.853$, $p<0.0001$). They also noted that the increase in F_{50} was significantly larger in asthmatic subjects compared with healthy subjects ($p<0.005$). In a later study Malmberg *et al.* (1995) again observed that F_{50} recorded at the trachea on the right side of the cricothyroid cartilage was significantly correlated to the forced FEV_1 during normal breathing ($r=-0.77$, $p<0.01$) in asthmatics. However, FEV_1 was not significantly correlated with F_{50} for the chest wall recordings during normal breathing ($r=-0.50$, $p<0.1$) (Malmberg *et al.*, 1995). A study by Tabata *et al.* (2016) also reported a significant increase in the frequency at which 99% of the spectral power lies (F_{99}) in 14 patients after inhaling methacholine during a bronchial challenge test (Tabata *et al.*, 2016). Other studies have reported the use of intensity and complexity based features such as Katz Fractal Dimension to classify lung sounds associated with bronchoconstriction (Li and O'Connell, 1996; Gnitecki *et al.*, 2004). A study by Fiz *et al.* (1999) also investigated changes in tracheal audio-based features after patients were administered a bronchodilator. It was reported that the centroid frequency of exhalation sounds decreased after bronchodilation (Fiz *et al.*, 1999). These findings support the hypothesis that airway obstruction levels and the positive response to medication are correlated with respiratory audio-based features of normal asthmatic breath sounds.

The frequency distribution of tracheal breath sounds has a high inter-subject variation which is dependent on resonant frequencies generated in the trachea. Intra-subject variations of healthy subject's frequency distribution have been reported to be very repeatable, when recorded from the trachea and chest wall (Sanchez and Vizcaya, 2003). Although normal breath sounds at the chest wall contain lower frequencies in comparison to tracheal breath sounds, an increase in pitch and sound intensity has been observed at these low frequencies in asthmatic lung sounds (Schreur *et al.*, 1995). This suggests that it is possible to record from the chest wall and detect regional ventilation changes, as with the stethoscope, in addition to recording at the trachea.

The baseline spectral profile from asthmatic normal breath sounds may differ from that of healthy breath sounds without airway obstruction occurring (Pasterkamp *et al.*, 1997; Schreur *et al.*, 1995). This is an interesting observation as it highlights how asthma can alter the shape of the airways without completely obstructing the airflow. It has been reported that asthmatic normal breath sounds tend to be higher in intensity due to higher levels of turbulence in the airways. Recently, it was shown that an increase in the highest frequency during the inspiratory phase (HFI), recorded at the right upper anterior chest at

the second intercostal space in the mid-clavicular line, correlated with a decrease in forced expiratory flow at 50% vital capacity (FEF₅₀) in 131 asthmatic children ($r=-0.45$, $p<0.001$) (Habukawa *et al.*, 2009). According to Malmberg *et al.* (1995), the increase in frequency directly relates to an increase of flow velocity through the narrowed bronchi which results in increased kinetic energy and turbulence (Malmberg *et al.*, 1995). This subsequently causes a higher pitched sound to be heard from the trachea and chest wall. The ability to detect changes in acoustic features from asthmatic normal breath sounds demonstrates the feasibility of using such methods as a tool in objectively diagnosing and monitoring asthma.

Audio-based methods have previously been employed to detect the presence of continuous adventitious respiratory sounds associated with asthma (Lozano-García *et al.*, 2017; Lozano *et al.*, 2016). Wheezes are a common example of continuous adventitious respiratory sounds caused by bronchoconstriction or secretions in the airways and are commonly generated during expiration (Brand *et al.*, 2008). Wheezes are continuous musical like whistle sounds with dominant frequencies within 80-1000 Hz, however, this can vary between infants and adults (Charbonneau, 2000; Jain and Vepa, 2008). Adventitious breath sounds have distinctive temporal and spectral features, and therefore it has been possible to detect adventitious sounds using time-frequency analysis methods (Taplidou and Hadjileontiadis, 2007; Chah *et al.*, 2009). However, adventitious respiratory sounds are not present in each asthmatic subject and they may only be audible at different stages of airway obstruction in different people.

2.6.6 Audio analysis of COPD breath sounds

Similarly to asthma, researchers have investigated the use of audio-based features to differentiate sounds from COPD to those from asthmatic and healthy participants. Malmberg *et al.* (1995) reported that although audio-based features from asthmatic respiratory sounds were significantly different from healthy subjects, COPD quartile frequency features (F_{25} , F_{50} & F_{75}) from chest wall and tracheal recordings were not significantly different from healthy subjects. However, it was found that F_{50} from the chest wall recordings was significantly lower for COPD subjects in comparison with asthmatic subjects ($p<0.0001$). A recent study with a large cohort of COPD subjects investigated if COPD could be detected using a multichannel lung sound analyser (Vyshedskiy and Murphy, 2016). They reported that the ratio of inspiratory duration to

expiratory duration was lower in COPD patients (n=100) than a cohort of age-matched healthy subjects (n=100). It was also observed that the ratio of low frequency inspiratory energy to high frequency inspiratory energy was greater in COPD subjects than in healthy subjects.

Malmberg *et al.* (1995) reported that F_{50} from tracheal and chest wall breath sound recordings from COPD patients did not correlate with FEV₁, indicating that there is no relationship between airway obstruction levels and normal breath sounds from COPD subjects. One could argue that the insignificant relationship that occurs between COPD and FEV₁ is due to the heterogenic nature of COPD. Emphysema and chronic bronchitis often coexist in COPD patients and this may result in a greater variability of F_{50} values. Airway structural change and the site of disease in the bronchi and lung parenchyma may also differ between COPD and asthma, and this may account for the differences in the acoustic frequency content of breath sounds (Malmberg *et al.*, 1995).

COPD symptoms may alter with time and disease progression, factors which potentially have a direct effect on audio-based features. The noisy breathing of bronchitis patients, uncontaminated by crackles or wheezes, has a wide spectrum of frequencies, with its energy evenly distributed over a range of 200 - 2,000 Hz. Breath sounds at the mouth relate to turbulence in the upper airways, the trachea and the first two or three generations of the bronchi (Forgacs, 1971). Therefore an increase in breath sound intensity from chronic bronchitis patients may mirror those from asthmatic patients. This could potentially make it difficult to discriminate COPD from asthma solely based on breath sounds. Acoustic median frequency values (F_{50}) from averaged spectra may not be the answer to aid COPD diagnosis but may however be partnered with adventitious sound detection to collect more information regarding the pathophysiology of an individual's COPD symptoms.

2.7 Automatic Classification of Breath Sounds

Automatic classification of inhaler sound events is the first stage of signal processing in inhaler audio-based monitoring systems. Accurate detection and classification of inhaler sound events is pivotal in assessing patient inhaler adherence when employing audio-based methods. The previous section discussed how breath sounds are generated as well as some of the acoustic properties of breath sounds. Certain acoustic properties of chest wall and tracheal sounds may differ considerably to inhaler inhalation and

exhalation sounds. However, it is important to understand what audio-based respiratory classification methods may be applicable to classifying inhaler sounds such as inhalations and exhalations. Audio-based classification methods have been previously employed in many different applications in respiratory research such as differentiating between inhalation and exhalation sounds, detecting breath sounds within speech signals, classifying abnormal breath sounds, classifying snore sounds and cough sounds and classifying sleep/wake phases and obstructive sleep apnoea (OSA) based on snore sounds (Huq and Moussavi, 2012; Palaniappan *et al.*, 2016; Ruinskiy and Lavner, 2007; Dafna *et al.*, 2013, 2015; Sengupta *et al.*, 2016; Sola-Soler *et al.*, 2011).

Although each method will have different specific approaches in classifying breath sounds (different research aims, microphone setups, features, classifiers etc.), many audio-based classification methods share a similar fundamental structure. Figure 2.8 presents a block diagram which summarises the basic structure of audio-based classification methods.

There are generally two phases in audio-based classification; design (training) and validation (testing). Data is usually divided into training and testing sets accordingly. There are a number of ways of dividing data into training and testing datasets. Resubstitution involves employing all available data for training and then testing on the same dataset. Although this method can be inherently biased, it may be employed to test the upper limit of a classification system's accuracy and to test for over-fitting if compared to other methods (Dafna *et al.*, 2013; Bishop, 2006). Cross-validation is also a popular method which involves dividing the dataset by into k number of groups for example (k -fold cross validation). The classifier is then trained on $k-1$ of the groups and then subsequently tested on the remaining dataset group. This rotates k times until each group is tested separately. It has been previously used in in the feature selection phase in snore sound classification studies (Dafna *et al.*, 2013).

The hold-out method involves dividing data (either by recordings/samples or by participants) into separate training and test datasets. Although it has been reported that different estimates may be obtained according to how the dataset is divided (Jain *et al.*, 2000). However, this method is quite popular and has been used throughout the literature in respiratory audio-based classification (Lozano-García *et al.*, 2017; Lozano *et al.*, 2016).

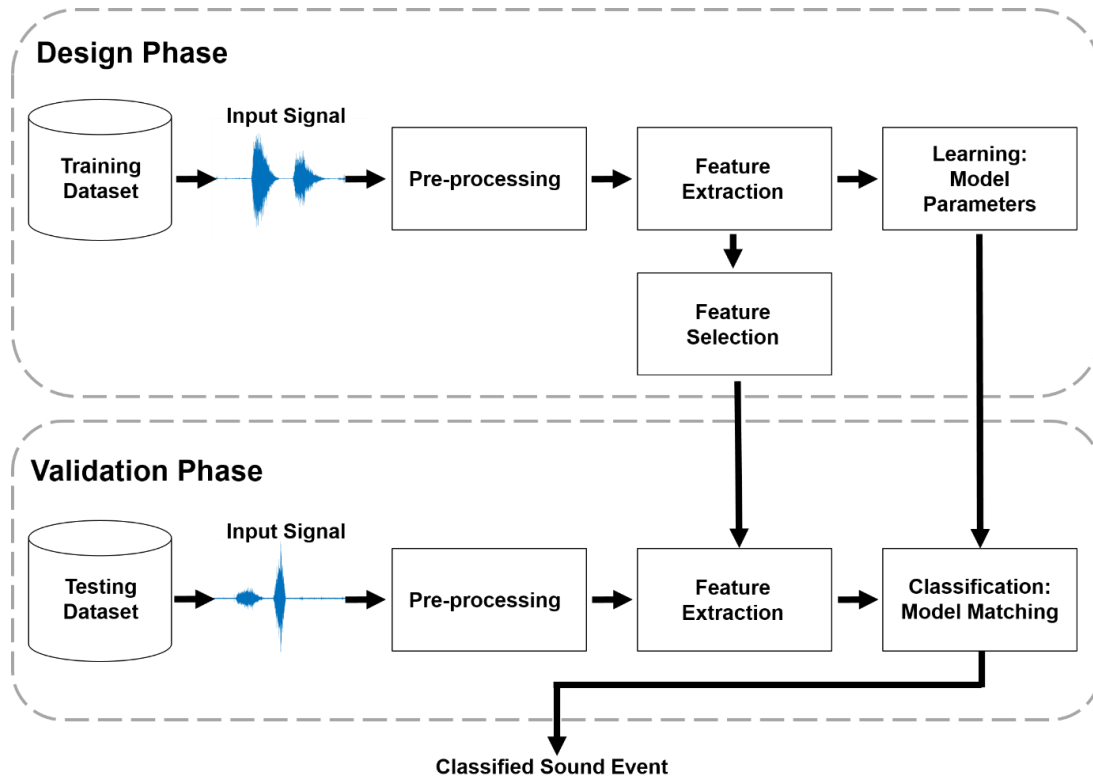


Figure 2.8. Block diagram of audio-based classification.

2.7.1 Pre-processing

The input signal is usually filtered to reduce background noise and to focus on specific frequency bands of interest. The input signal is then divided into a number of overlapping frames. Frame duration varies across the literature depending on the acoustic properties of input signal (usually 20–100 ms). A window is also applied to each frame in the form of Hanning or Hamming windows to reduce spectral leakage or distortion caused from the abrupt discontinuities at the edges of the frames.

2.7.2 Feature extraction

A range of temporal and spectral audio-based features are extracted from each frame to form a feature vector. Feature vectors form an n dimensional feature space which best separate the acoustic properties of each inhaler sound event. Temporal features used in classification of respiratory sounds include energy, duration and the zero crossing rate which can be calculated as;

$$Z = \frac{\sum_{n=1}^N |sign(x[n]) - sign(x[n-1])|}{2N} \quad (2.3)$$

where $[n]$ is an integer value depending on whether the value $[n]$ is positive ($sign = 1$), null ($sign = 0$) or negative ($sign = -1$).

Spectral features include the quartile frequencies that describe the distribution of power across the frequency spectrum (F_{25} , F_{50} and F_{75}). Some of the most popular spectral features employed in respiratory sound classification are the mel-frequency cepstral coefficients (MFCCs). MFCCs were introduced in speech recognition applications to separate the speech signal spectrum $S(z)$ into the source $U(z)$ (periodic signal generated by opening and closing of the vocal folds which generates the pitch) and vocal tract filter $H(z)$ which changes according to the word being spoken. The speech spectrum can be represented as;

$$S(z) = U(z) \cdot H(z) \quad (2.4)$$

In the time domain this equates to the convolution of the source with the vocal tract filter;

$$s[n] = u[n] * h[n] \quad (2.5)$$

where $s[n]$, $u[n]$ and $h[n]$ are the speech, source and filter responses in the time domain.

MFCCs incorporate the fact that the human auditory system is more sensitive to changes at lower frequencies (linear below 1000 Hz) than at higher frequencies (logarithmic above 1000 Hz) (Hasan *et al.*, 2004). To model human pitch perception, a series of triangular filter banks are applied to the speech spectrum which are spaced linearly below 1000 Hz and logarithmically above 1000 Hz according to the mel scale which is given as;

$$f_{mel} = 2595 \log_{10}(1 + f/700) \quad (2.6)$$

where f_{mel} is the frequency converted in the mel scale and f is frequency in the linear domain.

The steps to computing MFCCs are summarised as follows;

1. The Discrete Fourier Transform (DFT) is applied to the input windowed frame where the DFT is calculated as;

$$X[k] = \sum_{n=0}^{N-1} x[n]e^{-j2\frac{\pi}{N}kn} \quad (2.7)$$

where $X[k]$ represents a complex number representing the magnitude and phase of the k^{th} frequency component of the signal.

2. Apply mel-scaled filter bank to spectrum.
3. Calculate the log of the summed filter bank energies. Phase information not relevant in speech so the squared magnitude or power is only considered.
4. The discrete cosine transform (DCT) of the log values is calculated to give the coefficients.

Generally, the first twelve MFCC coefficients are known to contain the most relevant information while the 0th coefficient is the average energy of all frequency bands (Zheng *et al.*, 2001).

Increasing the number of features in the feature set can have a negative effect on the performance of a classification system. The number of training samples required grows exponentially with the number of features (dimensionality). This is known as the curse of dimensionality (Bishop, 2006). It has been suggested that having ten times more training samples than features is sufficient (Jain *et al.*, 2000). Furthermore, if the classification method is too complex it may cause over-fitting which results from a complex classification method training exhaustively on training data (Bishop, 2006). When the classification method is tested on new data, it therefore may not perform anywhere near the level as expected.

There are a number of methods available to select the appropriate number of features for the final classifier. This can help reduce the number of features and reduce dimensionality as a result. One of the most popular methods of feature selection is sequential forward selection (SFS) where the single best feature (as determined by a predetermined performance measure) is selected first and then the best combination of features are added one by one until performance plateaus or decreases. The main advantage of this method is that it will only select a subset of features hence making it less computationally complex compared to other methods (Jain *et al.*, 2000). Once a feature has been selected in this process it cannot be removed. Sequential backward

selection is like the reverse of SFS whereby all features are employed and then removed one by one until performance decreases. However, it is more computationally complex as all features are employed in the first iteration.

2.7.3 Classification methods

Specific classifiers are selected to partition the feature space in order to accurately class a new input feature vector or, in other words, classify each inhaler sound event or frame (classification may be event-by-event or frame-by-frame) into a specific class (inhalation, actuation/blister, exhalation). There are many different classifiers used in the respiratory acoustics research as shown in Table 2.5. Parametric classifiers assume a functional form to partition the feature space into classes (inhaler events) such as a linear function. They are simple as they do not require large amounts of data and are therefore quite fast computationally. Some of these include Naïve Bayes, linear and quadratic discriminant analysis classifiers. One of the main disadvantages is that some unknown parameters may not fit to the assumed function. There are also non-parametric classifiers are capable of fitting a large number of functional forms, they make no assumptions about the underlying data and can result in higher performance. However, they tend to require more data and are slower computationally. Some of these include k-Nearest-Neighbour (kNN), support vector machines, artificial neural network (ANN), and Hidden Markov Models (HMMs) (Jain *et al.*, 2000).

2.7.4 Performance measures

There are a range of performance measures that are used when testing a given audio-based respiratory sound classification method. Some of which include sensitivity, specificity, accuracy, area under the curve and positive predictive value.

There is a lack of audio-based classification methods to classify inhaler sounds, however, many studies have employed audio-based methods to classify inhalation and exhalation sounds. These studies may be of relevance to analysing inhaler audio recordings in terms of relevant audio feature extraction and classification methods. Table 2.5 lists a set of studies involving automatic classification of inhalation and exhalation respiratory sounds. It also details the audio-based features that were employed as well as the classifiers selected and the performance measures that were reported. Audio-based

classification methods have been employed in many other respiratory applications such as snore detection, sleep/wake classification and detecting breath sounds in song signals (Shokrollahi *et al.*, 2016; Dafna *et al.*, 2015; Nguyen and Won, 2015; Takahiro *et al.*, 2014; Dafna *et al.*, 2013; Ruinskiy and Lavner, 2007). However, they were not included in Table 2.5 as they were deemed not to be within the scope of this research.

Table 2.5. List of studies involving automatic classification of respiratory sounds.

Author	Objectives	Participants	Recording Information	Audio-Based Features	Classifier	Summary of Results
(Lozano-García <i>et al.</i>, 2017)	Classification of continuous adventitious sounds to improve assessment of bronchodilator response	25 (20 asthma, 5 healthy)	Four piezoelectric contact microphones (TSD108, Biopac) placed on the back on the base and near the upper lobe of the lungs. Fs=12,500 Hz	Instantaneous frequency, instantaneous envelope and Hilbert spectrum time-frequency distribution	Support Vector Machine (SVM) using a non-linear kernel function to map features into a higher dimensional space	Patients with positive response to bronchodilator had significant change in number of continuous adventitious sounds based on objective classification methods
(Lozano <i>et al.</i>, 2016)	Automatic differentiation of normal and continuous adventitious sounds	30 (asthma)	Four piezoelectric contact microphones (TSD108, Biopac) placed on the back on the base and near the upper lobe of the lungs. Fs=12,500 Hz	Instantaneous frequency, instantaneous envelope and Hilbert spectrum time-frequency distribution	SVM using a non-linear kernel function to map features into a higher dimensional space	Accuracy=94.6%±0.3% on recorded respiratory sounds and 92.8%±3.6% for simulated respiratory sounds

(Palaniappan <i>et al.</i>, 2016)	Differentiate between inhalation and exhalation sounds	69 (healthy)	WISE digital stethoscope placed on three locations (trachea, left and right posterior base of the lung).	Normalised Averaged Power Spectral Density (PSD), Changes in Normalised Average PSD across frames	Fuzzy Inference System using Mamdani and Sugeno methods	Correlation coefficient $r=0.982$
(Lei <i>et al.</i>, 2014)	Classification of breath sounds	64 (40 healthy, 15 flu, 4 bronchitis)	Digital voice recorder microphones. Fs= 8 kHz, 16 bits/sample	Frequency centroid, bandwidth, spectrum power, sub-band power, pitch, MFCC, spectral flux, spectral entropy, spectral roll-off, spectral centroid, 1st and 2nd order MFCC derivatives (dynamic features).	SVM, ANN and kNN	Method outperforms other classification methods such as template matching. Accuracy = 98.9%
(Abushakra and Faezipour, 2013)	Detect and classify inhalations and exhalations	125 (123 healthy, 2 lung cancer)	Non-contact Sony Vaio VPCEB42FM placed 3 cm from mouth. Fs=44.1 kHz	MFCCs	Sound event detection was performed using energy based features. Linear Threshold corresponding to the mean of the 6th MFCC was employed for classification	6th MFCC larger in inhalations. Performance measures: Accuracy = 93.2%

(Huq and Moussavi, 2012)	Differentiate between inhalation and exhalation sounds	93 (healthy)	Sony ECM-77B microphone placed on trachea. Fs=10, 240 Hz	Log Variance (LV), Duration, Area under the LV Curve, Ratio between first third of area under the LV curve to the final third of area under the LV curve, Falling gradient of the LV curve	Two majority vote approaches; 5VOTE - majority vote of all five features. 3VOTE - average vote of the parameters with the highest accuracy	Most prominent features were duration, volume and shape of the sound envelope. Accuracy = 95.6% Sensitivity = 95.5% Specificity = 95.6%
(Güler <i>et al.</i>, 2005)	Classification of respiratory sound pattern	57 (18 COPD, 19 restrictive lung disease, 20 healthy)	Two air-coupled electret microphones placed on the base of the lung.	LPC, cepstral coefficients	Single layer Neural network	Classification performance of 58% for segments and 67% for subjects

2.8 Automatic Detection and Classification of Inhaler Sounds

As audio-based inhaler monitoring has only been recently introduced, there is a lack of studies reported in the literature that investigated automatic classification of inhaler audio signals. Previous studies have employed audio-signal processing methods to automatically detect inhaler events (Holmes *et al.*, 2014a, 2013a). In a study by Holmes *et al.* (2014a), the INCA device was employed to obtain audio recordings of Diskus DPI use from 12 asthma patients. The study obtained 609 audio recordings of inhaler use which was split into training (202 audio recordings) and testing (407 audio recordings) datasets. A range of features were employed to characterise the different inhaler events. For blister sound detection, audio signals were divided into frames of 100 ms in duration with 10 ms overlap to obtain sufficient temporal resolution. Blister sounds are generally quite short in duration (approximately 100 ms), hence the motivation for 100 ms frames. The power within the frequency bands of 2-3 kHz and 20-200 Hz was employed as separate features. To detect inhalation and exhalation sounds, audio signals were divided into frames of 700 ms in duration with 20 ms overlap to obtain sufficient temporal resolution. Twelve MFCCs were extracted from each frame to obtain a short-time cepstrogram of the audio signal. Singular Value Decomposition (SVD) was then employed to obtain a normalised singular vector from the cepstrogram of the signal. The zero crossing rate (Z), which refers to the rate at which the audio signal crosses the x-axis was also extracted from frames to detect inhalation and exhalation sounds.

To differentiate between inhalation and exhalation, the average PSD within the 2.52-4 kHz frequency band was obtained. It was reported that inhalations contained more power within this frequency band than exhalations. A flow chart of the reported algorithm for automatic detection of inhaler sounds is presented in Figure 2.9 (Holmes *et al.*, 2014a). In order to obtain algorithm performance measures (sensitivity, specificity and accuracy), the test dataset were pre-labelled manually by two independent raters through aural and visual assessment. The algorithm generated an accuracy of 92.1% for blister detection, 91.7% for inhalation detection and 93.7% for exhalation detection. However there were some limitations to the study. A Cohen's kappa statistic that measured the inter-rater agreement during the manual labelling process, highlighted only moderate agreement

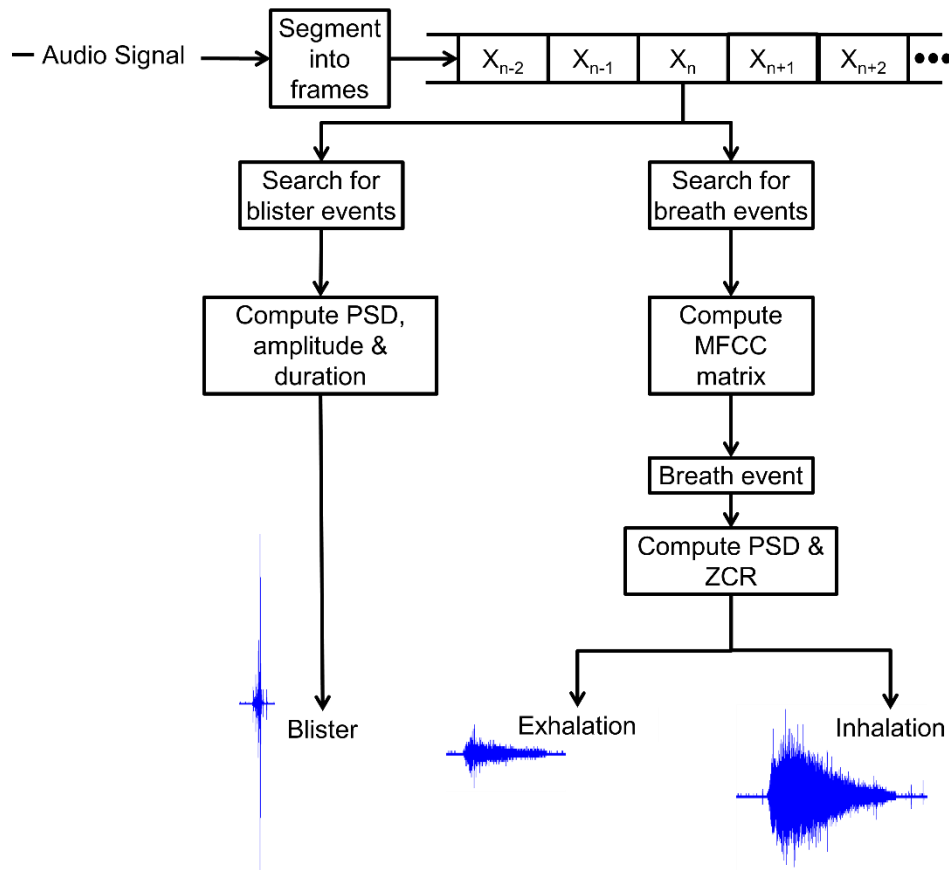


Figure 2.9. Block diagram of automatic inhaler sound detection algorithm (Holmes *et al.*, 2014a).

between independent raters for some of the patient data. This shows the limitation in comparing an objective algorithm against subjective assessment. Furthermore, the algorithm employed a range of thresholds as a means of classifying different inhaler events rather than using statistical modelling. Considering that the hold-out method employed in this study did not split patients between training and testing, this may have introduced a bias which may have accentuated algorithm performance. Additionally, performance measures were only based on data that generated strong agreement between independent raters which may consist of data with less noise present. It has yet to be investigated whether similar methods are applicable for other DPIs and pMDIs. However, this study reported promising results for the potential implementation of audio-based inhaler monitoring systems to remotely monitor patient inhaler user technique.

Kikidis *et al.* (2015) investigated the use of convolution neural networks to detect pMDI actuation sounds. The authors used a microphone (connected to a smartphone) that was fixed onto the front side of a pMDI. The pMDI audio signals were acquired from five healthy participants who were asked to actuate the pMDI in open air and away from their

mouth in different real life noisy environments. This process produced 200 actuation recordings and the same number of non-actuation sound files. The study reported an accuracy of 98% at detecting pMDI actuation sounds (Kikidis *et al.*, 2015).

Other studies examined three algorithmic approaches (Support Vector Machines, Random Forests, and AdaBoost) for the detection of pMDI sounds including actuations, inhalations and exhalations actuations (Nousias *et al.*, 2016; Lalos *et al.*, 2016). In these studies, inhaler audio recordings were obtained using a wireless Bluetooth microphone attached to the pMDI and a Smartphone. Nousias *et al.* (2016) obtained pMDI audio data from five healthy participants. The Short Time Fourier Transform (STFT) was used as the basis for the extraction of features that are then used for the classification of four sound types or classes (inhaler actuation, inhalation, exhalation, background noise). In this study, the dataset was comprised of 280 samples per sound class giving a total of 1120 sound samples in the dataset (sampled at 4 kHz, 4 bits/sample). They reported that AdaBoost outperformed the alternative approaches leading to accuracies above 96% (Nousias *et al.*, 2016).

Lalos *et al.* (2016) developed an energy efficient wireless audio-based method of remotely detecting pMDI events. In this study, a dataset from two healthy participants consisting of 500 actuations and 500 noise segments (dataset 1) along with 200 actuations, 200 inhalations, 200 exhalations and 200 noise segments (dataset 2) were obtained. An accuracy of over 96% was reported. However, the recent studies that employed audio-based methods to detect pMDI sound events all used very small cohorts of healthy participants and did not consist of real life inhaler recordings from patients with chronic respiratory diseases.

2.9 Estimation of Respiratory Flow Parameters

The second stage of signal processing in audio-based inhaler monitoring systems is the estimation of pertinent flow parameters from the detected inhalation audio signal. This allows for objective assessment of patient inhalation technique. The aim is to estimate flow parameters of a patient's inhaler inhalation using features extracted from the inhalation audio signal in order to objectively assess inhalation technique. It has been thoroughly discussed previously in this literature review how drug delivery in pMDIs and DPIs is heavily dependent on the flow parameters of the patient's inhalation. However,

there is a lack of monitoring systems and devices available to remotely monitor patients' inhalation flow parameters during inhaler use.

Audio-based methods of estimating inhaler inhalation flow parameters do not require sensors within the airflow path of the inhaler. In this way, the resistance of the inhaler will be unaffected as the audio recording device is non-invasive to the inhaler. However, in order to estimate inhalation flow parameters using audio-based methods, an objective gold standard reference measurement of inhalation flow is required to correlate with audio-based features. Therefore, it is important to review methods that have been employed to estimate respiratory flow as they may be relevant to measuring inhaler inhalation flow parameters.

Estimating parameters such as respiratory flow rate, volume and effort are of particular interest in the diagnosis of asthma, COPD and sleep apnoea studies (Vandenbussche *et al.*, 2015; Motamedi-Fakhr *et al.*, 2017; Teulier *et al.*, 2013; Cilluffo *et al.*, 2016). Respiratory flow and volume parameters are usually measured using gold standard pneumotachograph spirometer devices that record flow parameters as a patient breathes through a mouthpiece (Raman and Druzgalski, 2015). Other popular methods of monitoring respiratory flow parameters include measuring thoracoabdominal movement (movement of the thorax/chest and abdomen) of patients using strain gauges and piezoelectric contact accelerometers situated in adhesive belts that are worn around the chest and abdomen. However, a major drawback of these types of sensors is that they only measure changes in one dimension (Vandenbussche *et al.*, 2015).

Respiratory inductance plethysmography (RIP) belts can record the full cross sectional movement of the chest and abdomen by recording inductance changes in wire coils contained within the belts (Vandenbussche *et al.*, 2015; Lo and Huang, 2016). This allows for monitoring changes in volume and airflow along with other parameters such as thoracoabdominal asynchrony (Motamedi-Fakhr *et al.*, 2017). They can highlight levels of obstruction in patients through changes in phase of the RIP signals. Furthermore, the summation of the chest and abdomen belt signals allows to detect changes in tidal volume (Vandenbussche *et al.*, 2015). Therefore, RIP belts are usually the preferred choice over other contact sensors when estimating flow parameters non-invasively from thoracoabdominal movements. However, one of the main disadvantages with RIP is that the belts require complex calibration methods which may be challenging for elderly patients or infants with neurological disorders (Moussavi *et al.*, 2000). Also, depending on the task, the belts may move and need to be re-calibrated as a result. Less-complex

calibration methods for RIP methods may further improve the clinical applicability of this analysis. New calibration methods have been introduced that calibrate the RIP data on a breath-by-breath basis that do not require the user to perform specific respiratory tasks (Lo and Huang, 2016). This may greatly benefit researchers using RIP belts in future respiratory studies. Other non-invasive methods of monitoring respiratory parameters have been reported using lasers, however they currently cannot measure cross sectional changes in volume (Hagman *et al.*, 2015). Further research is required to investigate their widespread use in clinical settings.

2.10 Respiratory Flow Estimation Using Audio-Based Methods

The complex calibration methods required for using RIP resulted in a clinical need for other non-invasive methods of measuring respiratory airflow. Audio-based methods have been employed in several studies to estimate respiratory flow parameters and respiratory rate (Table 2.6). These methods are based on the relationship between audio-based features that are extracted from breath sounds (either inhalation or exhalation sounds) and the corresponding flow signal. Study participants are usually instructed to breathe through a pneumotachograph mouthpiece at specific target flow rates while flow and audio signals of exhalations and inhalations (recorded from the trachea or chest wall) are recorded simultaneously.

Audio-based features that are commonly employed to estimate flow from tracheal and chest wall breath sounds include the average power and the envelope of the audio signal (Reljin *et al.*, 2015; Yadollahi and Moussavi, 2011; Que *et al.*, 2002). Studies have also reported the use of complexity audio-based features such as the Shannon entropy (H) to estimate flow. Entropy is a measure of complexity or uncertainty of the inhalation acoustic signal.

Once the selected audio-based features have been extracted from the inhalation/exhalation sound, they are correlated with corresponding flow signals to determine the most suitable model that best describes the relationship between flow and audio-based features. The most popular models employed in audio-based flow estimation are linear and power law models. Linear models can be defined as;

$$\hat{F} = y \cdot A + z \quad (2.8)$$

where A is the amplitude of the breath sound, $\hat{F}$ is the estimated flow and y (slope) and z (intercept) are constants.

Power law models can be defined as;

$$A = k \cdot \hat{F}^\alpha \quad (2.9)$$

where k and α are constants (Yadollahi *et al.*, 2013; Reyes *et al.*, 2014).

This can be re-arranged as a linear model in a logarithmic scale such as;

$$\hat{F} = a \cdot A + b \quad (2.10)$$

where $a = \frac{1}{\alpha}$ and $b = -\log \frac{k}{a}$.

Audio-based flow estimation models have been reported to generate high accuracy with estimation errors below 10% (Yadollahi and Moussavi, 2011; Yadollahi *et al.*, 2013). However, in some cases, only the upper 20-40% of the respiratory signals are employed to avoid error due to rapid changes in flow at the initial phase of inhalation and exhalation (Yadollahi and Moussavi, 2006b; Yadollahi and Moussavi, 2008). Several studies reported that the model parameters that represent the relationship between flow and sound, such as the slope and intercept of the regression model, differ between the inhalation to exhalation phases due to differences in the mechanisms of sound generation (Yadollahi and Moussavi, 2006b; Yadollahi and Moussavi, 2008). There were no studies found in the literature that investigated if the relationship between respiratory flow and sound differs across patients with respiratory diseases such as asthma and COPD. However, a study by Yadollahi *et al.* (2013) reported that flow-sound model coefficients change in OSA patients between wakefulness and sleep (Yadollahi *et al.*, 2013). Furthermore, it was previously reported that gender, height and smoking can also significantly influence audio-based flow estimation (Yadollahi and Moussavi, 2011). Therefore, generalised models may not be appropriate for audio-based flow estimation. Table 2.6 lists a number of studies reported in the literature that investigated the relationship between breath sounds, primarily recorded from the trachea, and flow rate.

Table 2.6. List of studies involving respiratory flow estimation using audio-based signal processing methods.

Author	Participants	Flow Signal Measurement	Audio Recording Information	Audio-Based Features	Regression Model	Summary of Results
(Tabata <i>et al.</i>, 2016)	51 (asthmatic children)	Spirometer	Handheld microphone placed on the right upper anterior chest at the second intercostal space. Fs=10,240 Hz	F_{50} , F_{75} and F_{99}	Linear	Audio-based features of inhalation sounds significantly correlated with PIFR F_{50} $r=0.232$ F_{75} $r=0.234$ F_{99} $r=0.226$ However, much higher correlation values were reported at an intra-patient level ($r > 0.8$)
(Reljin <i>et al.</i>, 2015)	5 (healthy)	RIP belts-chest and abdomen	Subminiature electret Knowles Electronics BT-21759-0000 microphone placed on	Shannon entropy Blanket Fractal Dimension (BFD)	Linear and exponential	Normalised root mean square error (NRMSE) = 15.877%±9.246% Smallest normalised root mean square error obtained was using BFD with exponential model

			trachea. Fs=44.1 kHz, 16 bits/sample			
(Reyes <i>et al.</i>, 2014)	9 (heathy)	Spirometer	Subminiature electret Knowles Electronics BT-21759- 0000 microphone placed on trachea. Fs=44.1 kHz, 16 bits/sample	PSD Power	Power Law	No specific airflow estimation results reported. Linear relationship between respiratory rate derived from tracheal sounds and spirometer generated $R^2=0.9693$
(Yu <i>et al.</i>, 2013)	20 (healthy)	Pneumotachometer mask	WM-56A103 Panasonic microphone placed on trachea	Logarithm of the Shannon entropy	Linear	No airflow estimation results reported. Employed audio-based flow signal to estimate apnoea with 95% Sensitivity, 92% Specificity, 76% PPV, 98% NPV

			Fs=22.05 kHz			
(Yadollahi et al., 2013)	18 (OSA patients)	Pneumotachometer mask	Sony ECM-77B microphone placed on trachea. Fs=16 kHz	Energy	Power Law	Flow estimation errors were $3.7 \pm 3.1\%$ and $8.4 \pm 12.5\%$ for inhalation and exhalation flow respectively
(Yadollahi and Moussavi, 2011)	93 (healthy)	Pneumotachograph connected to a differential pressure transducer	Sony ECM-77B microphone placed on trachea. Fs=16 kHz	Average Power	Power Law	Average flow estimation error below 10% during inspiration and expiration phases. Gender, height and smoking significantly influenced model parameters
(Yadollahi and Moussavi, 2008)	4 (healthy)	Pneumotachograph connected to a differential pressure transducer	Siemens accelerometer EMT25C placed on trachea.	Average Power, Logarithm of Variance, Logarithm	Linear	Logarithm of Variance generated strongest relationship with flow. Model coefficients change with flow rate, particularly at high flow rates

			Fs=10,240 Hz	of Range, Logarithm of Envelope		
(Yadollahi and Moussavi, 2007)	10 (healthy)	Pneumotachograph connected to a differential pressure transducer	Siemens accelerometer EMT25C placed on trachea. Fs=10,240 Hz	Logarithm of Range	Linear	Flow estimation errors were $8.82 \pm 2.79\%$ and $10.15 \pm 2.73\%$ for inhalation and exhalation flow respectively
(Yadollahi and Moussavi, 2006a)	10 (healthy)	Pneumotachograph connected to a differential pressure transducer	Siemens accelerometer EMT25C placed on trachea. Fs=10,240 Hz	Shannon Entropy	Linear	Flow estimation errors were $8.3 \pm 2.8\%$ and $9.6 \pm 2.8\%$ for inhalation and exhalation flow respectively

(Beck <i>et al.</i>, 2005)	8 (healthy)	Pneumotachograph mouthpiece	Alpha Omegae piezoelectric contact accelerometer placed on the neck (anterior cervical triangle). Fs=4,800 Hz, 12bits/sample	Amplitude	Power Law	Correlation coefficient values for inhalation and exhalation were $r=0.972$ and $r=0.967$ respectively
(Harper <i>et al.</i>, 2003)	4 (healthy)	Pneumotachograph connected to a differential pressure transducer	PPG Sensor accelerometer placed at the trachea. Fs=10,240 Hz, 12 bits/sample	Average Power	N/A	Relationship between average power of inhalation and exhalations and airflow
(Yee Leng and	10 (healthy)	Pneumotachograph connected to a differential	Siemens accelerometer EMT25C	Average Power	Linear	Flow estimation error was $5.8\pm3\%$

Moussavi, 2002)		pressure transducer	placed on trachea. Fs=10,240 Hz			
(Hossain and Moussavi, 2002b)	10 (healthy)	Pneumotachograph connected to a differential pressure transducer	Siemens accelerometer EMT25C placed on trachea. Fs=10,240 Hz	Average Power	Linear	Flow estimation error was $13.1\pm7.8\%$, $10.2\pm3.3\%$ and $18.7\pm10.6\%$ when the model was calibrated using tracheal sounds from low, medium and high flow ranges respectively
(Hossain and Moussavi, 2002a)	10 (healthy)	Pneumotachograph connected to a differential pressure transducer	Siemens accelerometer EMT25C placed on trachea. Fs=10,240 Hz	Mean Amplitude, Average Power	Linear, Log-Linear and Power Law	Linear relationship between Mean Amplitude and flow generated strongest correlation ($r=0.79\pm0.7$)

(Que <i>et al.</i>, 2002)	17 (11 healthy, 3 patients with unstable airway obstruction and 3 asthma patients)	Pneumotachograph mouthpiece	Armaco model 1306 electret microphone placed on trachea. Fs=3 kHz, 12 bits/sample	Acoustic envelope	Linear	No quantitative result on flow estimation performance reported
(Gavriely and Cugell, 1996)	6 (healthy)	N/A	N/A	Spectral Power (area under the spectral curve)	Power Law	Relationship between spectral power of tracheal and chest wall breath sounds follows a power law relationship
(Soufflet <i>et al.</i>, 1990)	9 (healthy)	Pneumotachograph mouthpiece	Neutrik 3381 microphone placed on trachea.	Average Power, Mean Frequency	Hierarchical clustering analysis	Flow estimation accuracy was approximately 85%

			Fs=5,210 Hz, 16bits/sample			
(Lessard and Wong, 1986)	12 (healthy)	Pneumotachograph mouthpiece	Stethoscope placed on the neck (anterior cervical triangle). Fs=4,096 Hz	Mean Frequency, Frequency of Maximum Power and Frequency at 90th Percentile of Total Power	Linear	Mean frequency is linearly correlated with flow up 45 L/min then levels off.

It could be argued that exhalation flow rate estimation is beyond the scope of this thesis as it does not present clinically relevant information in terms of inhaler adherence. Therefore, inhaler audio-based flow estimation should be focused on the inhalation event of inhaler use as it is directly associated with inhaler drug delivery. It is important to now discuss previous studies that applied similar methods to those listed in Table 2.6 to estimate flow parameters of inhaler inhalations.

2.10.1 Inhaler inhalation flow estimation using audio-based methods

The vast majority of studies that investigated the relationship between respiratory audio-based features and flow employed audio signals recorded from the trachea and chest wall. It would be hypothesised that inhaler inhalation sounds recorded using a non-contact microphone may have somewhat different acoustic properties as previously discussed. However, the audio-based features and flow estimation models reported in Table 2.6 may still be quite relevant in estimating inhaler inhalation flow parameters using non-contact microphones.

A study by Holmes *et al.* (2013c) was the first study to use audio-based features to estimate inhaler inhalation flow parameters in the Diskus DPI (Holmes *et al.*, 2013c). The aim of the study was to estimate PIFR and IC of inhaler inhalations using audio-based methods. In this study, the INCA device was employed to record inhaler inhalations from 15 healthy participants at a range of inspiratory flow rates. The Diskus DPI was placed inside an airtight container which had a pneumotachograph spirometer connected to it in order to obtain objective measurements of PIFR and IC of inhalations. Inhalation audio signals were band pass filtered at a range of high pass and low pass cut-off frequencies ranging from 20 Hz (high pass cut-off) to 450 Hz (low pass cut-off). Audio-based features that were employed to estimate PIFR and IC included the average PSD (which is the total spectral power normalised by the number of FFT points), mean absolute deviation (*MAD*) and root mean square (*RMS*).

To estimate PIFR using audio-based features, linear models were employed to estimate the relationship between audio-based features and PIFR. It was reported that the average PSD within the 300-600 Hz frequency band of the inhalation sounds generated the strongest correlation with PIFR ($R^2=0.9079$, $p<0.001$). This audio-based method of estimating PIFR using the INCA device was later validated in a study by Seheult *et al.*

(2014b) using Diskus DPI inhalation audio recordings from 92 patients consisting of asthma and COPD patients (Seheult *et al.*, 2014b). It was reported that the correlation between PIFR calculated from audio-based features and PIFR recorded from a gold standard spirometer was strong ($R^2=0.884$).

To estimate IC, Holmes *et al.* (2013c) modelled the inhaler inhalation flow profile as a semi-elliptic curve as shown in Figure 2.10 (Holmes *et al.*, 2013c).

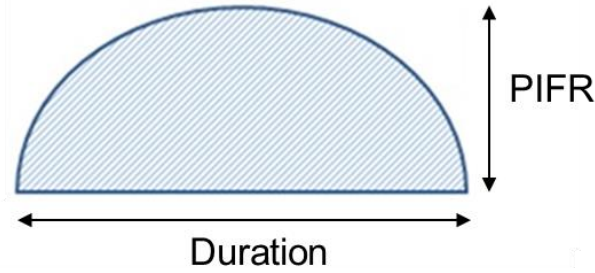


Figure 2.10. Area of semi-ellipse from which the volume or IC of an inhaler inhalation can be estimated.

The IC was calculated as the area under the curve of the semi-ellipse. By defining the peak of the semi-ellipse as the audio-based measure of PIFR and estimating the duration of the inhalation sound using manual segmentation, the IC was calculated using the following equation (Holmes *et al.*, 2013c);

$$IC = \frac{1}{2} \cdot \pi \cdot \widehat{PIFR} \cdot \frac{d}{2} \quad (2.11)$$

where $\widehat{PIFR}$ is the audio-based estimation of PIFR and d is the duration of the inhalation.

These studies show promising opportunities for audio-based methods to remotely monitor two clinically important inhalation flow parameters, PIFR and IC. This may help healthcare professionals assess patient inhaler inhalation technique on a regular basis and help patients improve their adherence as a result. However, this method does not estimate the inhalation flow profile. The flow profile used to estimate IC (as illustrated in Figure 2.10) does not represent the true inhalation flow profile of patient inhalations. Also, this method was only tested on the Diskus DPI and no other inhaler. The frequency bands employed in these studies were also quite narrow. It was shown in a previous study by Holmes *et al.* (2014a) that the power of Diskus inhalation sounds is not concentrated in one particular frequency band but rather spread across the entire spectrum (up to 4 kHz

in the case of INCA device recordings) (Holmes *et al.*, 2014a). It has yet to be reported whether the wider frequency spectrum of the inhalation sounds contains pertinent information and can be used to estimate flow rate.

2.11 Quantification of Inhaler Drug Delivery Using Audio-Based Methods

The third and final stage of signal processing in audio-based inhaler monitoring systems involves extracting features from inhaler inhalation audio signals to estimate the amount of medication delivered to the patients. It has been discussed that audio-based methods can automatically detect and classify different events associated with inhaler use such as drug preparation, inhalation and exhalation sounds. It is also possible to assess inhalation technique specifically by estimating PIFR and IC using audio-based methods. By combining these two phases of audio-signal processing, it is possible to objectively assess patient user technique. There is a clinical need, however, for inhaler monitoring systems to not only monitor patient user technique, but to also quantify the effect of poor user technique on drug deposition in the airways. However, no inhaler monitoring system reported in the literature, other than studies with the INCA system, can estimate the clinical efficacy of patients' user technique i.e. quantify the amount of drug delivered to the patient based on their user technique.

Studies that employed the INCA system have reported a statistically significant relationship between critical user technique errors (as detected using audio-based methods) and the drug delivery of the Diskus DPI. A study by Holmes *et al.* (2013b) reported a significant relationship between the audio-based features of inhalation sounds and the total emitted dose (TED) from a Diskus DPI (Holmes *et al.*, 2013b). This may allow healthcare professionals to quantify the amount of drug removed from the inhaler during a patient's inhalation.

In order to further quantify inhaler drug delivery from audio-based measurements, Seheult *et al.* (2014b) carried out both *in-vitro* and *in-vivo* studies to investigate the relationship between inhalation audio-based features and dose delivery measurements in the Diskus DPI (Seheult *et al.*, 2014b). For the *in-vitro* experiment, the Diskus DPI was connected to a Next Generation Impactor (NGI) cascade impactor (Figure 2.11). The cascade impactor is divided into a series of compartments which models the different

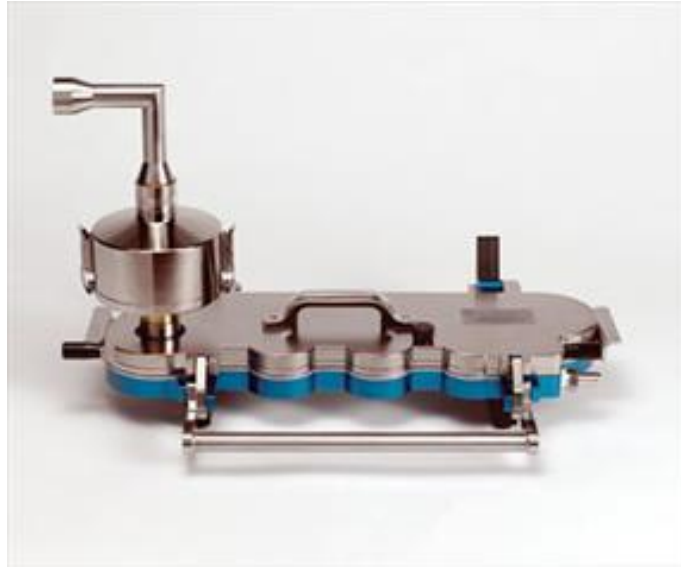


Figure 2.11. NGI cascade impactor used for *in-vitro* inhaler drug delivery testing [Copley Scientific Limited, Nottingham, UK].

generations of the respiratory system. The air inlets on each compartment decrease in diameter along the cascade impactor as to replicate the smaller airways.

Consequently, only smaller aerosol particles can reach the lower compartments of the cascade impactor. The advantage of using a cascade impactor is that it can measure fine particle fraction (FPF – the percentage of fine particle dose to the claimed labelled dose) and throat deposition levels. The cascade impactor was then connected to a Critical Flow Controller flow pump which simulated inhaler inhalations at 30 L/min, 60 L/min and 90 L/min. The INCA device was attached to the Diskus DPI to record the simulated inhalation audio signals. It was observed that $PIFR_{est}$ (audio-based measure of PIFR) was a significant predictor of FPF for salmeterol ($R^2=0.9509$, $p<0.001$), fluticasone ($R^2=0.9509$, $p<0.001$) and salbutamol ($R^2=0.7104$, $p<0.01$) medications in the Diskus. In the *in-vivo* study carried out by Seheult *et al.* (2014b), it was reported that there was a significant difference in serum concentrations of salbutamol (contained within blood samples) when $PIFR_{est}$ was higher than 60 L/min in the Diskus DPI across 10 healthy participants ($p<0.0001$). This highlights how estimating inhalation flow parameters using audio-based methods may assist in remotely monitoring drug delivery from inhalers.

A study by Holmes *et al.* (2014b) employed audio-signal processing methods to detect exhalations into the Diskus DPI mouthpiece as previously discussed (Holmes *et al.*, 2014b). By using a cascade impactor, the effects of exhalation flow rate, the distance between the mouth and the inhaler mouthpiece, exhalation duration and relative air humidity on the delivered dose of the Diskus DPI were investigated. It was reported that

all four factors had a significant influence on drug delivery ($p < 0.05$). The distance between the mouth and the inhaler mouthpiece was the most significant factor followed by relative air humidity and exhalation flow rate (Holmes *et al.*, 2014b).

A more recent study by Sulaiman *et al.* quantified specific critical user technique errors in the Diskus DPI using serum concentrations of salbutamol in blood samples similar to the previous *in-vivo* methods reported (Seheult *et al.*, 2014b; Sulaiman *et al.*, 2017). The INCA system was employed to objectively detect specific user technique errors in 14 healthy participants. It was reported that exhaling into the mouthpiece of the Diskus DPI (as detected by the INCA system) reduced peak salbutamol levels by 62%. Insufficient inhalation effort lead to a 52% reduction in peak salbutamol levels (Sulaiman *et al.*, 2017).

It is evident from the findings reported in these studies that audio-based inhaler monitoring systems may be employed in clinical practice to not only remotely monitor user technique, but to also quantify the dose of medication actually delivered to the patient. This presents a major clinical advantage over other current inhaler monitoring systems.

2.12 Audio-Based Adherence Measures

The final section of audio-based inhaler monitoring systems consists of calculating an adherence measure based on the signal processing of the audio data (first stage) and presenting these measures to patients in an intuitive manner to promote inhaler adherence (second stage). By analysing the sequence of inhaler events and inhalation flow rate using audio-based methods, a more clinically accurate measure of adherence can be obtained. Recent studies have reported the clinical benefit of assessing both temporal and user technique adherence using audio-based monitoring systems. D'Arcy *et al.* (2014) reported that adherence measures that only took temporal adherence into account had no significant relationship with Asthma Quality of Life Questionnaire (AQLQ) in a cohort of 69 asthma patients (D'Arcy *et al.*, 2014). Furthermore, Sulaiman *et al.* (2016d) reported that temporal adherence measures, which have been used previously such as mean adherence and mean daily dose (Choo *et al.*, 2001; Osterberg and Blaschke, 2005; Charles *et al.*, 2007), failed to reflect patient clinical outcomes (Sulaiman *et al.*, 2016d). By taking user technique into account, using the INCA system, a more quantitative measurement of the cumulative doses taken by the patient was estimated and lead to an objective adherence measure that was more reflective of changes in AQLQ ($R^2 = 0.53$ $p < 0.01$)

(D'Arcy *et al.*, 2014). An *Area Under the Curve* audio-based adherence metric was calculated using a trapezoid function of the cumulative measurements over 30 days to obtain adherence measures such as *Attempted Adherence*, *Technique Rate* and *Actual Adherence* (which accounts for both temporal and user technique adherence) (Sulaiman *et al.*, 2015; Sulaiman *et al.*, 2016a). Attempted Adherence was defined as the ratio of the attempted dosing (where the audio analysis algorithm confirms that the patient blistered the Diskus DPI and so attempted to use the inhaler) to the expected doses as a percentage (Sulaiman *et al.*, 2016a). These measures can give information on overdosing for example. Common critical errors reported using the INCA system with the Diskus DPI include insufficient inspiratory effort, exhaling into the mouthpiece and insufficient breath hold (Sulaiman *et al.*, 2016e). Furthermore, accounting for critical user technique errors can give a more realistic measure of patient adherence (referred to as Technique Rate in (Sulaiman *et al.*, 2016a)). By subtracting the Technique Rate from an Interval Adherence Measure (ratio of attempted interval adherence to the expected interval adherence as a percentage), an Actual Adherence measure can be calculated.

Sulaiman *et al.* (2016d) employed these measures in a cohort of patients with severe asthma (n=239) where it was reported that Actual Adherence was just 61.8% in comparison to 84.4% according to the dose counter of a Diskus DPI (Sulaiman *et al.*, 2016d). In another study that recruited a cohort of COPD (n=244), Actual Adherence was calculated as 22.6% for the COPD cohort (Sulaiman *et al.*, 2016a). These adherence measures were employed in another study that consisted of 82 asthma and 21 COPD patients which reported that only 20% of the patients used their inhaler correctly and at the correct time (Sulaiman *et al.*, 2016e). Moreover, it was reported that only 6-7% of the COPD patients using the Diskus DPI had good adherence over 80% of the time in the month following discharge from the hospital (Sulaiman *et al.*, 2016a; Moran *et al.*, 2017). This suggests that some patients still tend to have poor adherence even after being hospitalised. Estimating adherence solely from the inhaler dose counter may over estimate adherence when compared to the audio-based Actual Adherence measures (Sulaiman *et al.*, 2016a).

2.12.1 Comparing audio-based adherence measures to current clinical standard of assessment

Moran *et al.* (2017) reported that audio-based adherence measures in the Diskus DPI (using INCA) did not correlate with patient self-reports and only showed a small association with prescription re-fill data (Moran *et al.*, 2017). This finding suggests that patient reports are not reliable measure of adherence. Furthermore, the Actual Adherence audio-based adherence measure was the only measure to reflect changes in AQLQ, Asthma Control Test (ACT) and peak expiratory flow in a cohort of 239 patients with severe asthma (Sulaiman *et al.*, 2016a). In another study it was reported that 56% of patients (in a cohort of 100 with asthma and COPD) that had a significant drop in AQLQ over a three month period had an Actual Adherence of less than 80% (Sulaiman *et al.*, 2015). This gives further motivation to improve current audio-based methods of assessing patient adherence, not just in the Diskus DPI but in other inhaler devices also.

2.13 Providing Objective Feedback on Patient Inhaler Adherence

The provision of objective and longitudinal information regarding inhaler use can help clinicians identify non-adherent patients, understand the causes of poor adherence and adapt a medication regimen to the patients' needs. It may significantly influence a patient's beliefs and attitude towards medication use, improve medication-taking routines and influence overall disease control as a result. It may encourage dialogue between patients and healthcare professionals, allowing for the development of more personalised strategies to improve adherence to treatment (Sabaté, 2003; Epstein *et al.*, 2004; Zolnieriek and Dimatteo, 2009; Mahtani *et al.*, 2011; Fenerty *et al.*, 2012; Foster *et al.*, 2012; McCormack *et al.*, 2011; Meddings *et al.*, 2012; Patel *et al.*, 2012; Zaugg *et al.*, 2016).

Several studies have shown that feedback significantly improved patient's adherence (Nides *et al.*, 1993; Onyirimba *et al.*, 2003; Giraud *et al.*, 2011; McCormack *et al.*, 2011; Nikander *et al.*, 2011; Spencer *et al.*, 2012; Mac Hale *et al.*, 2014; Nieuwlaat *et al.*, 2014). There is a lack of available systems in place that provide feedback on temporal and user technique adherence. The INCA system is currently being used in clinical practice which allows healthcare professionals to download and visualise the patient's personalised

adherence report. These methods of providing objective personalised feedback to the patient have been recently introduced and are currently on-going in clinical research (Sulaiman *et al.*, 2016b; O'Dwyer *et al.*, 2016; Imran *et al.*, 2014; Sulaiman *et al.*, 2016c). Sulaiman *et al.* (2018) reported the effect of objective feedback as provided by the INCA system on inhaler adherence compared to standard education without objective feedback. A three-month prospective multicentre randomised controlled study was carried out, in which patients with severe uncontrolled asthma were recruited from specialist asthma clinics and randomised to receive both visual feedback and education on their adherence using the INCA system, (active $n=111$) or education alone (control $n=107$). They reported that, at the end of the three-month period, the adherence mean rate of the active group was 73% compared to 63% for the control group ($p=0.02$) (Sulaiman *et al.*, 2018).

Furthermore, in order to encourage patients to improve their adherence, the INCA system provides a dash board report informing patients of their progress during their treatment. This form of presenting the audio-based adherence measures to patients is currently being used in clinical trials and research is currently underway to investigate if objective feedback improves patient adherence in comparison to those patients who do not receive such information regarding their adherence (Mokoka *et al.*, 2017; O'Dwyer *et al.*, 2016). Table 2.7 summarises the advantages and disadvantages of current standard methods of adherence assessment (patient self-reports, healthcare professional checklists), electronic monitoring devices and audio-based monitoring systems (Taylor *et al.*, 2018b). Previous reviews have discussed the use of the different specific electronic monitoring devices in further detail (Howard *et al.*, 2014; Pritchard and Nicholls, 2015; Kikidis *et al.*, 2016).

Table 2.7. Summary of advantages and disadvantages of current methods of monitoring patient inhaler adherence.

Method of Monitoring Adherence	Advantages	Disadvantages
Patient self-report	Simple and low cost	Subjective, inaccurate, prone to overestimation, cannot provide objective information on user technique over the course of treatment
Healthcare professional checklist assessment	Simple, low cost, can provide information on user technique	Subjective, prone to overestimation, may give equal rating to all technique errors, only assesses adherence at one point in time, cannot monitor adherence outside of clinical consultation
Pharmacy re-fill data	Simple, low cost, objective, can provide information on patient persistence towards their medication	Cannot monitor temporal and user technique adherence, dependent on healthcare infrastructure
Electronic monitoring devices (general)	Objective, can monitor temporal adherence, some devices can monitor user technique adherence, some devices can record patient location, some are commercially available	Cost (technology based for smart application development and human resource based for interpretation of analysed data), only few devices available that can monitor user technique adherence, mostly cannot

		quantify inhaler drug delivery
Electronic monitoring devices (audio-based monitoring systems)	Objective, can monitor temporal and user technique adherence, can quantify inhaler drug delivery, can provide adherence measures more reflective of changes in respiratory function, can provide personalised feedback adherence reports regarding temporal and user technique adherence	Cost (technology based for future smart application development and human resource based for interpretation of analysed data), may be sensitive to background noise, not yet commercially available

2.14 Chapter Conclusion

To conclude this review of the literature, it is evident that poor inhaler adherence is a growing complex problem and has significant implications for the long term treatment of chronic respiratory diseases. Many patients make critical errors while using pMDIs and DPIs which significantly reduce the amount of medication delivered to the patient. There are numerous training devices available to patients that can help improve user technique, however, they cannot remotely monitor how patients use their inhaler outside of the clinic. Analysing patient user technique over the course of treatment is of significant interest to healthcare professionals as it can help personalise treatment to the patient. There is a lack of methods available to objectively assess inhaler user technique. Electronic monitoring devices are becoming increasingly popular in engineering and clinical research to objectively assess patient inhaler adherence. However, the majority of devices available are not compatible with both pMDIs and DPIs and do not record information regarding user technique.

Audio-based inhaler monitoring systems, such as the INCA system, employ audio signal processing methods to automatically assess patient user technique. Previous INCA

system research has shown promising signs of introducing new standards of adherence assessment into clinical practice. However, previous INCA system research needs to be brought to the next level in terms of improving signal processing methods of assessing patient adherence, applying audio-based analysis to a range of different inhalers for the first time and employing audio-based analysis of inhaler use to potentially track the patient's response to treatment. This is needed to enhance precision medicine in chronic respiratory diseases.

Chapter 3. Research Questions and Hypothesis

A number of research questions emerged from the review of the literature in Chapter 2. It is evident that audio-based signal processing methods show promising opportunities to objectively monitor patient inhaler adherence and to quantify drug delivery from inhalers. Till today, the INCA system is the only monitoring system that provides a platform to further develop audio-based methods to objectively assess patient user technique. However, the research area of inhaler audio-based monitoring has primarily focused on the Diskus DPI. There is a clinical need to investigate the use of audio-based methods to objectively assess adherence (specifically user technique) in other inhaler devices such as the pMDI (the most commonly used inhaler worldwide), Turbuhaler DPI and the Ellipta DPI. Furthermore, it is unknown whether audio-based features are affected by the inhaler design. This may be of significant importance when developing audio algorithms to objectively assess adherence across different inhalers.

Furthermore, the INCA device has been the primary acquisition device used to obtain audio recordings from inhalers. The INCA device has to be physically attached to the Diskus inhaler and is limited to a sampling rate of 8 kHz with 8 bits per sample audio resolution. Therefore, there is a need to investigate the use of acquiring inhaler audio signals using microphones not attached or distant to the inhaler (such as in a wearable device) and with higher sampling rates and greater bit depth resolution.

Regarding DPIs, there is a clinical need to estimate the full inhalation flow profile as it directly influences the amount of drug delivered to the patient as discussed in Chapter 2. There are currently no available methods to monitor patient DPI inhalation profiles in clinical practice with no studies published in the literature to date that employed audio-based methods to estimate DPI inhalation flow profile. Furthermore, there is a lack of

information regarding the spectral properties of inhalation sounds and how they are affected by flow rate. It is unknown whether spectral features such as F_{50} , for example, can be employed to estimate inhalation flow rate during inhaler use.

Moreover, there is a clinical need to also focus on predicting patient clinical outcomes based on audio-based adherence measures. More specifically, it has yet to be investigated whether audio-based features of patient inhaler inhalations change according to lung function over the course of treatment. This may allow healthcare professionals to intervene before an exacerbation occurs or monitor the efficacy of inhaler medication.

The main objectives of this thesis include developing signal processing methods to objectively assess patient inhaler user technique in a range of different inhalers. The studies reported in this thesis aim to provide new novel clinical measures of patient adherence as well as providing new methods of tracking patient response to medication over the course of treatment. This thesis also aims to investigate the clinical benefit of audio-based adherence measures against standard clinical assessment of inhaler user technique.

The main hypothesis of this thesis is that audio signal processing methods can be developed to objectively assess user technique in both DPIs and pMDIs. It is also hypothesised that audio-based analysis of inhaler use is more accurate than standard clinical assessment and can provide information regarding patient response to treatment. To test these hypotheses, a number of specific research questions were derived.

3.1 Employing Non-Contact Audio-Based Methods to Monitor Inhalation Technique in Inhaler Devices

1. Can non-contact audio-based methods be employed to estimate PIFR in both DPIs and pMDIs using a non-contact microphone distant from each inhaler?
2. What inhalation audio-based features generate the strongest correlation with PIFR in DPIs and pMDIs?
3. Does the position of peak frequencies in the power spectral density of inhaler inhalation sounds change with flow rate?
4. What level of variation do audio-based features generate at different flow rates?
5. Are inhalation audio-based features influenced by the inhaler design?

6. Do anthropometric features such as BMI influence inhaler inhalation audio-based features?

3.2 Audio-Based Objective Measurement of Peak Inspiratory Flow Rate during Patient Inhaler Use and its Application to Detecting Changes in Lung Function

7. What is the relationship between energy independent complexity features such as the Shannon entropy and PIFR and could this feature be employed in audio-based monitoring systems to monitor inhalation technique in asthma and COPD patients?
8. Does the position of peak frequencies in the power spectral density of inhaler inhalation sounds remain consistent across patients with asthma and COPD and does this affect the use of spectral features to estimate PIFR?
9. Do factors such as PIFR, inhalation duration, anthropometric features (such as BMI) and lung function significantly influence the position of peak frequencies in the power spectral density of inhaler inhalation sounds?
10. Do tracheal inhaler inhalation sounds generate greater variability than sounds recorded from a non-contact microphone and does this affect PIFR estimation from audio-based features?
11. Is there a statistically significant relationship between FEV1, PIFR and inhaler inhalation audio-based features during induced bronchoconstriction?
12. Is there a statistically significant relationship between FEV1, PIFR and inhalation audio-based features in the Diskus DPI after the administration of a bronchodilator such as salbutamol?

3.3 Estimation of Inhalation Flow Profile from a Dry Powder Inhaler Using Audio-Based Methods

13. Can the acoustic envelope (amplitude envelope) of inhalation sounds be employed to accurately estimate the inhalation flow profile from the Ellipta DPI?

14. What model best describes the relationship between inhaler inhalation acoustic envelope and flow signals; linear or power law?
15. Is it possible to calibrate a model to estimate the inhalation flow profile using only one inhalation recording?
16. Does the flow rate of the calibration inhalation recording influence the accuracy of audio-based flow estimation?
17. Can a single-calibration audio-based flow estimation model perform sufficiently within different signal-to-noise ratio (SNR) levels?

3.4 Development and Validation of an Audio-Based Algorithm to Objectively Assess Patient Pressurised Metered Dose Inhaler User Technique

18. Can temporal and spectral audio-based features be employed to automatically and accurately detect pMDI actuation sounds?
19. Does the attachment of a Clement Clarke In-Check Flo-Tone device to the mouthpiece of a pMDI increase the intensity of pMDI inhalations sounds?
20. Can audio-based features be employed to develop an intuitive graphical user interface to assist the labelling of inhaler sound events in pMDI audio signals?
21. Can temporal and spectral audio-based features be employed to automatically and accurately detect pMDI inhalations with the In-Check Flo-Tone?
22. Can temporal and spectral audio-based features be employed to automatically and accurately detect exhalations during pMDI use?
23. What classification method generates the highest measure of performance (accuracy, sensitivity and positive predictive value) in classifying pMDI sounds such as actuation, inhalation and exhalation?
24. Can temporal and spectral audio-based features be employed to estimate PIFR and IC of pMDI inhalations using the In-Check Flo-Tone?
25. Can audio-based methods estimate PIFR and IC in the pMDI with a high level of accuracy at different SNR levels?
26. Does patient user technique improve with a pMDI with the application of the In-Check Flo-Tone and does tuition from an expert clinical reviewer improve user technique?

27. Do objective audio-based methods provide a more clinically accurate assessment of patient inhaler user technique in comparison to subjective checklist methods?

To address these research questions, this thesis is organised into a number of studies which focus on the development of audio-based signal processing methods to objectively assess user technique in a range of DPIs and the pMDI.

Chapter 4. Employing Non-Contact Audio-Based Methods to Monitor Inhalation Technique in Inhaler Devices

The studies described in this chapter investigate research questions 1-6 from Chapter 3. As previously discussed in Chapter 2, there is a clinical need for more objective methods to monitor inhaler inhalation technique in other DPIs and pMDIs. Poor inhalation technique, specifically poor PIFR, significantly reduces the clinical efficacy of inhalers. Previous studies employed the INCA device attached to a Diskus DPI to record inhaler inhalations at relatively low sampling rate and bit resolution (8 kHz with 8 bits per sample). There is a need to investigate the use of non-contact methods with higher quality audio acquisition (distant to the inhaler to simulate a wearable device) to objectively assess inhalation technique, specifically the PIFR of inhalation. Furthermore, little is known regarding the spectral properties of inhaler inhalation sounds. This requires investigation in order to further improve audio-based monitoring of inhalation technique. In the study described in Section 4.1, non-contact audio-based methods are employed to investigate the relationship between audio-based features and PIFR in three commonly used inhalers; Turbuhaler DPI, Diskus DPI and Evohaler pMDI. The spectral properties of inhaler inhalation sounds are also investigated as well as the variation of audio features at different inspiratory flow rates. Finally, in the study reported in Section 4.2, a pilot study investigation into the influence of different inhaler devices (Turbuhaler DPI, Diskus DPI, Ellipta DPI and Evohaler pMDI) and anthropometric features of the user (BMI etc.) on inhalation audio-based features is presented.

The studies presented in this chapter have resulted in the following peer-reviewed publications;

- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2016 Monitoring Inhaler Inhalations Using an Acoustic Sensor Proximal to Inhaler Devices. *Journal of Aerosol Medicine and Pulmonary Drug Delivery* 29 439-46.
- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2015 Influences of gender and anthropometric features on inspiratory inhaler acoustics and peak inspiratory flow rate. In: *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE*, Milan, Italy.

4.1 Investigation into the Relationship between Inhalation Audio-Based Features and Peak Inspiratory Flow Rate

4.1.1 Introduction

Despite previous studies employing audio-based methods to estimate PIFR through the Diskus, little is known regarding the spectral properties of inhalation sounds across different inhaler devices (Holmes *et al.*, 2013c; Holmes *et al.*, 2013b; D'Arcy *et al.*, 2014; Seheult *et al.*, 2014b). Spectral properties of normal (i.e. free from adventitious sounds) tracheal and chest wall breath sounds have been reported to be very repeatable at an intra-subject level (Sanchez and Vizcaya, 2003). Also, the position of peak frequencies in the spectral domain is repeatable regardless of PIFR in tracheal breath sounds (Beck *et al.*, 2005). Given these repeatable spectral characteristics are prominent in breath sounds, in this study, it is hypothesised that these spectral properties also exist in inhaler inhalation sounds. This may be of interest for inhaler acoustic analyses research. The use of tracheal and chest wall contact acoustic sensors may not be practical for monitoring inhaler inhalation technique longitudinally as they are contact sensors which may become uncomfortable for patients to wear over long periods of time. Therefore, a non-contact microphone fixed near the inhaler mouthpiece (which may simulate a wearable device) may be a more suitable approach for analysing inhaler inhalation sounds.

The main aim of this study was to investigate the relationship between audio-based features of inhalation sounds (recorded using a non-contact microphone distant to inhaler devices) and PIFR in three commonly used inhalers (Diskus DPI, Turbuhaler DPI, and

Evohaler pMDI). This study is intended to provide a baseline for future audio-based methods of estimating PIFR during inhaler use. The variation of temporal and spectral audio-based features at an intra-subject level was also investigated as well as the repeatability of the position of peak frequencies of the PSD of inhalation sounds across a range of flow rates. It was hypothesised that there is a strong statistically significant correlation between audio-based features of inhalation sounds recorded using non-contact microphones and the PIFR of inhaler inhalations in a range of different inhalers, including DPIs and pMDIs. Furthermore, it was hypothesised that the variation of audio features may differ between DPIs and pMDIs inhaler devices. Finally, it was hypothesised that the position of peak frequencies in the PSD of inhalation sounds remains unchanged regardless of inspiratory flow rate.

4.1.2 Methods

4.1.2.1 Participants

Eleven healthy (age range: 22-31) adult males were recruited. All participants were free from respiratory tract infections and were non-smokers. Baseline spirometry was performed to ATS/ERS recommendations to confirm that all participants had normal lung function (Miller *et al.*, 2005).

4.1.2.2 Inhaler recording setup

Three custom built polyethylene terephthalate (PET) airtight containers were assembled for three commonly used inhalers; Diskus DPI [GlaxoSmithKline, London, UK], Turbuhaler DPI [AstraZeneca, Södertälje, Sweden] and Evohaler pMDI [GlaxoSmithKline, London, UK]. No active drug was contained in any inhalers for this study. The airtight containers were connected to a Vitalograph Pneumotrac 6800 [Vitalograph Ltd, Co. Clare, Ireland] pneumotachograph spirometer, which was connected to a data acquisition laptop, to obtain reference PIFR measurements of inhalations. A custom aperture was cut in each airtight container so that participants could seal their lips tightly around the inhaler mouthpiece. Several previous studies have reported using an airtight container as a method to calculate PIFR during inhaler inhalations (Magnussen *et al.*, 2009; Malmberg *et al.*, 2010; Holmes *et al.*, 2013c). The

airtight container design ensured that all air inhaled through each inhaler flowed through the spirometer from where flow rate can be measured objectively.

An Earthworks TC30 [Earthworks Inc., New Hampshire, USA] omnidirectional microphone was placed 5 cm away from the edge of the inhaler mouthpiece in the airtight container. This setup aimed to simulate a non-contact audio recording device distant to the inhaler to record inhalation sounds. The microphone employed has a flat frequency response from 9 Hz to 30 kHz. A Novation nio 2/4 [Novation, Buckinghamshire, UK] was employed as an audio interface and Adobe Audition V6.0 [Adobe System Inc., California, USA] was used to record audio data with a sampling rate of 44.1 kHz and resolution of 16 bits per sample in a data acquisition laptop. Inhaler recording sessions took place in a soundproof recording studio to limit background noise. The complete experimental setup is demonstrated graphically in Figure 4.1.

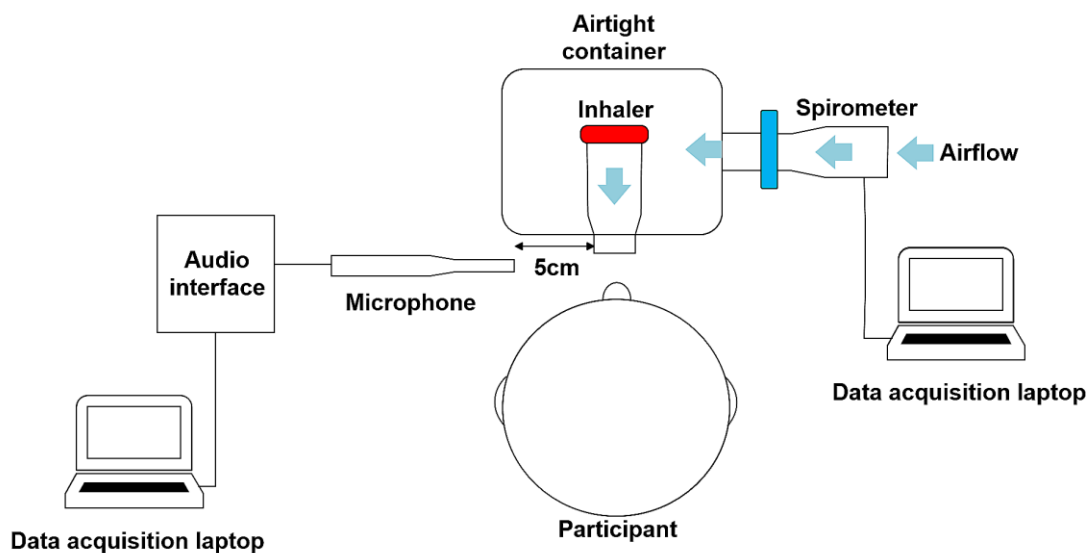


Figure 4.1. Inhaler Recording Experimental Setup.

4.1.2.3 Test protocol

Participants were instructed to exhale gently (to functional residual capacity), before inhaling through the inhaler mouthpiece at maximum inspiratory effort. Participants were asked to inhale at maximum inspiratory effort for 10 recordings. Based on the PIFR achieved, participants were then asked to subjectively lower their inspiratory flow rate (IFR). For the two DPIs, participants were generally able to inhale with PIFR between 80-90 L/min. Once 10 inhalations were recorded for this IFR band, participants were

asked to inhale 10 times at the next lowest IFR band i.e. 70-80 L/min. This procedure was repeated until 10 inhalations were achieved for each IFR band as low as 20-30 L/min. For each inhalation in all of the IFR bands, the PIFR was measured. Usually, PIFR refers to the peak flow rate of an inhalation at maximum inspiratory effort. As it was necessary to obtain a range of flow rates from the healthy participants (requiring different levels of inspiratory effort), inhaler inhalation PIFR is defined as the peak flow rate of each inhaler inhalation.

For the pMDI, the participants were capable of inhaling with PIFR up to 300 L/min. For this inhaler, participants were asked to inhale 10 times in the IFR band 250-300 L/min. Participants were then asked to subjectively lower their IFR and inhale 10 times for the IFR band 200-250 L/min. This was repeated for all IFR bands greater than 100 L/min. Below 100 L/min, participants were asked to inhale 10 times for IFR bands 75-100 L/min, 50-75 L/min and 25-50 L/min. All recordings were aurally and visually assessed by an expert reviewer using Adobe Audition. If participants did not inhale for at least two seconds in duration or had coughed, the audio recording was discarded and participants were asked to repeat the inhalation. Each airtight container was disinfected after each recording session to ensure no infections were passed between participants. The order of inhalers was randomised for each participant. Participants were given breaks in between each set of 10 inhalation recordings to eliminate any fatigue effect on the inhalation sounds or on the PIFR measurements.

4.1.2.4 Audio pre-processing

Baseline correction was performed on all inhalation audio recordings by removing any DC offset present in the audio signal. This was done by subtracting the mean amplitude from each audio recording. All inhalation sounds were high-pass filtered with a cut-off frequency of 200 Hz to remove low frequency noise. Each inhalation audio recording was divided into frames of length 23 ms with 50% overlap between each frame. This window size was chosen to give sufficient resolution of the PSD without smoothing out or distorting peaks in the PSD. A Hanning window was applied to each frame to reduce spectral leakage at the edges of the frames (Semmlow and Griffel, 2014). The Welch PSD was then estimated in order to extract a number of spectral features which could characterise the distribution of power across the frequency spectrum (Semmlow and Griffel, 2014). The Welch PSD is a non-parametric method of estimating the PSD which computes a modified periodogram at each windowed frame and then averages the

resulting periodograms. This reduces the variance of the estimates while making no assumptions regarding how the data were generated (Proakis, 1992; Alessio, 2015). The modified periodogram can be represented as;

$$\tilde{P}_{xx}^{(i)}(f) = \frac{1}{MU} \left| \sum_{n=0}^{M-1} x_i(n)w(n)e^{-j2\pi fn} \right|^2, i = 0, 1, \dots, L-1 \quad (4.1)$$

where M is the length of the frame,

$w(n)$ is the window function,

L is the number of frames,

U is a normalisation factor for the power in the window function to ensure the modified periodogram is asymptotically unbiased and is given as;

$$U = \frac{1}{M} \sum_{n=0}^{M-1} w^2(n) \quad (4.2)$$

The Welch PSD can then be computed as the average of the modified periodograms which is given as;

$$P_{xx}^W(f) = \frac{1}{L} \sum_{i=0}^{L-1} \tilde{P}_{xx}^{(i)}(f) \quad (4.3)$$

where the PSD is measured in V^2/Hz .

A five second sample of background noise was estimated during periods of breath hold for each participant. The PSD was estimated for each participant's breath hold and then removed from each participant's audio recordings using spectral subtraction to remove any high frequency noise. This method has been previously employed in breath sound analysis and has been a recommended method for noise removal (Malmberg *et al.*, 1995; Gavriely *et al.*, 1995; Rossi *et al.*, 2000).

The PSD was calculated for all 10 inhalation audio recordings at each IFR band for each participant. The average PSD was then computed over all 10 recordings at each IFR band in order to obtain a sufficient single estimate of the PSD of each participant at each IFR band. This resulted in one PSD estimate for each IFR band for each participant. Figure 4.2 shows an example of the PSDs of inhalation sounds (where each PSD

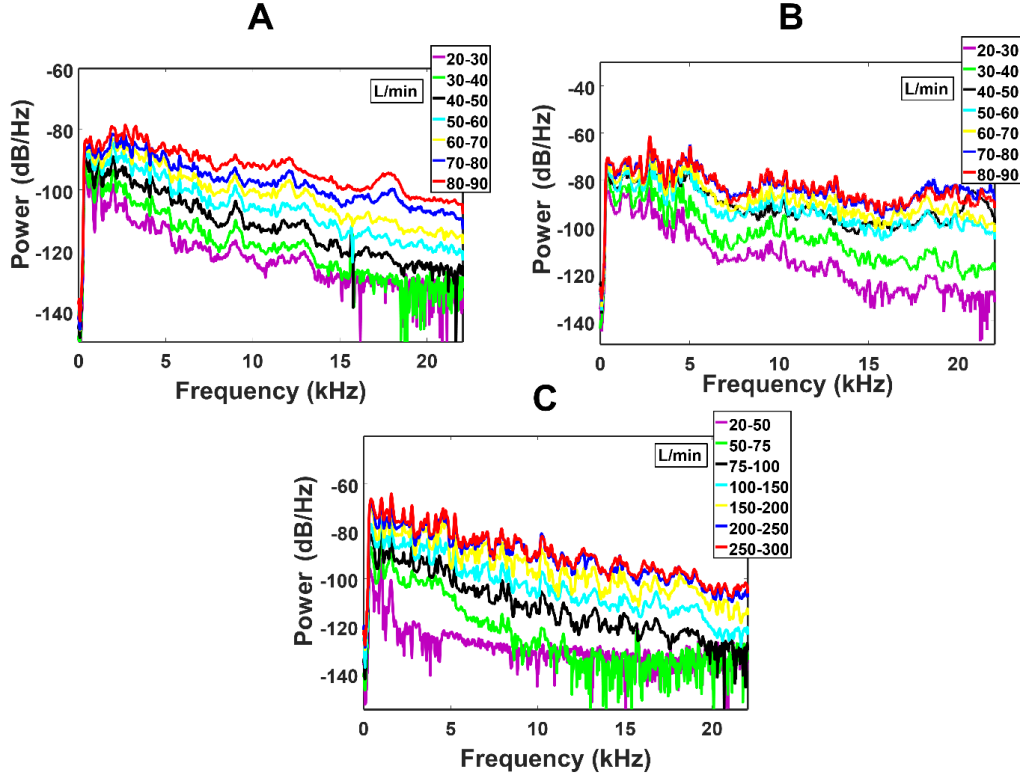


Figure 4.2. Averaged power spectral density estimates of inhaler inhalation sounds from one participant.

(A) Diskus, (B) Turbuhaler and (C) Evohaler. Each coloured line represents the average of 10 inhalation recordings at a specific PIFR.

represents the average of 10 PSDs) from one participant for the Diskus, Turbuhaler and Evohaler. Audio features were then calculated from the PSD and time domain audio signals of the inhalation sounds.

4.1.2.5 Inhaler inhalation audio-based features

Six audio-based features were employed to investigate the relationship between audio and PIFR of inhaler inhalations. The first, second and third quartile frequencies of the acoustic frequency spectrum, which correspond to the frequencies below which 25%, 50% and 75% of the total spectral power lie (F_{25} , F_{50} and F_{75}), were employed. The average PSD (P_{ave}) was calculated as the total spectral power normalised by the number of FFT points (measured in V^2/Hz) as calculated in previous studies (Holmes *et al.*, 2013c). This was then transformed to decibels (dB) using $10 \log_{10}(P_{ave})$. The *MAD* and *RMS* of the inhalation audio signals were also employed as features. The *MAD* is a measure of temporal variability and was calculated using the following equation (Holmes *et al.*, 2013c);

$$MAD = \frac{1}{N} \sum_{i=1}^N |x_i - \bar{x}| \quad (4.4)$$

where N is the length of the audio signal (x) and $\bar{x}$ is the mean of the audio signal x .

The RMS represents non-varying power of the inhalation audio signal and can be calculated using the following equation (Holmes *et al.*, 2013c);

$$RMS = \sqrt{\frac{1}{N} (x_1^2 + x_2^2 + x_3^2 + \dots x_N^2)} \quad (4.5)$$

Audio features were divided into two groups: Group 1 (F_{25} , F_{50} and F_{75}) and Group 2 (P_{ave} , MAD and RMS). Quartile frequencies (F_{25} , F_{50} and F_{75}) have been previously employed to estimate respiratory flow rate as well as to distinguish physiological differences between healthy individuals and those with asthma and COPD (Malmberg *et al.*, 1994; Tabata *et al.*, 2016). Also, it has yet to be reported how spectral features change with flow rate in inhaler inhalation sounds as mentioned in Holmes *et al.* (2013c) and if they may be employed to estimate inhaler inhalation flow rate (Holmes *et al.*, 2013c). The power of respiratory audio signals (P_{ave}) has been previously employed to estimate flow rate from chest wall (Hossain and Moussavi, 2004) and tracheal (Yee Leng and Moussavi, 2002) respiratory sounds. Also, the average PSD, MAD and RMS have been employed to estimate PIFR in the Diskus inhaler using an INCA device (Holmes *et al.*, 2013c).

4.1.2.6 Statistical analyses of inhaler inhalation sounds

A Generalised Least Squares (GLS) regression model, which accounts for random effects intercept at the subject level, was employed using Stata SE Version 12 [StataCorp LP, Texas, USA] to investigate the correlation between PIFR and the audio-based features separately.

To analyse variation in audio-based features, a Coefficient of Variation (CoV) was calculated for all audio-based features at each IFR band for each participant. The CoV values were then averaged across all participants to compute the average CoV of audio

features. The CoV was calculated as a percentage ratio of the standard deviation (σ) to the mean (μ) of audio features at each IFR band;

$$CoV = \frac{\sigma}{\mu} \times 100 (\%) \quad (4.6)$$

To determine the repeatability of the position of peak frequencies in the PSD across all PIFRs, Pearson's linear correlation coefficient was employed to correlate all PSD curves for all PIFR bands. This was repeated for all participants.

4.1.3 Results

Table 4.1 presents demographics and baseline lung function of the 11 participants enrolled in this study. All participants had an FEV1/FVC ratio > 0.7 and a predicted FEV1 $> 89\%$, confirming normal baseline lung function according to ATS standards.

A total of 2,150 inhaler inhalation recordings were obtained in this study consisting of 750 (10 inhalations for each IFR band for each participant) recordings from the Diskus DPI, 730 recordings from the Turbuhaler DPI and 670 recordings from the Evohaler pMDI. One participant's data was discarded from Evohaler acoustic analysis as the data were found to be corrupted.

4.1.3.1 Correlation between PIFR and audio-based features

It was found that all audio-based features employed were statistically significantly correlated with PIFR ($p < 0.001$) at a significance level of $\alpha = 0.05$. Table 4.2 presents the coefficient of determination (R^2) values for each audio-based feature for all three inhalers. It was noted that F_{50} generated the strongest correlation with PIFR for the Diskus ($R^2 = 0.85$), F_{75} for the Turbuhaler ($R^2 = 0.80$) and P_{ave} for the Evohaler ($R^2 = 0.75$). Figure 4.3 demonstrates the correlation between P_{ave} and PIFR for each inhaler. The P_{ave} feature was selected to present in Figure 4.3 as it was observed to generate the highest consistent R^2 values across all inhalers.

Table 4.1. Summary of participant demographics and baseline lung function data.

Parameter	Mean $\pm$ SD (Range)
Age (years)	24.36 $\pm$ 2.50, (22-31)
Height (cm)	179.36 $\pm$ 7.86, (167-190)
Weight (kg)	76.36 $\pm$ 8.66, (65-93)
BMI (kg m ⁻²)	23.79 $\pm$ 2.77, (21.2-28.7)
FEV1 (L)	4.48 $\pm$ 0.47, (3.92-5.18)
FEV1 predicted (%)	99.27 $\pm$ 5.74, (89-112)
FVC (L)	5.50 $\pm$ 0.72, (4.63-6.87)
FEV1/FVC ratio	0.82 $\pm$ 0.04, (0.72-0.88)
PEFR (L/min)	615.09 $\pm$ 72.06, (538-640)
FIVC (L)	5.12 $\pm$ 0.59, (4.55-6.13)
PIFR (L/min)	487.54 $\pm$ 46.45, (405-540)

BMI - body mass index

FEV1 - forced expiratory volume in 1 second

FVC- forced vital capacity

PEFR - peak expiratory flow rate

FIVC - forced inspiratory vital capacity

PIFR - peak inspiratory flow rate (spirometry)

Table 4.2. Correlation scores (R^2) between PIFR and audio-based features.

	F_{25}	F_{50}	F_{75}	P_{ave}	MAD	RMS
Diskus	0.80	0.85	0.84	0.77	0.59	0.55
Turbuhaler	0.64	0.58	0.80	0.70	0.54	0.56
Evohaler	0.41	0.37	0.18	0.75	0.60	0.60

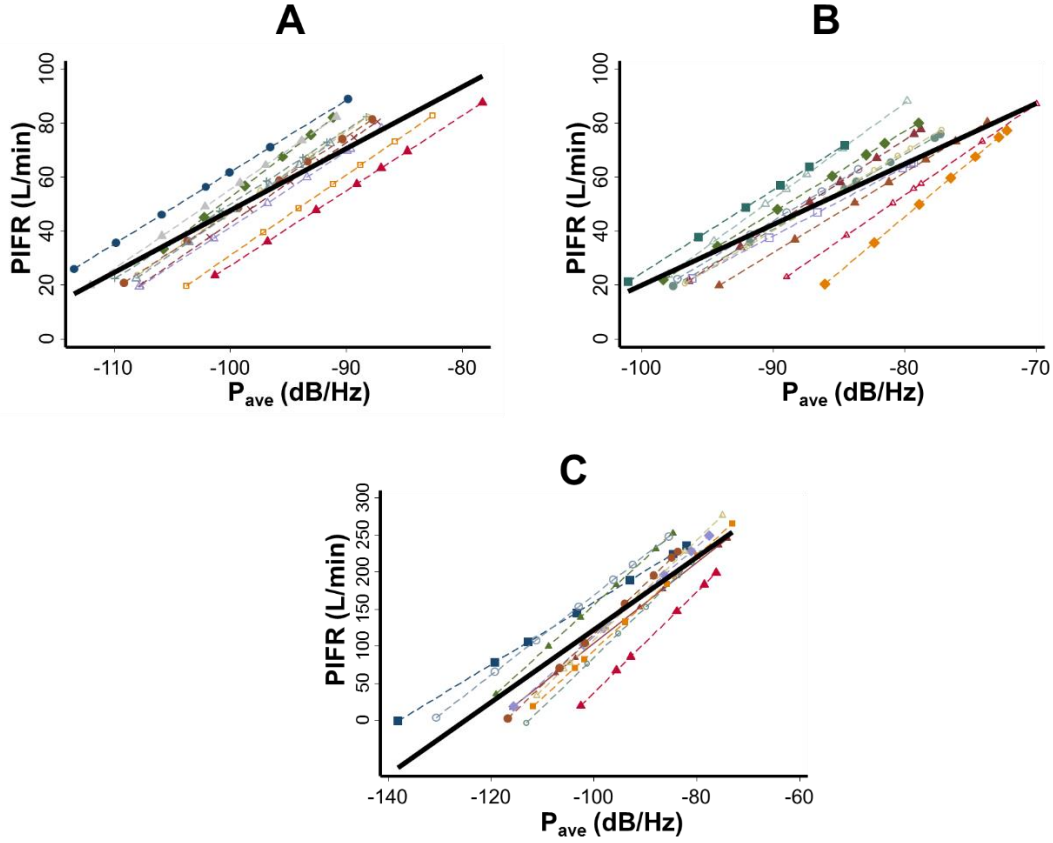


Figure 4.3. PIFR versus P_{ave} regression plots.

(A) Diskus, (B) Turbuhaler and (C) Evohaler. The plotted points are calculated PIFRs based on the regression equation for each participant. Each point represents the average (P_{ave}) values over 10 inhalation recordings for each PIFR. Each colour represents a different participant. The black line represents the overall regression model equation.

4.1.3.2 Variation of audio-based features

The results of the CoV analysis for all audio features for each inhaler are shown in Figure 4.4. It was observed that the average CoV of Group 1 features remained at approximately 20% in the Diskus and Turbuhaler across the entire IFR range. This level of variation in respiratory sounds compared favourably to previous literature (Sanchez and Vizcaya, 2003). It was found that Group 1 and Group 2 CoV values for the Evohaler were substantially higher below 100 L/min. This is due to minimal acoustic power generated at inhalations below 100 L/min. The average *MAD* and *RMS* CoV values tended to increase with flow rate in the Diskus and increase at 40-50 L/min in the Turbuhaler. Notably P_{ave} being transformed to the log domain minimised the CoV. However as P_{ave} (dB) was employed in the regression models, it was necessary to include it in the CoV analyses.

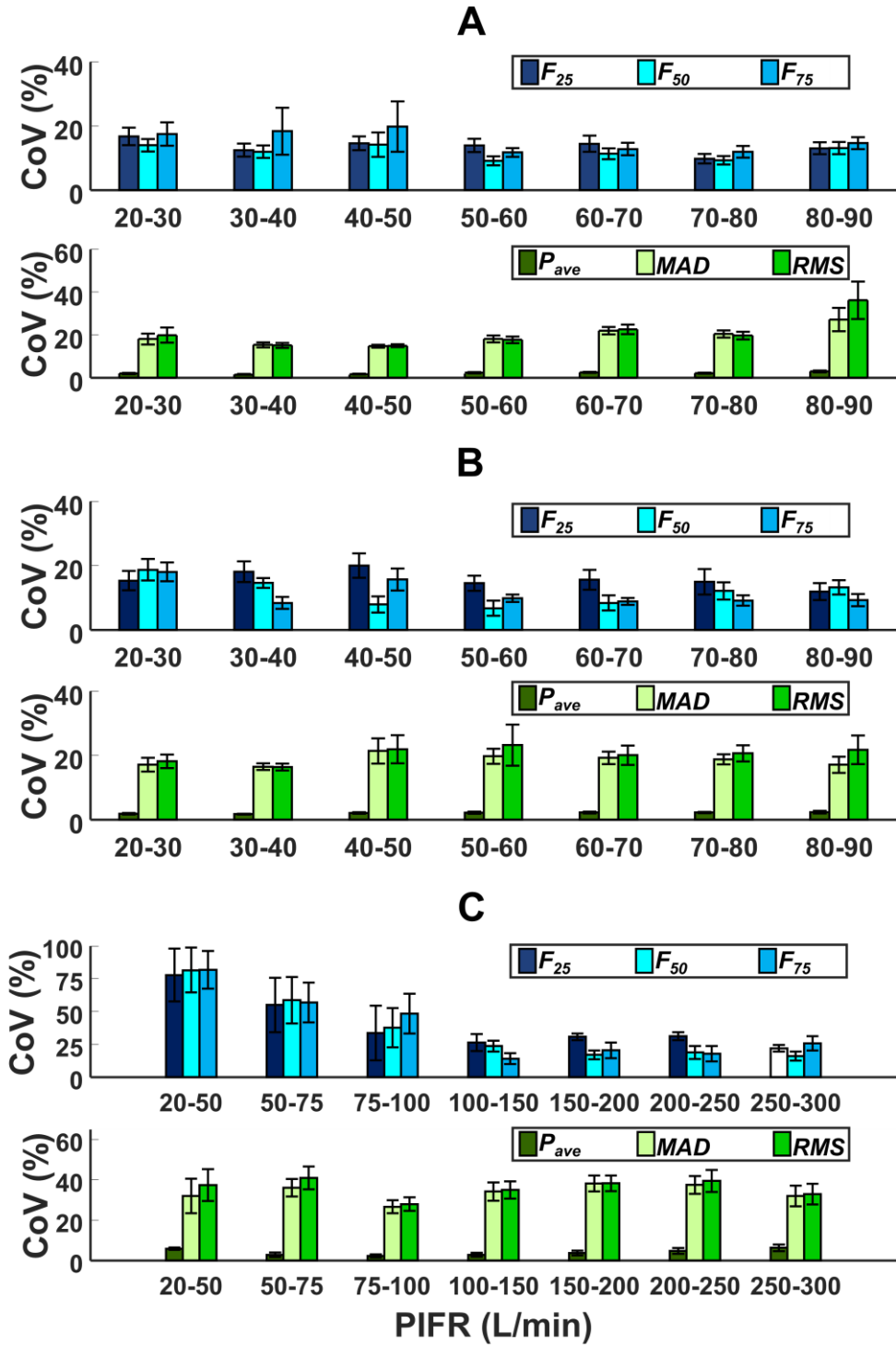


Figure 4.4. Average CoV of inhalation audio-based features.

Group 1 (top) and Group 2 (bottom) features mean CoV $\pm$ standard error across 11 participants for (A) Diskus, (B) Turbuhaler and (C) Evohaler.

4.1.3.3 Power spectral density peak frequency repeatability

The R^2 values from all participant data were divided into flow bands to determine the repeatability of the position of the peak frequencies in the PSD across different flow rates. Figure 4.5 displays the distribution of R^2 values for all participants relating to how all the PSD curves correlate with each other across all flow rates for each inhaler. All R^2 values for the Diskus, Turbuhaler and Evohaler were statistically significant ($p < 0.001$). An example of the PSD estimates of 10 inhalations from one participant for each inhaler can be found in Figure A1 (Appendix A). Moreover, the error bars in Figure 4.5 indicate that the PSDs of Evohaler pMDI inhalation audio signals were not as repeatable across the different flow ranges as was observed in the Diskus DPI and Turbuhaler DPI. This was most likely due to limited acoustic power at lower flow rates in the Evohaler pMDI.

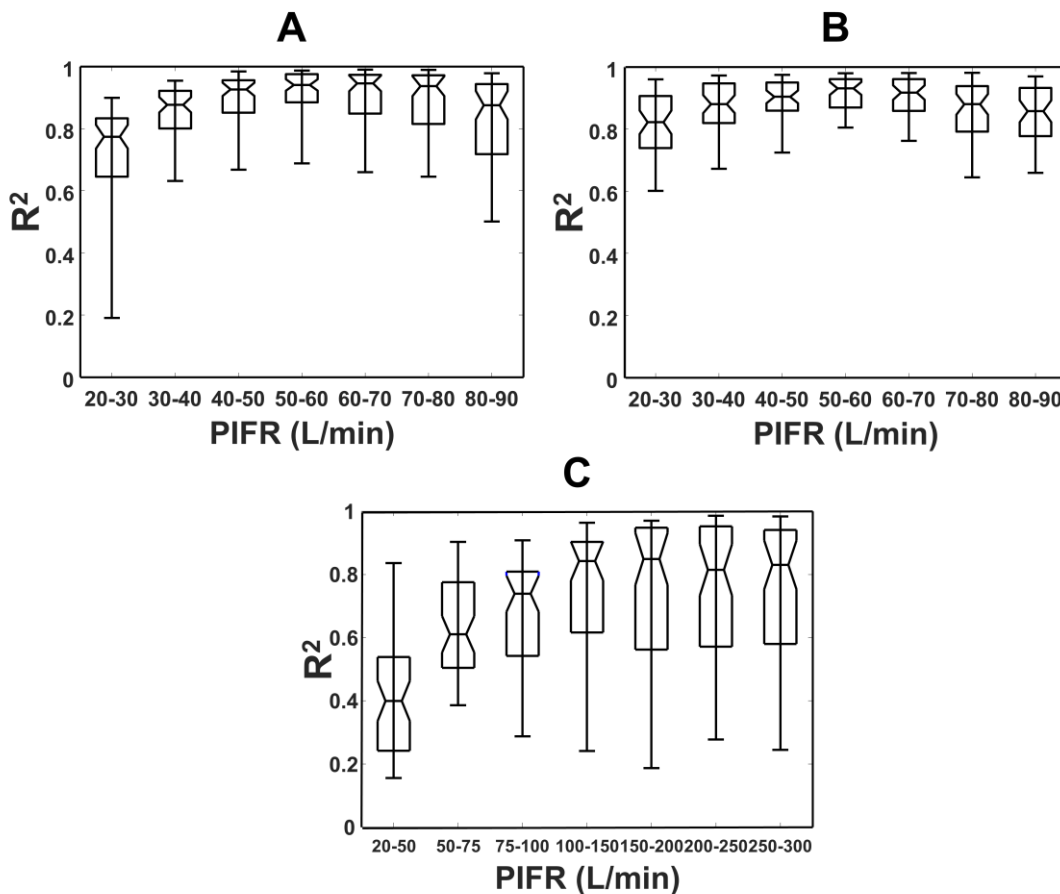


Figure 4.5. Boxplot of R^2 highlighting repeatability of peak frequencies of inhaler inhalation power spectral density.

Boxplot displaying 95% confidence interval notches of the median, the 25th and 75th percentile, and the 95% population (error bars) of R^2 values demonstrating spectral profile consistency across all IFR bands within each participant in (A) Diskus, (B) Turbuhaler and (C) Evohaler. All R^2 values were statistically significant ($p < 0.001$)

4.1.4 Discussion

All audio-based features employed were observed to be statistically significantly correlated with PIFR ($p < 0.001$). It was shown in this study for the first time that quartile frequency features that characterise the distribution of power across the PSD of inhalation sounds may be employed to estimate PIFR during inhaler use. This is based on the fact that as the flow rate of an inhalation increases, there is an increased emphasis on higher frequencies in the PSD which can be quantified using quartile frequencies. This is evident from Figure 4.2.

The P_{ave} feature was noted to generate the most consistent correlation with PIFR across all inhalers making it a reliable feature for PIFR estimation through inhalers. It has been previously reported that flow rate and acoustic power are strongly significantly correlated; therefore this result was expected (Yee Leng and Moussavi, 2002). The Turbuhaler generated the highest acoustic power, within the recommended flow rate ranges, followed by the Diskus and Evohaler. This behaviour can be observed in Figure 4.2. It also emphasises how the airflow resistance of inhaler devices affects the turbulent energy generated during inhalations. This has a direct impact on the acoustic power of inhalation sounds.

It was also observed from Figure 4.3 that there was some variability across participants in terms of inhalation audio feature values. This may suggest that audio features may vary from person to person even when the effects of sex, age and height are limited. Personalising future algorithms for PIFR estimation based on acoustic measurements may be more suitable if these methods are to be translated to a wearable device for inhaler users.

Temporal audio features (MAD and RMS) generated higher CoV compared to spectral features (F_{25} , F_{50} , F_{75} and P_{ave}), particularly in the Diskus and Turbuhaler. This may suggest that power-based features are more strongly significantly correlated with flow rate in the log domain, such as the P_{ave} feature. There was a noticeable difference between the variation of quartile frequency features (Group 1) in the Evohaler below 100 L/min and above 100 L/min. This is due to limited turbulent airflow existing in the Evohaler at flow rates below 100 L/min. The inhalation sounds were almost inaudible at lower flow rates resulting in poor acoustic measurements. This finding highlights the challenge of employing non-contact audio-based methods to objectively measure PIFR below 100 L/min in the Evohaler in future clinical applications. This is an important finding

considering that the recommended flow rate to obtain maximum therapeutic effect from pMDIs is <90 L/min.

It was demonstrated that the position of peak frequencies in the PSD of inhaler inhalation sounds remained consistent regardless of flow rate. This is an interesting finding as it compares favourably to previous studies that characterised normal breath sounds from the trachea and chest wall (Sanchez and Vizcaya, 2003; Beck *et al.*, 2005). This information will be of significant value for future algorithmic development in automatically detecting inhalation sound events.

There are a few limitations to this study. Firstly, the study recruited a small number of healthy participants which limits the generalisation of the results. This number of participants is however comparable to previous studies in inhaler inhalation acoustics (Holmes *et al.*, 2013c). Previous studies also recruited healthy participants to characterise respiratory sounds (Sanchez and Vizcaya, 2003; Mahagnah and Gavriely, 1994; Gavriely *et al.*, 1995). In addition, over 2,000 inhalation recordings were obtained in this study providing sufficient acoustic estimations to support the efficacy of this method. Secondly, the inhaler recordings were obtained in a soundproof environment which does not relate to realistic acoustic environments. The soundproof environment allowed for the acquisition of inhaler inhalation sounds with minimal background noise to study the acoustic properties of inhaler inhalation sounds. Finally, although quartile frequencies showed the strongest correlation with PIFR in the DPIs used in this study, it is not yet known if the PSD of inhalation sounds differ across a larger cohort of users. This may affect the use of quartile frequencies to estimate PIFR using a generalised model in future clinical applications. Future studies will investigate if the PSD of inhalation sounds remains consistent across users.

The INCA device is currently the only audio recording device available to acquire data for audio-based monitoring of adherence for DPIs. At present it is designed for the Diskus DPI only, it must be attached to the inhaler, and is limited to an 8 kHz sampling rate and 8 bits per sample resolution (Holmes *et al.*, 2014a). In this study, in order to gain a greater understanding of the acoustic properties of inhaler inhalation sounds, a non-contact high quality microphone (sampling rate of 44.1 kHz and 16 bits per sample resolution) was placed distant to the inhaler (5 cm) to record inhalation sounds proximal to the mouthpiece of the inhalers. The experimental setup aimed to simulate a wearable audio recording device for patients that use inhalers. Future wearable devices for monitoring inhaler use may be activated (to record inhaler audio) through proximity

sensors placed on the inhaler rather than relying on the mechanical function of the inhaler to activate an audio recording device. This means that there would be no need to design inhaler-specific monitoring devices in future.

Monitoring inhaler user technique in patients currently relies heavily on subjective checklists from healthcare professionals, quality of life questionnaires and self-reports from patients regarding their inhaler use (Burgess *et al.*, 2011). The clinical significance of this study lies in developing new novel objective methods to monitor inhalation technique in a range of different inhalers based on non-contact acoustic measurements. Objective monitoring of user technique in both pMDIs and DPIs, specifically inhalation technique, may improve the clinical efficacy of inhalers. It may also assist healthcare professionals in selecting an appropriate inhaler for patients depending on their PIFR through an inhaler. This may improve overall quality of life for patients using inhalers. However, further investigation is required to determine how audio-based features of inhalation sounds may change across users and different inhaler devices in order to further improve audio-based monitoring of inhaler adherence.

4.2 Quantifying the Effects of the User and the Inhaler Device on Inhaler Inhalation Audio-Based Features

4.2.1 Introduction

It has been previously discussed in Chapter 2 how gender and anthropometric features (weight, height etc.) may influence audio-based features of respiratory sounds recorded using chest wall and tracheal microphones. However, little is known regarding the effect of gender and anthropometric measurements on the audio-based features of inhaler inhalation sounds. This may be important to consider when developing audio-based algorithms to analyse inhaler audio recordings across a large cohort of users. Audio-based monitoring systems show promising opportunities to objectively assess patient inhaler user technique. However, in order to further improve audio-based monitoring of inhaler use, it is important to understand how audio-based features of inhalation sounds change across different inhaler devices. Therefore, there is a need to statistically compare inhalation audio-based features across different inhalers. Furthermore, tracheal sounds have yet to be analysed during inhaler use. It is of interest to compare tracheal inhalation

sounds to those recorded using a non-contact microphone as tracheal microphones may offer another means of acquiring inhalation sounds to monitor inhaler inhalation technique.

The aim of this pilot study was to investigate the relationship between gender, BMI, height and weight and audio-based features of inhaler inhalation sounds. It was hypothesised that there may be differences in audio-based features of inhaler inhalation sounds recorded using both tracheal and non-contact microphones across different users according to gender and anthropometric features. Furthermore, this study aimed to investigate whether audio-based features of inhaler inhalation sounds are significantly different across different inhaler devices. It was also hypothesised that inhalation audio-based features are influenced by the inhaler design.

4.2.2 Methods

4.2.2.1 Study participants

Sixteen healthy participants (nine males/seven females) were recruited for this study. Baseline lung function tests were performed according to ATS/ERS standards to confirm that all participants had normal respiratory health (Miller *et al.*, 2005). Further details on study participants are presented in Table 4.3.

Table 4.3. Participant anthropometric information (mean $\pm$ standard deviation).

	Male (n=9)	Female (n=7)
Age (Years)	25.8 $\pm$ 1	29 $\pm$ 4
Weight (kg)	77.5 $\pm$ 10.5	64.6 $\pm$ 9.8
Height (cm)	177 $\pm$ 6.1	167 $\pm$ 7.2
BMI	24.5 $\pm$ 2.2	23.4 $\pm$ 4.8

4.2.2.2 Experimental setup

Four commonly used inhalers were employed in this study; Turbuhaler DPI, Diskus DPI, Ellipta DPI and Evohaler DPI. Each inhaler was positioned inside a modified airtight adapter similar to the setup described in Figure 4.1. A Sony ECM-77B electret

microphone [Sony Electronics Inc., Tokyo, Japan] (flat frequency response between 40 Hz–20 kHz) was positioned inside an air-coupled chamber and placed directly over the suprasternal notch on the trachea. The air-coupled chamber was designed based on recommendations reported in (Kraman *et al.*, 1995). The tracheal microphone was held securely in place with medical adhesive tape. An omnidirectional non-contact condenser microphone (BSWA SM4201 [BSWA Technology Co., Beijing, China]) was positioned 5 cm from the inhaler mouthpiece to record the audio signals of inhalations at the inhaler mouthpiece. The microphone used had a flat frequency response in the range of 20 Hz–20 kHz. Both microphones were connected to a PreSonus AudioBox 44VSL audio interface [PreSonus, Baton Rouge, USA] and were recorded with Adobe Audition software. The audio signals were sampled at 44.1 kHz with 16 bits per sample resolution.

4.2.2.3 Test procedure

Participants were instructed to inhale through each inhaler with an IFR of 60 ± 5 L/min, while inhaler inhalation sounds were recorded with the distant and tracheal microphones. This was repeated until five recordings of inhalations were obtained in the flow range required. This was performed for all four inhalers. Participants were also asked to inhale at their PIFR also for five trials.

Audio analysis was only performed on 60 ± 5 L/min. This guaranteed that inhalations were flow matched across all participants. Having the inhalation sounds flow-matched across participants was important as it was observed in Section 4.1 that inhalation audio features are directly influenced by flow rate.

4.2.2.4 Audio signal pre-processing and feature extraction

Both distant (non-contact) and tracheal (contact) inhalation audio signals were segmented from the audio recordings using aural and visual methods. The PSD was estimated for each inhalation audio signal as previously described in section 4.1.2. All five PSD estimations were then averaged to produce one spectral estimation of 60 ± 5 L/min for each participant for each inhaler. A five second recording of background noise during breath hold was obtained to estimate noise for each participant. The audio signals of all inhalations, both non-contact and tracheal recordings, were high pass filtered with a cut-off frequency of 200 Hz to remove low frequency noise from the non-contact distant recordings and to remove heart sounds from the tracheal recordings (Sovijarvi *et al.*,

2000). Spectral subtraction was then employed to remove any stationary frequency background noise.

Spectral features that were extracted from the PSD included quartile frequencies (F_{25} , F_{50} & F_{75}), the frequency of maximum power (F_{max}) and the average power across the PSD (P_{ave}). Little is known regarding the spectral properties of inhaler inhalation sounds in the literature, therefore spectral analyses of non-contact inhaler inhalation sounds were performed on three frequency bands: 200-22,050 Hz, 200-7,350 Hz and 200-2,450 Hz. Spectral power of tracheal breath sounds ranges up to 2,500 Hz (Kraman *et al.*, 1998), however, inhaler inhalation tracheal sounds have yet to be investigated. Therefore, analyses were performed on three frequency bands for tracheal sounds: 200-7,350 Hz, 200-2,450 Hz and 200-1,225 Hz.

4.2.2.5 Statistical analyses of inhaler inhalation sounds

A 2-sample t-test was performed to determine statistically significant differences in audio features (both non-contact and tracheal) between males and females. Linear regression was performed in Minitab V16.1 to investigate the correlation between each audio feature and PIFR with height, weight and BMI measurements from all participants combined (n=16). Age was not included in this study as the participant age range (24-35) was deemed too narrow for statistical analysis of breath sounds. Moreover, correlation analysis was performed separately for each factor as the dataset was deemed not large enough to consider all factors within one regression model. A one-way ANOVA was also performed on each audio feature across all inhalers to investigate if audio features are influenced by the inhaler design.

4.2.3 Results

A total of 320 non-contact (distant) and tracheal inhaler inhalation audio recordings (60 ± 5 L/min) and 320 PIFR measurements were obtained for this study to analyse the influences of gender and anthropometric features on inhaler inhalation sounds and PIFR. The results from the 2-sample t-tests (p-value) and linear regression (R^2) are presented in Table 4.4. Only statistically significant results ($p < 0.05$) after Bonferroni correction are presented. PIFR was not significantly correlated with height, weight or BMI and therefore was excluded from Table 4.4. The one-way ANOVA analysis indicated that audio features are highly statistically significantly different between inhalers ($p < 0.001$). This

Table 4.4. Statistical analyses of non-contact and tracheal inspiratory inhaler sounds with gender, height, weight and BMI.

			F_{25}	F_{50}	F_{75}	F_{max}	P_{ave}
Turbuhaler	Non-contact	Gender (p-value)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	0.002**
		Height (R^2)	<i>n.s</i>	0.25*	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Weight (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		BMI (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
	Tracheal	Gender (p-value)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Height (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Weight (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		BMI (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
Diskus	Non-contact	Gender (p-value)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	0.001**
		Height (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	0.23*
		Weight (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	0.44*
		BMI (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	0.38*
	Tracheal	Gender (p-value)	0.026*	0.048*	0.034*	<i>n.s</i>	<i>n.s</i>
		Height (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Weight (R^2)	0.34*	<i>n.s</i>	<i>n.s</i>	0.2*	<i>n.s</i>
		BMI (R^2)	0.5*	<i>n.s</i>	0.24*	0.44*	<i>n.s</i>
Ellipta	Non-contact	Gender (p-value)	0.012*	0.019*	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Height (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Weight (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		BMI (R^2)	<i>n.s</i>	<i>n.s</i>	0.21*	<i>n.s</i>	<i>n.s</i>
	Tracheal	Gender (p-value)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Height (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Weight (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	0.36*	0.39*
		BMI (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	0.33*	<i>n.s</i>
Evohaler	Non-contact	Gender (p-value)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Height (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Weight (R^2)	<i>n.s</i>	<i>n.s</i>	0.27*	<i>n.s</i>	<i>n.s</i>
		BMI (R^2)	<i>n.s</i>	<i>n.s</i>	0.42*	<i>n.s</i>	<i>n.s</i>
	Tracheal	Gender (p-value)	0.007**	<i>n.s</i>	0.008**	<i>n.s</i>	<i>n.s</i>
		Height (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		Weight (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>
		BMI (R^2)	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>	<i>n.s</i>

**p<0.01, *p<0.05, *n.s* – not significant

suggests that audio features are influenced by the inhaler design. It was noted that audio features depend on the inhaler resistance to airflow. The Turbuhaler DPI has the most resistance to airflow followed by the Ellipta DPI and Diskus DPI (which are quite similar), followed by the Evohaler pMDI. Figure 4.6 shows an example of the relationship between P_{ave} and inhaler airflow resistance in non-contact (distant) and tracheal audio data.

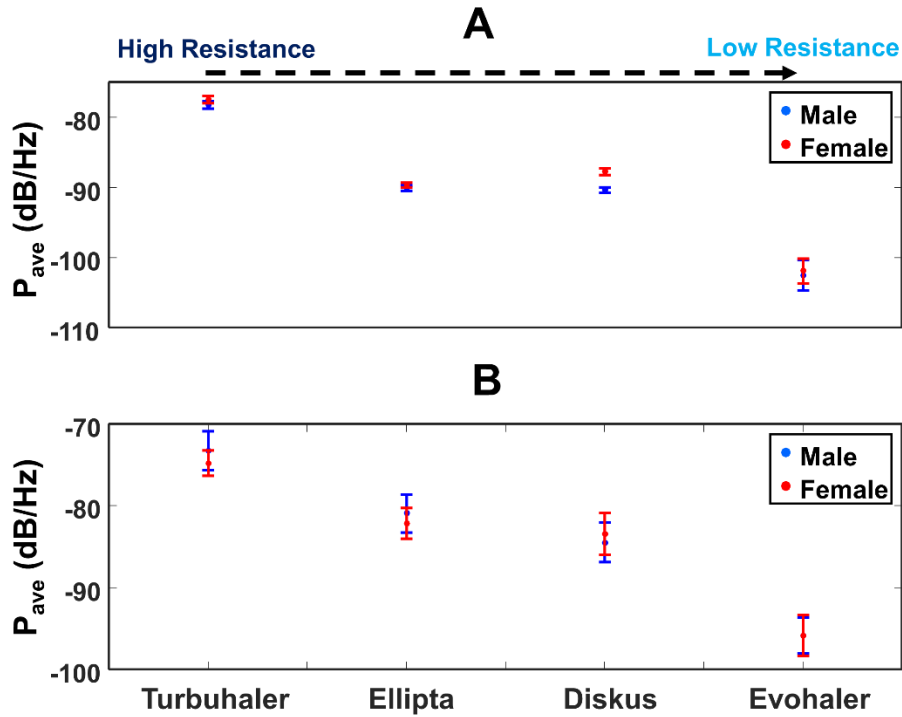


Figure 4.6. Average P_{ave} values ($\pm$ std. error) of inhaler inhalations for male and female groups.

(A) Distant microphone (200-22,050 Hz) and (B) tracheal microphone (200-7,350 Hz) recordings of inhalation sounds at 60-70 L/min for Turbuhaler, Ellipta, Diskus and Evohaler. The Turbuhaler generates the largest power as it has the highest airflow resistance. This is followed by the Ellipta and Diskus inhalers which have medium airflow resistance and finally the pMDI which has the lowest airflow resistance. The fact that there exists a noticeable difference between gender groups only for Diskus non-contact recordings may highlight the effect of the mouth seal around the inhaler mouthpiece rather than the influence of gender.

4.2.4 Discussion

This study investigated the influence of gender, height, weight and BMI on the spectral features of non-contact and tracheal inhaler inhalation sounds from healthy participants. The results presented in Table 4.4 suggest that gender and anthropometric features may influence the spectral properties of inhaler sounds, particularly in tracheal sounds.

Tracheal recordings were employed in this pilot study to compare against the non-contact microphones. It is evident from Figure 4.6 that tracheal audio features generate more variation across participants in comparison to non-contact recordings. Therefore, it may be argued that tracheal microphones may not be suitable for monitoring inhaler use remotely as audio-based methods for analysing tracheal inhalation sounds may need to be personalised to each user. Differences between gender groups were observed in

quartile frequencies in the tracheal data for the Diskus and Evohaler with females generating higher F_{25} , F_{50} and F_{75} frequencies in both inhalers. There were no significant differences between males and females in the Ellipta in the tracheal sounds however a larger cohort of participants may be required to quantify this further. As previously mentioned, the male group had a higher average weight in comparison to the female group which may be a factor considering weight significantly correlated with tracheal quartile frequencies in the Diskus and Ellipta inhalers. It was observed that the Ellipta generated higher F_{75} values in comparison to other inhalers. This suggests that higher frequencies may be of importance for future automatic detection of inhalation sounds in the Ellipta DPI in future applications.

There were some limitations to this study. The number of participants was relatively small ($n=16$) to quantify the effects of specific factors such as gender and anthropometric features. However, this pilot study was carried out to explore the possibility of differences existing in inhalation audio-based features across different inhaler designs and the user. Future studies should investigate the findings of this pilot study with a larger cohort of patients with respiratory diseases. In addition, the inhalation flow profile could have a significant effect on the inhalation audio-based features. It was reported in Chapter 4 Section 4.1 that audio-based features are correlated with flow rate (Taylor *et al.*, 2016b). Therefore, the audio-based features may be influenced by the inhalation flow profile, not just PIFR. However, PIFR was deemed as a sufficient flow parameter to compare inhalations in this pilot study. However, inhalation flow profiles should be considered in future studies.

Although the audio features employed in this study have been previously used in the research area of respiratory acoustics (Hossain and Moussavi, 2004; Yee Leng and Moussavi, 2002; Malmberg *et al.*, 1994), there are some limitations to applying these features to non-contact inhaler sounds. It was observed that all participants recorded similar values for F_{max} in the non-contact recordings for the Turbuhaler at approximately $2,790 \pm 6$ Hz when the 200-22,050 Hz and 200-7,350 Hz bands were analysed. This is because this frequency is an acoustic signature of the Turbuhaler design and therefore does not represent the true F_{max} values for each individual's physiological inhalation signal. Using different frequency bands limited these effects by ignoring 2,790 Hz. It is evident from Figure 4.6 that the audio based features are clearly influenced by the inhaler design. In this particular example, the P_{ave} feature is influenced by the resistance of the inhaler. Even though all inhalations had equivalent flow rate for each inhaler, the

turbulent energy generated at 60 L/min in each inhaler differed, therefore, this influences the audio features. This is important to note for future audio-based classification algorithms for different inhalers

Non-contact and tracheal inhaler audio data have different spectral properties and further research is required to investigate this further in larger cohort of real patients with respiratory disease. Moreover, it has yet to be reported if airway narrowing (a decline in lung function) in asthma patients translates to changes in audio features of inhalation inhaler sounds. Future research is required to determine the influence of lung function on inhaler inhalation audio features.

4.3 Chapter Conclusion

To conclude, in this chapter, it was observed that audio-based features of inhalation sounds, recorded using a non-contact microphone at a relatively high sampling rate and bit resolution (compared to the INCA system), were statistically significantly correlated with PIFR. Therefore, non-contact audio-based methods may be employed to objectively measure PIFR in future clinical applications. Quartile frequencies generated strong correlations with PIFR in DPIs. It was found that the average power generated the most consistent correlation with PIFR in the Diskus DPI, Turbuhaler DPI and Evohaler pMDI. The variation of inhalation audio features differed greatly between DPIs and pMDIs. This highlighted the lack of acoustic energy generated in the pMDI during inhalation which may make it challenging to objectively measure PIFR in pMDIs using audio-based methods. The position of peak frequencies in the PSD of inhaler inhalation sounds was observed to be repeatable regardless of flow rate. The results of the pilot study presented in Section 4.2 of this chapter provide evidence suggesting that non-contact inhalation sounds recorded at the mouthpiece may be influenced by the inhaler design and the user. However, tracheal sounds generate higher inter-subject variability and may not be suitable for remotely monitoring inhaler inhalation technique as a result.

The clinical impact of the studies presented in this chapter is associated with the potential of non-contact audio-based methods being implemented into future clinical applications to remotely assess inhalation technique, specifically PIFR. This may help healthcare professionals train patients to improve their inhalation technique. Furthermore, it may help healthcare professional's select a suitable inhaler device for patients according to their inhalation technique. Objectively assessing inhalation technique may be used to

quantify drug delivery from inhalers also and can lead to more enhanced precision medicine in treating chronic respiratory diseases. Future research should investigate the use of non-contact audio-based methods to assess patient inhalation technique using audio recordings from patients with chronic respiratory diseases.

Chapter 5. Audio-Based Objective Measurement of Peak Inspiratory Flow Rate during Patient Inhaler Use and its Application to Detecting Changes in Lung Function

The studies described in this chapter investigate research questions 7-12 from Chapter 3. The findings reported in Chapter 4 highlighted the potential use of a range of temporal and spectral audio-based features to objectively assess PIFR during inhaler use. There is a need to investigate the use of non-contact audio-based features to objectively assess inhalation technique in patients with chronic respiratory diseases such as asthma and COPD. It has also yet to be investigated whether patients' PIFR changes according to their lung function and whether estimating PIFR using audio-based methods can monitor these changes in respiratory health during an exacerbation and after receiving treatment. In the study presented in Section 5.1 of this chapter, non-contact audio-based methods are employed to investigate the relationship between inhalation audio-based features and PIFR from the Diskus DPI in a cohort of patients with different respiratory conditions including asthma and COPD. The spectral properties of inhalation sounds are investigated within and across patients to determine whether spectral features are robust at estimating PIFR across patients using a generalised approach. In the study presented in Section 5.2 of this chapter, a pilot study investigation into the relationship between lung function, inhaler PIFR and inhalation audio-based features is presented in order to determine if audio-based methods of estimating PIFR have the potential to detect exacerbations and improvements in respiratory health over the course of treatment.

The studies presented in this chapter have resulted in the following peer-reviewed publications;

- **Taylor T E**, De Looze C, MacHale P, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2016 Characterization of Patient Inhaler Inhalation Sounds Using Non-contact and Tracheal Microphones. *Biomedical Physics & Engineering Express* 2(5):055021.
- McCartan T A, **Taylor T E**, Sulaiman I, Costello R W and Reilly R B 2016 7 Changes in inhaler inhalation acoustic features during induced bronchoconstriction: A pilot study. In: *Engineering in Medicine and Biology Society (EMBC), 2016 38th Annual International Conference of the IEEE*, Orlando, Florida, USA.

5.1 Characterisation of Patient Inhaler Inhalation Sounds Using Non-Contact and Tracheal Microphones

5.1.1 Introduction

The study reported in Chapter 4 Section 4.1 employed non-contact audio methods (microphone placed distant to the inhaler) to estimate PIFR from both DPIs and pMDIs using a cohort of healthy participants. Inhaler inhalation sounds were recorded using a larger sampling rate of 44.1 kHz and bit resolution of 16 bits per sample compared to previous inhaler flow audio-based estimation studies (Holmes *et al.*, 2013c; Holmes *et al.*, 2013b; D'Arcy *et al.*, 2014; Seheult *et al.*, 2014b). Chapter 4 reported that audio-based features of inhalations were significantly linearly correlated with PIFR and that the position of peak frequencies in the PSD of inhalation sounds remained unchanged regardless of flow rate at an intra-subject level. However, there is a need to investigate the use of non-contact methods to estimate PIFR from patient inhaler audio recordings. Furthermore, it has yet to be reported whether the position of peak frequencies in the PSD of inhaler inhalations is repeatable across patients and whether this affects the use of spectral features to estimate PIFR.

Audio-based features of tracheal recordings of normal breath sounds (free from adventitious sounds) have been reported to be also correlated with flow rate as discussed

in Chapter 2. The PSD profile of tracheal sounds has also been reported to be repeatable (in terms of the position of peak frequencies in the PSD profile) at an intra-subject level (Sanchez and Vizcaya, 2003). However, this has yet to be investigated for tracheal inhaler inhalation sounds. As tracheal sounds contain pertinent physiological information, it is of interest to compare the acoustic properties of tracheal inhaler inhalation sounds to sounds recorded using a non-contact microphone which may represent a wearable monitoring device for inhalers.

This study aimed to investigate the correlation between PIFR and audio-based features of inhaler inhalation sounds recorded from non-contact and tracheal microphones from patients with respiratory conditions such as asthma and COPD. This study also aimed to further characterise inhaler inhalation sounds by investigating the repeatability of the positions of peak frequencies in the PSD of inhaler inhalations across patients accounting for age, gender, BMI and lung function. It was hypothesised that non-contact methods would generate stronger correlations with PIFR than tracheal sounds, due to higher inter-patient variability in tracheal sounds, and could therefore be employed to monitor patient inhalation technique in future inhaler monitoring devices. It was also hypothesised that differences may be observed in the PSD of inhaler inhalation sounds across patients, which may influence the use of spectral features to estimate PIFR.

5.1.2 Methods

5.1.2.1 Patient recruitment

Fifty three out-patients with asthma (n=26), COPD (n=14) and other respiratory conditions (ORC) (n=13), such as OSA and chronic cough were recruited from respiratory clinics at Beaumont Hospital, Dublin, Ireland. It was of interest to determine the acoustic properties of inhalations across a wide variety of patients with upper and lower respiratory conditions. Patients were included for this study if they were over 16 years of age and were capable of giving informed consent. All patients were trained on how to use the Diskus inhaler. Baseline spirometry was performed on all patients according to ATS/ERS recommendations (Miller *et al.*, 2005). The study was approved by the Hospital Ethics Committee at Beaumont Hospital, Dublin, Ireland.

5.1.2.2 Experimental setup

A Diskus DPI was placed inside a custom built polyethylene terephthalate airtight container which was connected to a Vitalograph Pneumotrac 6800 spirometer (Figure 5.1) similar to the setup used in Chapter 4. No drug was contained inside of the inhaler. A BSWA SM4201 phantom powered condenser non-contact microphone was positioned 5 cm to the side of the inhaler facing towards the centre of the mouthpiece to record inhalations. This 5 cm distance simulated the distance between a smart device (watch or ring device) on a patient to the patient's mouth during inhaler inhalation.

The inhaler airtight container, non-contact microphone and spirometer were all fixed onto a custom built support board (Figure 5.1). A healthcare professional could then hold the support board as patients inhaled through the inhaler. The support board also had a handle attached underneath to allow patients obtain a firm grip of the apparatus for support. Figure 5.1 illustrates the inhaler recording setup.

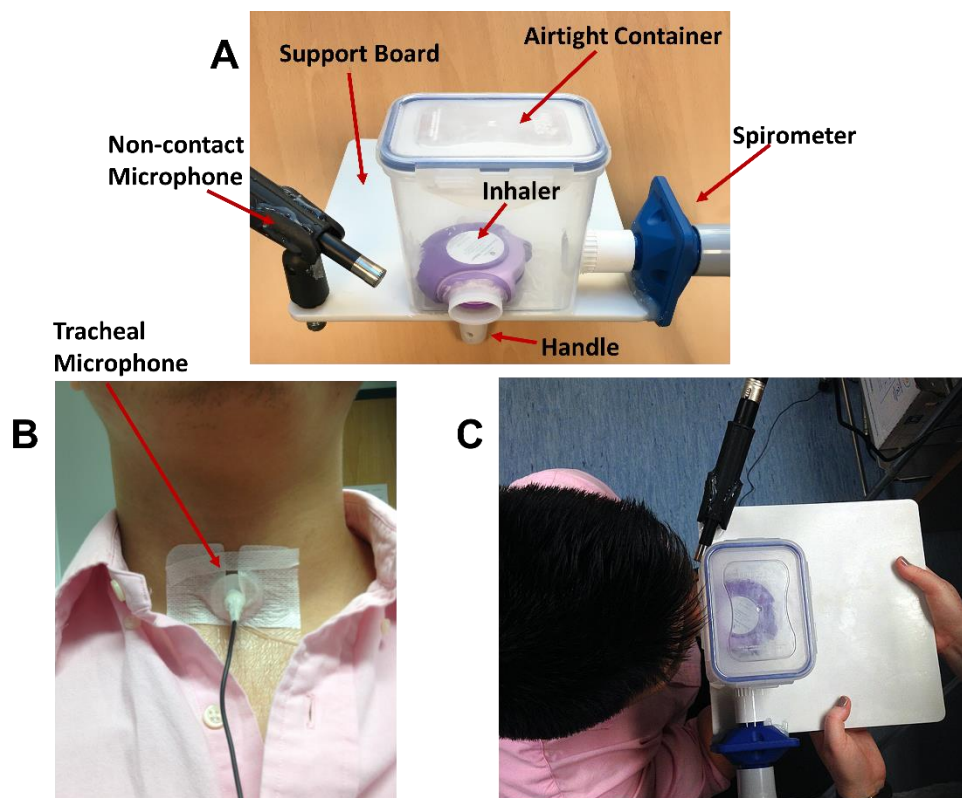


Figure 5.1. Pictures of patient inhaler recording experimental setup.

(A) Labelled experimental setup, (B) tracheal microphone on patient and (C) healthcare professional assisting patient during inhaler inhalation recording.

A Sony ECM-77B electret microphone was positioned inside a custom 3D printed air-coupled chamber and placed over the suprasternal notch of patients to record tracheal inhalation sounds similar to Section 4.2 in Chapter 4 (Figure 5.1B). This microphone has been employed in previous studies that analysed lung and tracheal sounds (Yadollahi and Moussavi, 2011; Taplidou and Hadjileontiadis, 2007). The tracheal microphone was held securely in place using medical adhesive tape. Both non-contact and tracheal microphones were connected to a PreSonus AudioBox 44VSL and were recorded simultaneously in stereo using Adobe Audition. Non-contact and tracheal audio signals were sampled at 44.1 kHz with a resolution of 16 bits per sample. All recordings took place in Beaumont Hospital, Dublin, Ireland.

5.1.2.3 Patient inhaler inhalation protocol

Once baseline spirometry was performed, each patient was instructed to inhale through the mouthpiece of the Diskus at their maximal flow rate for as long as possible and were then asked to hold their breath for two to three seconds if possible. This was repeated until two to four inhalation recordings were obtained. The number of inhalations was not equal for all patients due to time constraints in the clinic and also fatigue in some patients, particularly elderly patients. Breaks of two to five minutes were given to patients between each inhalation to eliminate the effect of fatigue on the inhalation sounds. If a patient had inspiratory wheeze or coughed during an inhalation, the audio recording was discarded.

5.1.2.4 Audio signal processing

The DC offset was removed from audio signals by subtracting the mean amplitude of the entire inhalation signal for every recording. All audio signals were high pass filtered with a cut-off frequency of 200 Hz. This cut-off frequency was chosen to remove low frequency noise from the non-contact audio signals and to remove heart sounds from the tracheal audio signals. Heart sounds consist of frequencies within 20-200 Hz (Sovijarvi *et al.*, 2000). Tracheal recordings of normal breathing sounds contain acoustic power primarily at lower frequencies up to 3,000 Hz (Reyes *et al.*, 2014; Reljin *et al.*, 2015). Tracheal sounds were low pass filtered below 7,000 Hz in this study to allow for higher frequencies to be obtained due to the additional turbulent energy created from the inhaler resistance during the forced inhalation manoeuvre. This cut off frequency also eliminated the effects of any higher frequencies from the sound generated at the mouthpiece of the

inhaler being picked up by the tracheal microphone. A range of audio-based features were then extracted from the inhaler inhalation audio signals. Figure 5.2 shows examples of the audio signals and spectrogram time-frequency representations of the inhalation sound recorded from the non-contact and tracheal microphones from a single patient. It is evident from Figure 5.2 that non-contact inhalation sounds contain a broader range of frequencies in comparison to tracheal inhalation sounds. This is due to the tissue of the suprasternal notch acting as a low pass filter on the tracheal sounds.

Spectral features

Inhalations were segmented using aural and visual methods as in previous studies (Holmes *et al.*, 2013c; Taylor *et al.*, 2016b). Welch's PSD of each inhalation audio signal was estimated using Equations (4.1), (4.2) and (4.3) (units in V^2/Hz). The PSD was also estimated for each patient's breath hold to estimate background noise in the recording

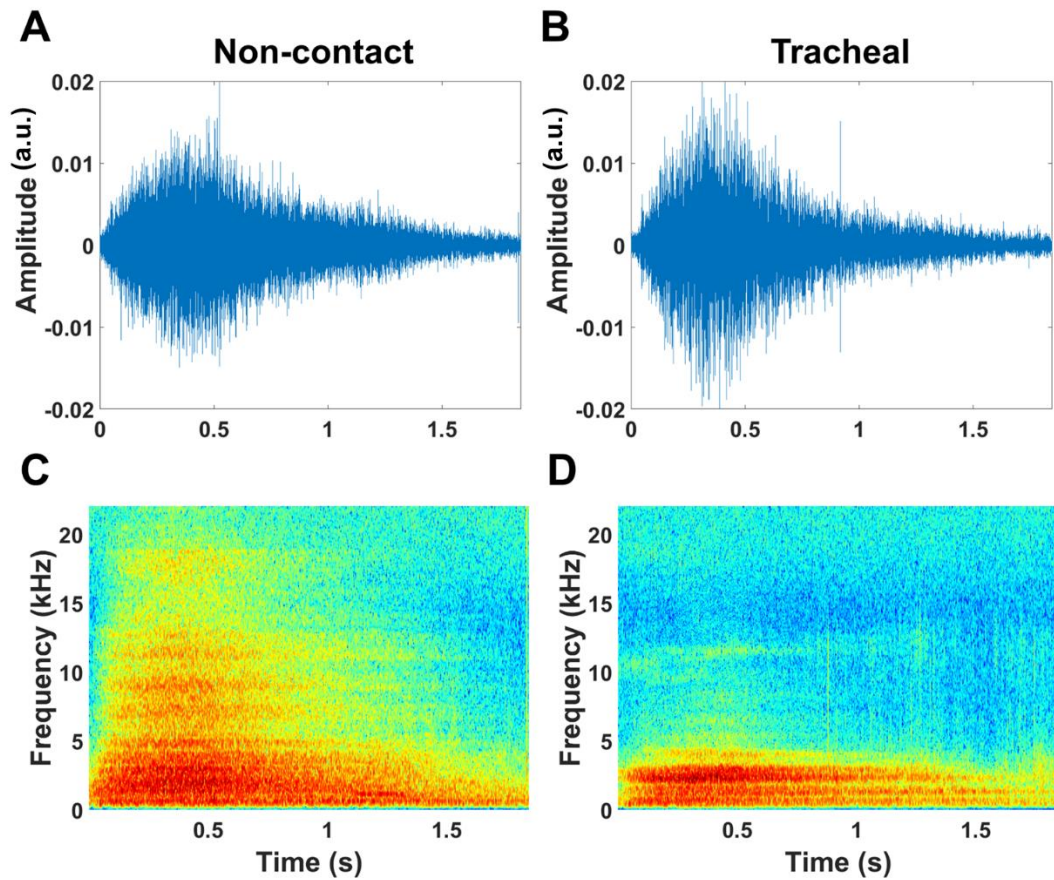


Figure 5.2. Audio time domain signals and spectrograms of inhaler inhalation sounds. (A) Non-contact and (B) tracheal inhalation recordings along with the non-contact recording spectrogram (C) and tracheal spectrogram (D) of an inhaler inhalation at a PIFR of 62 L/min from an asthma patient.

room. The background noise was then removed from the inhalation signals of each patient using spectral subtraction as performed in Chapter 4. This method has been employed in previous respiratory acoustics studies (Gavriely *et al.*, 1995; Malmberg *et al.*, 1995; Dafna *et al.*, 2013; Taylor *et al.*, 2016b).

Quartile frequencies were calculated from the inhalation PSD estimations (F_{25} , F_{50} and F_{75}). These features were included as they have been previously employed in inhaler inhalation acoustics studies to estimate PIFR (Taylor *et al.*, 2016b). Furthermore, they have been used to study variability of tracheal respiratory sounds longitudinally (Sanchez and Vizcaya, 2003). The average power of the PSD (P_{ave}) of the inhaler inhalations was employed in the audio-based feature set in this study as it was previously employed to estimate PIFR in the Diskus inhaler (Holmes *et al.*, 2013c; Taylor *et al.*, 2016b). Spectral power has also been employed in other acoustical estimation of respiratory flow studies (Yee Leng and Moussavi, 2002). The P_{ave} feature was computed from the PSD estimation and then converted to decibels (dB) using $10 \log_{10}(P_{ave})$ as previously done in Chapter 4.

Temporal features

The *MAD* and *RMS* features were employed in this study as calculated previously in Equations (4.4) and (4.5) of Chapter 4. The Shannon entropy (H) of the inhalation signals was employed in this study also as it has been employed previously to estimate flow rate and volume from tracheal recordings of normal breath sounds (Yadollahi and Moussavi, 2006a; Reyes *et al.*, 2014; Reljin *et al.*, 2015). Entropy is a measure of complexity or uncertainty of the inhalation audio signal. Entropy is computed by employing a probability density function (p) to estimate the probability of certain events or values of the audio signal. The probability density function of the inhalation signal may be computed using a histogram approach; however, Normal kernel density estimators give more accurate, smoother estimations of the probability density function. By applying multiple Gaussian kernel smoothing functions centred at different values of the signal, it obtains the number of observations of different values of the audio signal that fall within the window. This results in a more continuous estimation of the probability density function being obtained. The kernel function smooths out the contribution of an observed value of the signal across neighbouring values. The bandwidth of the kernel function is critical here as under/over smoothing the estimation may occur if the bandwidth is set too small/large. The Normal kernel estimator probability density function of each inhalation

audio signal was computed using the following equations (Silverman, 1981; Yadollahi and Moussavi, 2006b; Reyes *et al.*, 2014);

$$\hat{f}(x) = \frac{1}{n} \cdot \frac{1}{h} \sum_{i=1}^N K\left(\frac{x - x_i}{h}\right) \quad (5.1)$$

where x_i is the i^{th} observation of the audio signal x ,

N is the number of observations,

K is the Normal kernel function given as;

$$K(x) = \frac{1}{\sqrt{2\pi}} e^{-\frac{x^2}{2}} \quad (5.2)$$

h is the kernel bandwidth which was set to the optimum value by applying the following equation as was also performed in previous respiratory acoustics studies (Yadollahi and Moussavi, 2006b);

$$h = 1.06\sigma_x \cdot n^{\frac{1}{5}} \quad (5.3)$$

where σ_x is the standard deviation of the inhalation audio signal.

The numbers of observations for each value in the audio signal were then transformed to a probability density function by normalising each number by the sum of all observations in the kernel estimation. This ensured all values in the pdf summed to one. The Shannon entropy was then calculated from the normalised Normal kernel pdf using the following equation;

$$H(p) = - \sum_{i=1}^N p_i \log_2 p_i \quad (5.4)$$

where p is the pdf and N is the number of outcomes or bins of the pdf where $p_i, i = 1, \dots, N$.

5.1.2.5 Statistical analyses of inhaler inhalation sounds

Correlation between PIFR and inhalation audio-based features

Audio-based features were extracted from each patient's highest PIFR inhalation. The highest PIFR was selected as it represented the patient's best effort. A linear regression model was employed to determine the relationship between each audio-based feature and PIFR separately across all patients. The resulting linear regression model consisted of one inhalation from each patient to investigate the correlation between inhaler PIFR and inhalation audio-based features. Statistical outliers were removed from the regression analysis by removing observations that had standardised residual values of either greater than 2.5 or less than -2.5. It would be expected that approximately 1% of the data would lie outside of these limits. However, if more than 1% of the observations lay outside of these limits, then all of the observations outside of the standardised residual limits were removed as these observations may be deemed unacceptable for the regression analysis.

Inhalation PSD profile repeatability

PSDs were estimated for all inhalation signals for each patient. The correlation values (r) between PSD profiles at an intra-patient level were obtained using Pearson's Linear Correlation Coefficient as previously performed in Chapter 4 Section 4.1 (Taylor *et al.*, 2016b). The resulting r values obtained from each patient (comparing PSD profiles within patients) were grouped together and categorised as the intra-patient PSD correlation distribution. To analyse inter-patient correlations, one PSD profile from each patient (the inhalation with the highest PIFR for each patient) was selected. The correlation values between all PSD profiles (one PSD profile per patient) across patients were then computed. The resulting r correlation values (comparing PSD profiles across patients) were then categorised as the inter-patient PSD correlation distribution. As there were more correlations to perform at the inter-patient level, over 10 times more values than at the intra-patient level, the inter-patient distribution was divided into 10 randomly sampled distributions of r values, each distribution being of the same length as the intra-patient distribution. All of the inter-patient r correlation value distributions, 10 in total, were each statistically compared to the intra-patient correlation distribution using a Mann-Whitney non-parametric test. Statistical tests were corrected for multiple comparisons using Bonferroni correction.

Effects on inhalation PSD profile repeatability

For each r value that was computed at the intra-patient level, the differences in inhalation PIFR and duration between the inhalations for each corresponding r value were computed. The effects of PIFR and duration on the PSD profile correlation r values were determined using stepwise deletion linear regression. A stepwise deletion linear regression method was also employed to determine the effects of the differences in PIFR, inhalation duration, age, BMI and FEV1/FVC ratio on the PSD profile correlations across patients. This was performed to determine the effects of these factors on the position of the peaks and troughs of the PSD profile. The significance level was adjusted for multiple tests using Bonferroni correction. The stepwise deletion regression method was previously employed to determine the influence of anthropometric features and lung function on PIFR through the Diskus inhaler (Seheult *et al.*, 2014a). All statistical analyses were performed using Minitab V16.1.

5.1.3 Results

Table 5.1 presents demographics and baseline lung function of the 53 patients recruited in this study. Five of the 53 patients had corrupted audio data from the non-contact microphone and eight of 53 patients had corrupted audio data from the tracheal microphone. A total of 123 inhaler inhalations (48 patients) were employed for non-contact audio analyses and 115 inhaler inhalations (45 patients) were employed for tracheal audio analyses.

A paired t-test highlighted a significant increase in PIFR across all patients when comparing their first inhalation to their final inhalation during the recording session ($p < 0.001$). This significant increase in PIFR may be as a result from repeated inhaler training from healthcare professionals.

Table 5.2 presents the correlation values (adjusted R^2) from the linear regression analysis involving PIFR and inhalation audio-based features ($n=44$ for non-contact (after the removal of four outliers), $n=45$ for tracheal (no outliers) after the removal of statistical outliers). It was observed that the non-contact audio signals generated stronger correlations with PIFR than the tracheal audio-based features. The Shannon entropy (H) of the inhalation sound was noted to have the strongest correlation with PIFR ($R^2=0.82$, $p < 0.001$) in the non-contact recordings (Figure 5.3). The P_{ave} of the inhalation sounds

Table 5.1. Patient demographics and baseline spirometric measurements.

	All (n=53)	Asthma (n=26)	COPD (n=14)	Other Respiratory Conditions (n=13)
No. inhalations	126	57	38	31
Age (years)	55.9±18.7 (17-83)	43.7±18.9 (17-73)	69.6±6.8 (59-81)	65.8±10.3 (42-83)
Gender (M/F)	20/33	8/18	6/8	6/7
Height (cm)	164.3±10 (143-188)	164.6±10.6 (145-188)	160.4±9.1 (143-180)	168±8.6 (157-181)
Weight (kg)	79.1±17.5 (50-115)	77.6±15.9 (51.2-110)	75.7±17.6 (50-110)	85.9±20.3 (56-115)
BMI^a (kg/m²)	29.2±5.5 (19.7- 40.3)	28.6±5.3 (19.7-40.3)	29.4±5.9 (20.9-39.6)	30.3±5.9 (21.3-4.4)
FEV1^b (L)	2.26±0.92 (0.65-4.44)	2.76±0.89 (1.48-4.44)	1.35±0.48 (0.65-2.36)	2.28±0.59 (1.65-3.31)
FVC^c (L)	3.09±1 (1.71-5.57)	3.45±1.19 (1.11-5.61)	2.46±0.55 (1.71-3.59)	3.04±0.61 (2.31-4.29)
FEV1/FVC Ratio	0.71±0.14 (0.31-0.93)	0.78±0.09 (0.61-0.93)	0.56±0.16 (0.31-0.81)	0.74±0.07 (0.61-0.83)

^a BMI – body mass index

^b FEV1 – forced expiratory volume in one second

^c FVC – forced vital capacity

Table 5.2. Adjusted R^2 correlation values between audio-based features and PIFR of inhaler inhalations.

	F_{25}	F_{50}	F_{75}	P_{ave}	H	MAD	RMS
Non- contact	0.56***	0.71***	0.64***	0.79***	0.82***	0.75***	0.67***
Tracheal	0.08*	0.03	0.03	0.29***	0.28***	0.23***	0.24***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

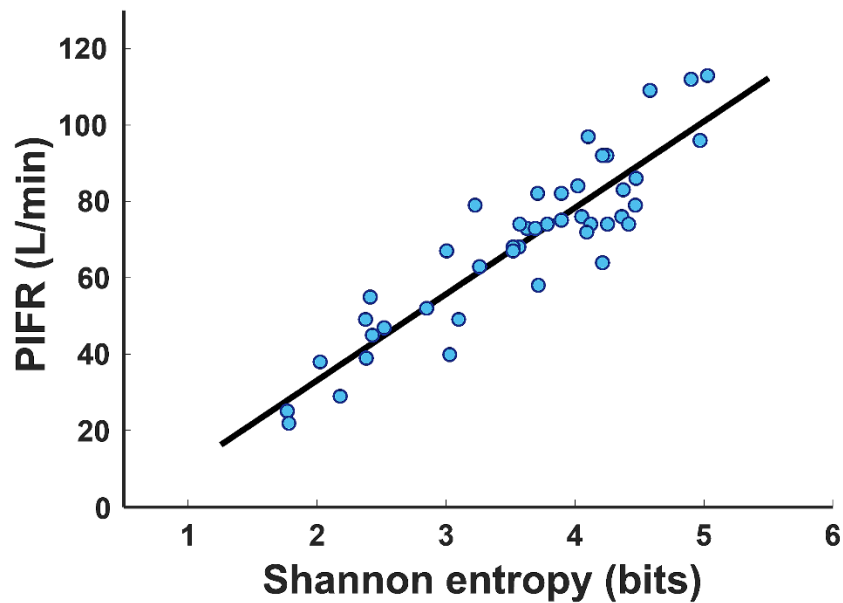


Figure 5.3. Linear relationship between PIFR and the Shannon entropy (H) of non-contact inhalation sounds from patient cohort.

The plot consists of the observed Shannon entropy values (blue data points), each value representing one inhalation from each patient, and calculated regression line (thick black line) ($R^2=0.82$, $p<0.001$).

generated the strongest correlation with PIFR in the tracheal recordings ($R^2=0.29$, $p<0.001$). Figure 5.4 illustrates inhaler inhalation PSD profiles (represented in dB) from a single patient and also from three different patients to compare inhaler inhalation PSDs at both intra-patient and inter-patient levels. It is evident from Figure 5.4 that the position of peak frequencies in the PSD profiles at an intra-patient level remained largely unchanged across different flow rates both in non-contact and tracheal data.

The PSD profile correlation analyses at the intra-patient generated 108 r values for the non-contact data and 98 r values for the tracheal data. The inter-patient correlations generated 1,128 r values for the non-contact data and 990 r values for the tracheal data. It was observed that the intra-patient correlations were statistically significantly larger than the inter-patient correlations for both non-contact and tracheal data ($p<0.001$). Figure 5.5 illustrates the distribution of r values relating to intra-patient and inter-patient PSD profile correlations. The inter-patient distribution in Figure 5.5 represents one of the 10 randomly sampled inter-patient r value distributions.

In the non-contact data, the stepwise deletion regression showed that differences in inhalation PIFR and duration between inhalation recordings had significant effects on

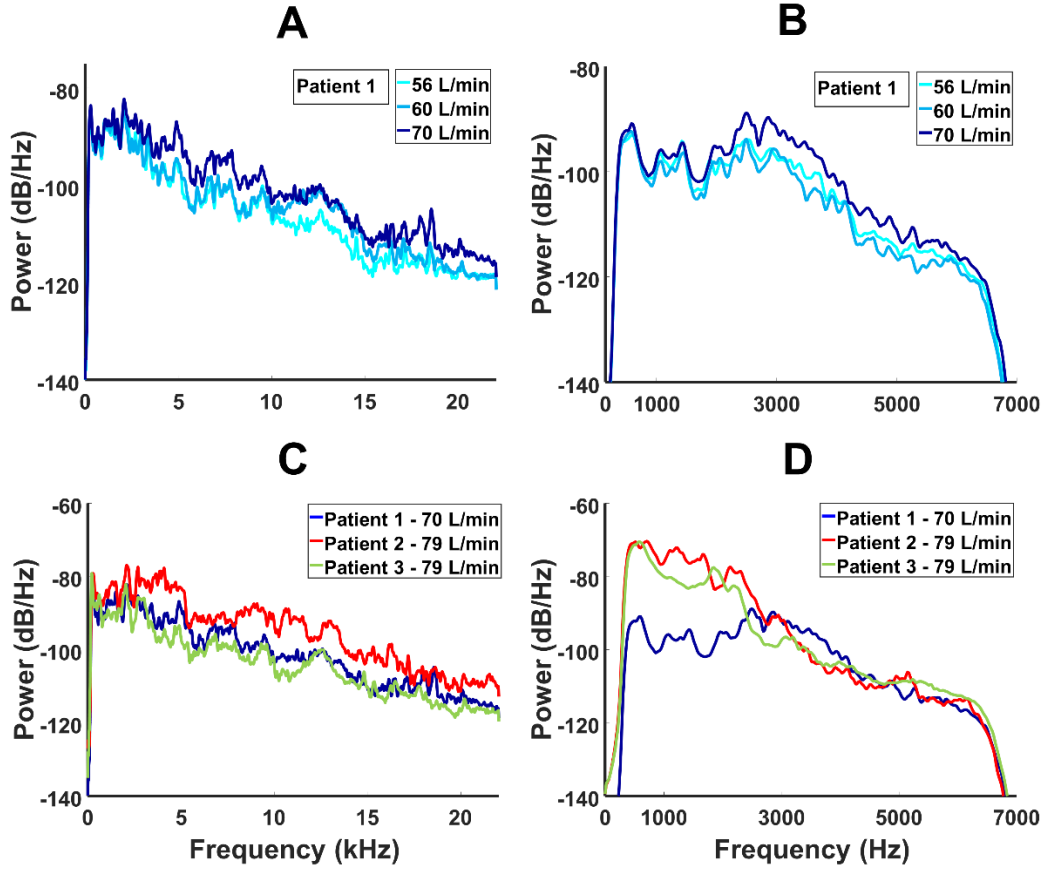


Figure 5.4. Power spectral density estimates of three inhalations across and within patients.

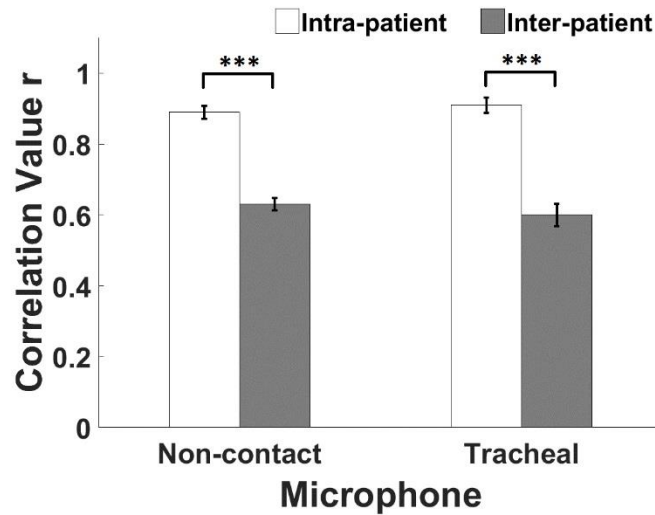
Power spectral density estimates from a single asthma patient (intra-patient) recorded using (A) non-contact microphone and (B) tracheal microphone. Also illustrated are three inhalation sounds from three different patients (one asthma patient (Patient 1 - blue), two COPD patients (Patient 2 - red and Patient 3 - green)) (inter-patient) recorded using (C) non-contact microphone and (D) tracheal microphone.

PSD profile correlations at an intra-patient level ($R^2=0.18$, $p<0.001$). The regression equation is given as follows;

$$r = 0.9205 - 0.0079 \text{ Duration} - 0.0048 \text{ PIFR} \quad (5.5)$$

At the inter-patient level it was observed that the differences in PIFR and age between inhalation recordings from two patients had weak significant effects on the r correlation values ($R^2=0.15$, $p<0.001$). The regression equation of inter-patient PSD profile correlations of the non-contact is given as follows;

$$r = 0.7236 - 0.0031 \text{ PIFR} - 0.0017 \text{ Age} \quad (5.6)$$



***p<0.001

Figure 5.5. Median ($\pm$ standard error) of Pearson's linear correlation coefficient r values of intra and inter-patient PSD profile correlations in the non-contact and tracheal inhalation audio signals.

In the tracheal data, it was noted that inhalation PIFR and duration had no significant effects on PSD correlations at an intra-patient level. At the inter-patient level, it was found that age and inhalation duration had weak significant effects on r correlation values ($R^2=0.02$, $p<0.01$). The regression equation of inter-patient PSD profile correlations of tracheal data is given as follows;

$$r = 0.6178 - 0.0023 \text{ Age} - 0.013 \text{ Duration} \quad (5.7)$$

5.1.4 Discussion

It was observed in this study that audio-based features from both non-contact and tracheal inhaler inhalation recordings were significantly correlated with PIFR ($p<0.001$). The Shannon entropy (H) of the inhalation sounds generated the strongest correlation with PIFR compared to the other selected audio-based features in the non-contact recordings ($R^2=0.82$, $p<0.001$). For the tracheal recordings, the average power of the PSD (P_{ave}) of inhalation sounds generated the strongest correlation with PIFR ($R^2= 0.29$, $p<0.001$). Correlation R^2 values were smaller in the tracheal audio dataset compared to the non-contact recordings. This may be due to much greater inter-patient variability existing in tracheal sounds in comparison to sounds recorded near the mouthpiece of the inhaler using non-contact methods. This would be expected as it has been reported previously how tracheal recordings of normal breath sounds have high inter-subject

variability (Sanchez and Vizcaya, 2003). Also, the inter-patient variability that was observed in the PSD profiles, in both non-contact and tracheal data, may explain some of the variability which may have decreased the R^2 values in estimating PIFR particularly in the quartile frequency features (F_{25} , F_{50} and F_{75}). Furthermore, it is evident from Figure 5.4C and 5.4D that the power of tracheal inhalation sounds varies much more across patients than non-contact recordings. This agrees with the previous findings of the pilot study reported in Chapter 4 Section 4.2 (Taylor *et al.*, 2015). The weaker correlations observed in the tracheal data may also be as a result of the audio-based feature selection in this study. Perhaps other audio-based features may generate stronger correlations with PIFR in tracheal recording across patients in future studies.

The position of peak frequencies in the inhalation PSD profile remained mostly unchanged at the intra-patient level in both non-contact and tracheal data. This agreed with the findings reported in Chapter 4 (Taylor *et al.*, 2016b) and other studies in normal tracheal breath sounds (Sanchez and Vizcaya, 2003). As the duration of a recording session was approximately 10-15 minutes per patient, the repeatability of PSD profiles that was observed at the intra-patient level was based on a short period of time. This study may act as a baseline for future inhaler audio-based studies that may investigate the PSD profile repeatability longitudinally. There is a deficit in the literature on how inhaler inhalation audio-based features change over time in patients with respiratory diseases. It is not known whether inhalation audio-based features reflect changes in patient's lung function, such as during an exacerbation period or in the recovery period during treatment. The non-contact methods of analysing inhalation technique presented in this Chapter and in Chapter 4 may provide the opportunity to remotely monitor changes in patient's lung function longitudinally.

The R^2 values and factor coefficients of the stepwise deletion regression for both non-contact and tracheal data were considerably small, hence it could be argued that PIFR, inhalation duration and age did not explain the vast majority of variability in the data. This may suggest that other factors such as the patient's mouth seal around the mouthpiece of the inhaler may have a stronger effect on the inhalation PSDs, particularly in the non-contact data. The PSD profile of inhaler inhalation sounds may vary across patients on an individual basis given that the inter-patient correlations being significantly lower than the intra-patient correlations.

Tracheal sound analysis has contributed greatly to the respiratory audio analyses literature, therefore, tracheal sounds were employed in this study to compare to sounds

recorded using a non-contact microphone placed distant to the inhaler mouthpiece. Tracheal microphones may become uncomfortable for patients over time if they were to be employed to monitor inhaler user technique remotely, hence, non-contact microphones may provide a more suitable option for future clinical applications. Non-contact microphones placed near the mouthpiece could potentially be employed in a wearable device (such as a smart watch or ring device).

There were some limitations to this study. The inhalation flow profile may explain some of the variability in the audio data. Audio-based features of inhaler inhalations are directly affected by flow rate and, therefore, may be influenced by the entire flow profile and not just the PIFR. The inhalation flow profile may have varied across all patients recruited in this study. However, for the purpose of this study in comparing non-contact and tracheal audio-based features, PIFR was deemed a sufficient flow parameter to employ in statistical analyses. Also, it would have been desirable to record at least one inhalation from each patient at a pre-chosen standardised flow rate. These flow-matched inhalations could have then been employed to determine the influence of anthropometric features and lung function on specific inhalation audio-based features (similar to the pilot study reported in Chapter 4 Section 4.2) as well as the PSD profile as discussed in this study. Previous studies in the literature regarding respiratory audio analysis employed flow-matched respiratory sounds (Malmberg *et al.*, 1995), however, in these studies the flow profiles may have been similar due to the little resistance in the airflow path. It is more challenging to match inhaler inhalations in terms of flow rate due to the flow profile potentially varying from patient to patient. The PIFR may be matched but the flow profile may differ across patients (as previously illustrated in Figure 2.2). There exists additional airflow resistance when inhaling through a DPI. Consequently, instructing patients to inhale at a specific target flow rate may not have been feasible considering lung function varied throughout the cohort of patients recruited in this study.

It was observed that inhaler PIFR significantly increased across all patients when comparing their first inhalation to their final inhalation ($p < 0.001$). This may suggest that inhaler tuition may benefit patients as reported throughout the literature (Giraud *et al.*, 2011; Göriş *et al.*, 2013). Audio-based methods offer the potential to objectively monitor user inhalation technique of patients with chronic respiratory diseases such as asthma and COPD, and therefore may assist inhaler training in future clinical applications. Further investigation is required to determine whether audio-based measures of PIFR can be used

to track changes in lung function during an exacerbation and in the recovery period during treatment after an exacerbation.

5.2 Investigation into the Relationship between Audio-Based Features of Inhaler Inhalation Sounds and Lung Function During and After Bronchoconstriction

5.2.1 Introduction

Asthma exacerbations are defined as acute or subacute progressive worsening of shortness of breath, coughing, wheezing and chest tightness, or any combination thereof (Busse, 2007). They are associated with considerable morbidity and economic cost (Bateman *et al.*, 2008), largely due to their unpredictability and difficulty to detect. There are no reliable methods of early exacerbation detection that can be employed remotely. A history of recent exacerbations is the most reliable predictor of exacerbations (Miller *et al.*, 2007).

As previously discussed in Chapter 2, patients are instructed to inhale through a DPI forcefully and deeply in order to receive the optimum delivered dose. As patients need to inhale at maximum effort, the PIFR of their inhalations may change over time, particularly during an exacerbation. However, this needs to be further investigated. It has been reported that significant changes in COPD patient's inhaler PIFR may be observed between the exacerbation and recovery periods (Broeders *et al.*, 2004). There is a deficit in the literature regarding changes in asthma patient's inhaler PIFR during and after exacerbations. Audio-based methods have been previously employed to objectively measure PIFR during inhaler use (Holmes *et al.*, 2013b; Holmes *et al.*, 2013c; Seheult *et al.*, 2014b; Taylor *et al.*, 2016b; Taylor *et al.*, 2016a), a critical measurement of inhalation technique. It has yet to be investigated whether changes in asthma patients' inhaler PIFR during and after exacerbations reflect changes in lung function and whether these changes in PIFR can be objectively measured using audio-based methods. Previous studies have reported that audio-based features of breath sounds recorded from chest wall and tracheal microphones undergo changes during induced bronchoconstriction such as during a bronchial challenge test (BCT) (Sánchez Morillo *et al.*, 2013; Malmberg *et al.*, 1994; Fiz *et al.*, 1999). Furthermore, audio analysis of adventitious sounds in patients after

receiving a bronchodilator has showed promising opportunities to monitor the response to the treatment (Lozano *et al.*, 2016; Lozano-García *et al.*, 2017). However, as previously mentioned in Chapter 5, contact sensors may not be practical for monitoring inhaler inhalation technique remotely, despite the fact that these sounds contain important physiological information.

As a BCT consists of inducing bronchoconstriction of the airways (simulated exacerbation) followed by the administration of a bronchodilator (response to treatment) after the test, this pilot study aimed to replicate patient inhaler use during an exacerbation period and during the recovery period of inhaled therapy treatment. Analysis of PIFR and audio-based features of inhaler inhalations during this test may reveal a feature that is an early detector of exacerbations, or a marker of exacerbation severity. This would facilitate the development of an exacerbation detection algorithm based on inhaler inhalation audio-based features that could allow longitudinal remote monitoring of respiratory health for future clinical applications.

The aim of this pilot study was to investigate changes in inhaler PIFR and inhalation audio-based features during and after a BCT in a cohort of patients referred by their clinician with potential asthma. It was hypothesised that inhaler PIFR and subsequently inhalation audio-features change significantly during and after an induced exacerbation, reflecting changes in lung function in patients with hyperresponsive airways such as asthma patients. Therefore, the use of audio-based monitoring of inhaler inhalations may be employed in clinical practice to predict asthma exacerbations and monitor the response to treatment in future.

5.2.2 Methods

5.2.2.1 Patient recruitment

Data were collected from eight patients (four male, four female) undergoing a BCT in two centres with respiratory medicine units, Beaumont Hospital Dublin and Bon Secours Hospital Dublin, Ireland. Patients recruited for this pilot study reported symptoms of asthma during a consultation with their clinician. In order to determine whether these patients have hyperresponsive airways which is associated with asthma, they were referred to undergo a BCT in order to assist in diagnosing the presence of asthma. Table 5.3 presents demographics and baseline lung function of patients recruited

in this study. Ethics approval for the study was granted by the relevant ethics committee in both hospitals.

Table 5.3. Patient information (n=8) and baseline lung function (mean $\pm$ standard deviation).

Age (years)	58.8 $\pm$ 15.1
Weight (kg)	81.1 $\pm$ 11.6
Height (cm)	168 $\pm$ 9.1
BMI	30.8 $\pm$ 5.1
FEV1 (L/min)	3.1 $\pm$ 0.99

5.2.2.2 Experimental setup

The non-contact recording setup that was employed in Section 5.1 to record Diskus DPI inhalation sounds and PIFR was also employed in this study also (Figure 5.1). The Sony ECM-77B (Sony Inc., Japan) tracheal microphone was fixed inside a custom built air-coupled chamber and was attached to the patient's neck at the suprasternal notch using an adhesive neck band. The tracheal and non-contact microphones were connected to a PreSonus AudioBox 44VSL, which was connected to a data acquisition laptop. All audio signals were sampled at 44.1 kHz with 16 bits per sample resolution.

5.2.2.3 Test procedure

Bronchial challenge test protocol

BCTs are commonly used in respiratory medicine to test airway hyperresponsiveness in the diagnosis of respiratory disease (Marcon *et al.*, 2014). During the BCT, patients inhale successive provocative doses of a bronchoconstrictor agent (BA) such as histamine or methacholine. If patients are responsive to the test, the BA will stimulate receptors on the airway smooth muscle resulting in a 20% drop in FEV1. This drop in FEV1 may not be observed in patients who do not have hyperresponsive airways whereby the maximum dose may administered (Chinn *et al.*, 1997; Marcon *et al.*, 2014). In the BCTs performed in this study, spirometry was taken twice for each dose: Once 30 seconds after BA is administered, and the other 90 seconds after in order to obtain measurement of FEV1 throughout the test. Inhaler inhalation audio recordings were obtained after the second spirometry, prior to the succeeding dose of BA.

Patient recording protocol

To record Diskus DPI inhalations just after the second spirometry test, patients were asked to breathe at tidal volume through an empty Diskus DPI (containing no drug), ensuring they make a tight seal with the inhaler mouthpiece. A silent signal was given, at which point the patient would finish their next exhalation to functional residual capacity (which simulates the patient emptying their lungs prior to inhaling) and then inhale at maximum effort for as long as possible. Patients then held their breath with the inhaler in place for two seconds. The apparatus was then taken away from the patient, and the BCT continued until the next inhalation recording.

Baseline inhaler inhalation recordings were obtained prior to the beginning of the test, to record inhalation audio-based features at baseline lung function and ensuring patients were familiar with the apparatus. The inhalation with the highest PIFR was selected from these recordings to represent baseline lung function. Once the test was complete, patients were administered a bronchodilator (Salbutamol) to bring their lung function back to baseline. Spirometry was performed on the patient 15 minutes after the administration of the bronchodilator to confirm the patient's lung function had returned to baseline. A final Diskus inhalation audio recording was then obtained from the patient to represent the recovery period after bronchoconstriction once lung function had returned to baseline. A respiratory physiologist from the relevant hospital performed the tests on patients.

5.2.2.4 Signal processing and feature extraction

Inhalation audio signals were demarcated using aural and visual methods. The PSD of inhalation sounds was estimated as previously in Chapters 4 and 5. The audio signals were high pass filtered with a cut-off frequency of 200 Hz to remove the heart sounds from the tracheal microphone, and low frequency noise from the non-contact microphone. Audio analyses were performed on three frequency bands for non-contact (NC) and tracheal (T) audio analyses: 200-22,050 Hz, 200-4,000 Hz and 200-2,000 Hz. The selected frequency bands were employed for the following reasons, respectively: to assess the maximum frequency range of the recordings; to assess the audio-based features in a range used in remote monitoring devices such as the INCA device (Holmes *et al.*, 2014a; Holmes *et al.*, 2013c); and to assess audio-based features in a frequency range previously validated in respiratory acoustics studies (Malmberg *et al.*, 1994). Audio-based features that were employed included median frequency (F_{50}), the average PSD (P_{ave}), and MAD .

The Katz Fractal Dimension (KFD), a statistical index of waveform complexity, which has been used in previous respiratory acoustic studies, was calculated using the following equation as reported (Katz, 1988; Gnitecki *et al.*, 2004);

$$KFD = \frac{\log_{10}(n)}{\log_{10}(n) + \log_{10}(\frac{d}{L})} \quad (5.8)$$

where n is the number of increments between samples of the waveform,

d is the maximum distance from the first increment of the waveform,

L is the sum of the distances between successive increments.

The fractal increment of KFD (FIK) which is equal to $KFD-1$ was used, as in previous literature (Mandelbrot *et al.*, 1984). Another measure of audio signal complexity was calculated through estimating the Shannon entropy (H), which was employed previously to estimate respiratory flow rate (Taylor *et al.*, 2016a).

5.2.2.5 Statistical analyses

A generalised least square (GLS) regression model was employed to investigate the correlation between the percentage change in FEV1 from baseline ($\Delta FEV1\%$) and the percentage change in five audio-based features (F_{50} , P_{ave} , MAD , FIK and H) from baseline ($\Delta AF\%$). As patients inhaled at their PIFR, flow rates were not standardised across subjects or within subjects during the test. Therefore, percentage change was employed to standardise the changes in audio-based features observed within each patient. To more accurately model $\Delta AF\%$ during exacerbations, the GLS did not include inhalations recorded post bronchodilation. As the initial doses during a BCT are comparatively very small and the onset of action for BAs is greater than the time provided for each recording (Begin *et al.*, 1982), analysis was performed between the baseline recording and the final three recordings of the BCT. A paired t-test was employed to compare all audio-based features and inhaler PIFR at the end of the BCT to audio-based features and PIFR after salbutamol was administered, to investigate the recovery period of an exacerbation.

5.2.3 Results

A total of 67 inhaler inhalations (59 during the BCT and eight post bronchodilation) were recorded for this study to analyse the relationship between the $\Delta AF\%$ of inhaler inhalations and $\Delta FEV1\%$ compared to baseline level, during a BCT. The mean percentage drop in FEV1 across all patients was $16.4 \pm 6\%$. It was found that $\Delta FEV1\%$ was significantly negatively correlated with an increase in BA dosage in both responsive ($R^2=0.929$, $p<0.001$) and non-responsive ($R^2=0.702$, $p<0.001$) patient groups during a BCT. Figure 5.6 illustrates mean values of $\Delta FEV1\%$ and $\Delta MAD\%$ over the final three BA doses and post bronchodilation. The results from the GLS regression using $\Delta FEV1\%$ and $\Delta AF\%$ from responsive patients ($n=4$) and non-responsive patients ($n=4$) are shown in Table 5.4 and Table 5.5.

Table 5.4. Regression results (R^2 values) detailing the correlation between changes in lung function ($\Delta FEV1\%$) and audio features ($\Delta AF\%$) for responsive patients ($n=4$).

Frequency Band	Audio-based Feature				
	$\Delta F_{50}\%$	$\Delta MAD\%$	$\Delta P_{ave}\%$	$\Delta FIK\%$	$\Delta H\%$
$NC_{200Hz-22.05kHz}$	0.05	0.5***	0.51***	0.58***	0.54***
$NC_{200Hz-4kHz}$	0.08	0.55***	0.54***	0.58***	0.58***
$NC_{200Hz-2kHz}$	0.11	0.44**	0.42**	0.58***	0.42**
$T_{200Hz-22.05kHz}$	0.01	0	0	0.25*	0.02
$T_{200Hz-4kHz}$	0.04	0.02	0.03	0.25*	0.04
$T_{200Hz-2kHz}$	0.07	0.03	0.04	0.25*	0.05

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

NC - non-contact inhalation audio recordings

T - tracheal inhalation audio recordings

$\Delta F_{50}\%$ - percentage change in F_{50}

$\Delta MAD\%$ - percentage change in MAD

$\Delta P_{ave}\%$ - percentage change in P_{ave}

$\Delta FIK\%$ - percentage change in FIK

$\Delta H\%$ - percentage change in H

Table 5.5. Regression results (R^2 values) detailing the correlation between changes in lung function ($\Delta FEV1\%$) and audio features ($\Delta AF\%$) for non-responsive patients (n=4).

Frequency Band	Audio-based Feature	$\Delta F_{50}\%$	$\Delta MAD\%$	$\Delta P_{ave}\%$	$\Delta FIK\%$	$\Delta H\%$
$NC_{200Hz-22.05kHz}$		0.01	0.01	0	0	0.03
$NC_{200Hz-4kHz}$		0.03	0.02	0	0	0.04
$NC_{200Hz-2kHz}$		0.03	0	0.01	0	0.06
$T_{200Hz-22.05kHz}$		0	0.04	0.01	0.03	0.07
$T_{200Hz-4kHz}$		0	0.03	0.01	0.03	0.06
$T_{200Hz-2kHz}$		0	0.02	0.01	0.03	0.01

*p<0.05, **p<0.01, ***p<0.001

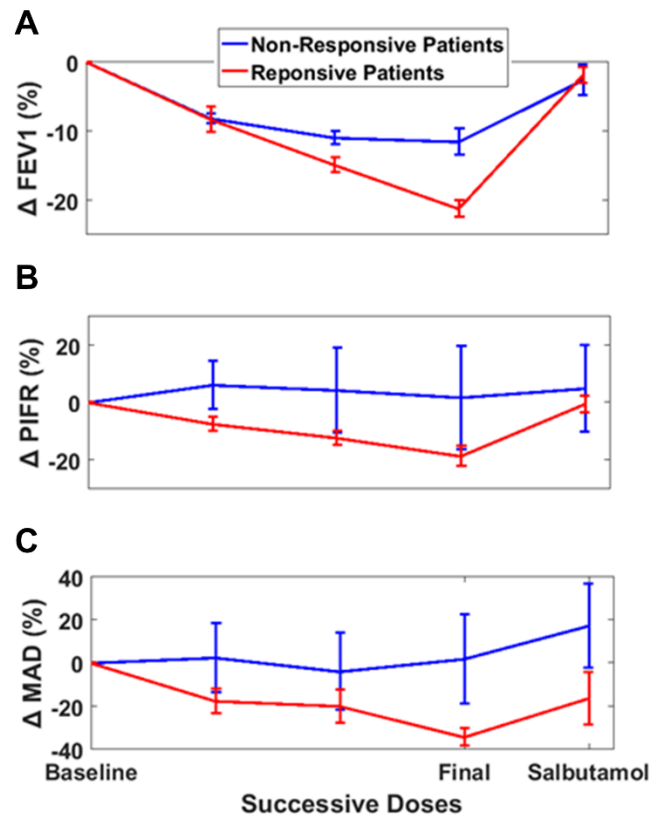


Figure 5.6. Changes in lung function, inhaler PIFR and audio-based features of inhaler inhalations during bronchial challenge test for responsive and non-responsive patients. Mean ($\pm$ std. error) of (A) $\Delta FEV1\%$, (B) $\Delta PIFR\%$ and (C) $\Delta MAD\%$ ($NC_{200Hz-4kHz}$) of inhaler inhalations for responsive and non-responsive patients during the final three doses of BA in a BCT. The values after the administration of a bronchodilator are also presented.

It was observed that all audio-based features except for $\Delta F_{50}\%$ were significantly correlated with $\Delta FEV1\%$ in the responsive patient group ($p < 0.001$) in the non-contact data. It was noted that $\Delta FIK\%$ was the only audio-based feature significantly correlated ($R^2 = 0.25$, $p < 0.05$) with $\Delta FEV1\%$ in the tracheal audio data. It was observed that $\Delta PIFR\%$ was significantly correlated with change in all audio-based features except $\Delta F_{50}\%$ in the full cohort ($p < 0.001$), and with $\Delta FEV1\%$ in responsive patients ($R^2 = 0.62$, $p < 0.001$), but not in non-responsive patients.

The final dose recordings of all patients were compared to post-bronchodilator recordings using a paired t-test across all patients. It was observed that $FEV1$, P_{ave} and MAD had significant changes with p-values of 0.001, 0.018 and 0.034, respectively. $PIFR$, FIK , H and F_{50} did not demonstrate significant changes in paired t-tests, however, a larger sample size (particularly with larger responsive patient cohort) may give more accurate statistical values. It is evident from Figure 5.6 that the non-responsive patient $PIFR$ does not change considerably between final dose and post salbutamol bronchodilator which affected the statistical analysis.

5.2.4 Discussion

It was observed in this study that inhaler inhalation audio-based features may undergo significant changes during bronchoconstriction due to a decrease in $PIFR$, as $FEV1$ decreases. The significant correlation in the responsive group, and the lack thereof in the non-responsive group suggest that during an exacerbation, the audio-based features of inhaler inhalations may correlate with the severity of the exacerbation (in terms of a decrease in $FEV1$).

It was also noted that the $\Delta PIFR\%$ of inhaler inhalations was negatively correlated with increase in BA dosage in responsive patients ($R^2 = 0.73$, $p < 0.001$). It has been reported in previous literature that inhaler inhalation audio-based features are strongly correlated with $PIFR$ (Holmes *et al.*, 2013b; Holmes *et al.*, 2013c; Taylor *et al.*, 2016b; Taylor *et al.*, 2016a). Therefore, the use of non-contact audio-based methods to estimate $PIFR$ may be a sufficient method to monitor changes in lung function in future clinical applications. This study did not employ standardised flow rates within or across patients. This would not have related to real life inhaler use as patients are generally instructed to inhale through a DPI at with maximum effort. Furthermore, the additional airflow

resistance of the inhaler would make it challenging for some patients to reach specific target flow rates.

The results in Table 5.4 highlight that $\Delta FIK\%$ generated the strongest correlation with $\Delta FEV1\%$ in responsive patients, suggesting that it may be utilised as an early predictor of asthma exacerbations. Further analysis is required with a larger cohort of patients to quantify these findings. Changes in PIFR and inhalation audio-based features were not observed in the non-responsive patients. It was observed that $\Delta FIK\%$ was also the only audio-based feature that had a significant correlation with $\Delta FEV1\%$ in the tracheal inhaler inhalation recordings. This may be due to the fact that while individual patients' airways have a significant relationship between audio-based features and $\Delta FEV1\%$, these relationships vary at an inter-patient level (as previously reported in Section 5.1 (Taylor *et al.*, 2016a)), which may result in non-significant results from GLS.

It can be seen in Figure 5.6 that non-responsive patients' $\Delta MAD\%$, like all other audio-based features, were quite erratic and did not change over the course of the BCT. In the responsive group, a decrease was observed throughout the test, with an increase occurring after the administration of salbutamol, as evident in Figure 5.6. The rate of change (slope) of FEV1, PIFR and audio-based features may not be equivalent for all patients (Marcon *et al.*, 2014). Therefore, future audio-based algorithms to monitor lung function over time may need to be personalised and a generalised linear modelling approach may not be the optimal method for predicting changes in lung function.

There were some limitations to this pilot study. The sample size was relatively small due to challenges in recruitment with over 10 patients not attending their scheduled bronchial challenge test. As the sample size is small, the statistical analyses require a larger cohort to obtain more accurate statistical measures between PIFR, FEV1 and inhalation audio-based features. However, previous studies suggest that there is a statistically significant linear relationship between inhaler PIFR and lung function measurements, such as FEV1, in asthma patients ($r=0.49$) (Prime *et al.*, 2015). In addition, the inhalation flow profile was not recorded in this pilot study. It was previously reported that IC was moderately statistically significantly correlated ($r>0.7$) with lung function measures such as FEV1 and FVC (Prime *et al.*, 2015). Future research should aim to estimate the inhalation profile of inhaler inhalations using audio-based methods as it may be of clinical relevance in monitoring changes in patients' lung function over time. Moreover, the literature suggests that inhaler PIFR is more strongly correlated with FEV1 in COPD patients (Prime *et al.*, 2015; Broeders *et al.*, 2004); therefore, remotely

monitoring PIFR in COPD patients may be more affective at predicting adverse clinical events such as exacerbations. However, due to the irreversible pathophysiology of COPD, it may not have been possible to induce an exacerbation in COPD patients as it was with asthma patients.

Audio-based methods have the ability to monitor inhaler user technique as well as quantifying drug delivery from inhalers (Seheult *et al.*, 2014b; Sulaiman *et al.*, 2017). This study provides a platform to further the clinical application of audio-based inhaler monitoring systems. The results from this pilot study suggest that audio-based features of inhaler inhalations are influenced by changes in FEV1 in patients with hyperresponsive airways (such as in asthma patients) which reflect changes in PIFR during an exacerbation and also in the recovery period. Monitoring changes in FEV1 by analysing audio-based features of inhaler inhalations may prove to be highly beneficial to clinicians and patients in future by detecting exacerbations before their symptoms have developed fully, allowing more efficacious treatment and preventing readmissions to hospital. Future research will investigate the correlation between new audio-based measures of PIFR and FEV1 over time in a larger cohort of asthma and COPD patients.

5.3 Chapter Conclusion

In this chapter it was observed that audio-based features of inhaler inhalation sounds recorded using non-contact methods (placing the microphone 5 cm from the inhaler mouthpiece) are more correlated with PIFR than those using tracheal methods across a cohort of patients with respiratory disease. Non-contact methods generate less inter-patient variability compared to tracheal sounds. However, differences exist in the PSD profiles of inhalation sounds across patients which may influence PIFR estimation, particularly when using spectral features. Therefore, generalised methods may not be suitable if spectral features are to be used to estimate PIFR in future clinical applications. Power and complexity based audio features are strongly correlated with PIFR and may be employed to objectively assess inhalation technique and monitor respiratory health remotely. Future research should investigate the use of audio-based methods to estimate the full inhalation flow profile, as audio-based features may be influenced by the full flow profile of inhalation as well as the PIFR. This may provide further clinically pertinent information to healthcare professionals regarding patient inhalation technique.

The findings presented in the pilot study in Section 5.2 suggest that changes occur in inhalation audio-based features as a result of changes in inhaler PIFR during induced bronchoconstriction. These changes were not observed in non-responsive patients indicating that PIFR may change significantly during and after an exacerbation in patients with asthma. Future research should employ a larger cohort of patients experiencing real life exacerbations to determine whether inhalation audio-based features can be employed to monitor respiratory health remotely. The clinical impact of the studies presented in this chapter lies in confirming that non-contact audio-based methods may be employed to assess patient inhalation technique, which may help personalise treatment to the patient. Objective audio-based measures of PIFR may also be employed to predict exacerbations and monitor the response to treatment, which would be of significant clinical benefit to both healthcare professionals and patients.

Chapter 6. Estimation of Inhalation Flow Profile from a Dry Powder Inhaler Using Audio-Based Methods

The study described in this chapter investigates research questions 13-17 from Chapter 3. The findings reported in the studies described in Chapters 4 and 5 suggest that audio-based methods may be employed to objectively measure PIFR during inhaler use, particularly in DPIs. As patients are required to inhale forcefully and deeply when using a DPI, there are a range of other flow parameters that influence the amount of drug delivered to the patient such as, IC and the inhalation ramp time as previously discussed in Chapter 2. Therefore, there is a clinical need to investigate the use of audio-based methods to objectively estimate the inhalation flow profile from DPIs. By estimating the inhalation flow profile, it allows for accurate estimation of the different flow parameters previously mentioned. Objective measurement of inhalation flow profile may give healthcare professionals a better understanding of patients' inhalation technique and respiratory health over the course of treatment rather than focusing on just the patient's PIFR of inhalation. In the studies reported in Chapters 4 and 5 it was noted that the inhaler inhalation flow profile may be correlated with audio-based features, however, this has yet to be explored. In addition, it has yet to be investigated if audio-based methods can be employed to estimate inhalation flow rate in the Ellipta DPI. In this Chapter, an audio-based method is described which can estimate the inhalation flow profile from the Ellipta DPI by extracting the acoustic envelope of the inhalation audio signal.

The study presented in this chapter has resulted in the following peer-reviewed publications;

- **Taylor T E**, Lacalle Muls H, Costello R W and Reilly R B 2018 Estimation of Inhalation Flow Profile Using Audio-Based Methods to Assess Inhaler Medication Adherence. *PLoS One* 13 e0191330.
- Lacalle Muls H, **Taylor T E**, Costello R W and Reilly R B 2016 Objective measurement of inhaler inhalation flow profile using acoustic methods. In: *The Annual Congress of the Spanish Society of Biomedical Engineering (CASEIB)*, Valencia, Spain. 23rd-25th November 2016.

6.1 Introduction

Audio-based methods have been employed to objectively assess inhaler inhalation technique in DPIs and pMDIs (Holmes *et al.*, 2013c; Taylor *et al.*, 2016a; Taylor *et al.*, 2016b). The INCA system uses a non-invasive audio recording device that attaches to a Diskus inhaler and can accurately assess inhalation technique, specifically PIFR and IC in patients with asthma and COPD (D'Arcy *et al.*, 2014; Sulaiman *et al.*, 2016e; Seheult *et al.*, 2014b). However, the flow-sound models employed to estimate PIFR and IC from inhalation audio recordings in these studies required numerous inhalation recordings from a cohort of participants. There is a need to introduce a faster, more efficient method of calibrating flow-sound models to accurately estimate not just PIFR and IC, but the entire flow profile of inhaler inhalations using the INCA device. Estimating the entire inhalation flow profile would allow healthcare professionals to monitor a range of inhalation flow parameters that influence drug delivery. It would also allow healthcare professionals to remotely assess if patients can maintain the required flow rate throughout inhalation when using their inhaler.

Changes in patient inhalation flow profiles may relate to physiological changes in respiratory conditions over time. It was previously reported that COPD patients tend to generate different inhalation profiles than asthma patients in terms of PIFR and IC and that inhalation profiles change according to disease severity (Hamilton *et al.*, 2015; Prime *et al.*, 2015; Mahler *et al.*, 2012). It was also reported previously that inhaler PIFR of COPD patients decreases by an average of approximately 15-18%, depending on the inhaler resistance, during an acute phase of an exacerbation and that PIFR and IC are statistically significantly correlated with lung function (Broeders *et al.*, 2004; Prime *et*

al., 2015). In the study reported in Chapter 5 Section 5.2, it was reported that a decline in lung function during a bronchial challenge test caused a decrease in inhaler PIFR which can be objectively measured using audio-based methods (McCartan *et al.*, 2016). Therefore, by developing an audio-based method of estimating the inhalation flow profile from DPIs, it may be employed to remotely monitor changes in respiratory health longitudinally also and possibly predict exacerbations before they occur.

Respiratory flow estimation using audio-based methods has been most thoroughly researched using microphones placed over the chest wall and trachea as discussed in Chapter 2. It was previously reported that accurate flow estimation may be achieved from tracheal audio recordings using only one audio recording with its corresponding flow signal for calibration (Yadollahi and Moussavi, 2006a). Although the acoustic properties of chest wall and tracheal sounds vary greatly to inhaler inhalation sounds recorded from a non-contact microphone (Taylor *et al.*, 2015; Taylor *et al.*, 2016a), accurately modelling the flow-sound relationship of inhaler inhalations based on one calibration recording has yet to be investigated. If it was possible to develop an accurate model of estimating inhalation flow profile from DPIs based on one calibration inhalation recording, it would have significant clinical impact by allowing healthcare professionals to easily calibrate personalised models to remotely monitor patient inhalation technique.

The aim of this study was to develop an accurate audio-based flow estimation model to estimate the inhalation flow profile from the Ellipta DPI. The hypothesis was that it was possible to accurately estimate the DPI inhalation flow profile based on only one calibration inhalation recording.

6.2 Methods

6.2.1 Participants

Twenty healthy participants were recruited for this study. Written consent was obtained from study participants. In order to test the proposed method on a wide range of inspiratory flow rates, it was deemed necessary to recruit participants with healthy lung function. Baseline spirometry according to ATS/ERS standards was performed on each participant (Miller *et al.*, 2005). This study was approved by the Hospital Ethics Committee at Beaumont Hospital, Dublin, Ireland.

6.2.2 Inhaler audio recording setup

Figure 6.1 shows the inhaler recording setup for this study. A placebo Ellipta DPI was placed inside a custom built airtight container, similar to the setup used in Chapters 4 and 5. For this study, an additional aperture was cut which allowed the INCA device to be placed directly onto the inhaler, as it would be in a clinical setting. This setup has been reported to give accurate audio-based measurements of flow rate in previous inhaler acoustics studies (Holmes *et al.*, 2013c; Seheult *et al.*, 2014b). A final aperture was cut to connect a Vitalograph Pneumotrac™ pneumotachograph spirometer [Vitalograph Ltd., Co. Clare, Ireland] to the airtight container. The spirometer was connected to a data acquisition laptop which allowed for reference measurements of PIFR and IC of inhalations using the Vitalograph Spirotrac® V software. The audio signal was obtained directly from the INCA device and connected to a National Instruments USB-6211 DAQ system [National Instruments, Texas, USA]. The microphone used inside the INCA device is a Knowles SPU0414HR5H-SB MEMS microphone [Knowles Acoustics, Illinois, USA]. The flow signal from the Pneumotrac™ pneumotachograph spirometer was obtained and connected to the DAQ also to record the inhalation flow profile signal.

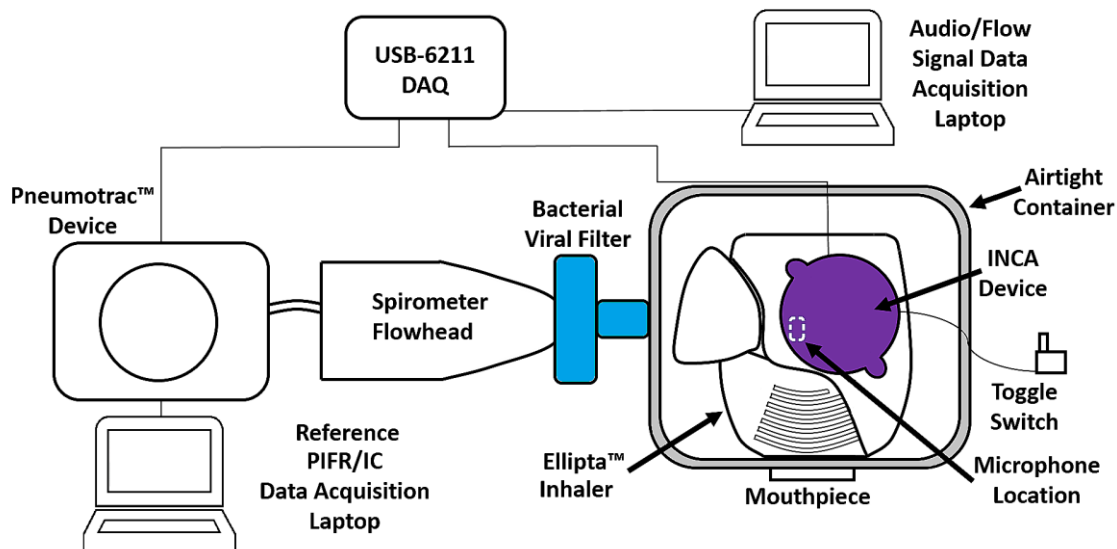


Figure 6.1. Inhaler recording setup.

A custom designed LabVIEW Virtual Instrument [National Instruments, Texas, USA] was developed in order to record inhaler audio and flow signals simultaneously. Both audio and flow signals were sampled at 48 kHz and with 16 bits per sample resolution. Recordings took place in a designated recording office room. The recording room was not soundproof and so was not a completely noise-free environment. However, as the microphone is situated close to the inhaler mouthpiece (approximately 2 cm), the recording environment was suitable to record inhalation audio signals with a sufficient signal to noise ratio to investigate the relationship between the audio and flow signals.

6.2.3 Participant recording protocol

Each participant was instructed to exhale to functional residual capacity before inhaling forcefully through the mouthpiece of the Ellipta inhaler at maximal flow rate for as long as possible. This was then followed by a two to three second breath hold. This was repeated until five inhalation recordings were obtained at maximal inspiratory flow rate. All participants were able to inhale at 70 L/min or above at maximum effort. These five recordings were categorised as a High flow range group. A reference measurement of PIFR was checked using Vitalograph Spirotrac® V software to give participants feedback on their inspiratory flow rate after each inhalation recording. Participants were then asked to reduce their inspiratory flow rate for five recordings between 50-70 L/min (Medium flow range) and a final five recordings between 25-50 L/min (Low flow range). This gave a total of 15 inhalation recordings per participant.

6.2.4 Audio and flow signal pre-processing

The DC component was removed from audio signals by subtracting the mean value of each signal from itself. Audio signals were high pass filtered with a cut-off frequency of 200 Hz using a second order Butterworth filter to remove low frequency noise. Flow signals were low pass filtered with a cut-off frequency of 4 Hz using a second order Butterworth filter. It was observed that a cut off frequency of 4 Hz could capture the rapid change in flow at the onset of inhalation while removing unwanted noise that did not represent the inspiratory flow. As the flow signals were originally recorded as voltage signals, the raw flow voltage (V) signals were converted to flow rate (L/min) using linear regression between the recorded reference PIFR on the Spirotrac® V software and the

peak voltage in the flow signal over 20 recordings for each participant (15 recordings used in the audio analyses and an additional five training recordings used for flow signal calibration). This was calibrated for each participant. The average R^2 value for converting the flow voltage signal to flow rate was 0.95 ± 0.03 ($\pm$ standard error) ($p < 0.0001$) across all participants.

As this study only focused on the inhalation event, all exhalations and other respiratory sounds such as coughs were discarded in the audio and flow signals. Inhalations were segmented by determining the onset and offset points of the inhalation in the flow signal. A threshold of 5 L/min was chosen to segment inhalations to remove baseline noise being included in the flow signal.

6.2.5 Audio-based feature extraction

An estimation of the acoustic envelope (amplitude envelope of the audio signal) of each inhaler inhalation was obtained using the Hilbert Transform (HT). This method has been employed in previous acoustical flow estimation studies (Yadollahi and Moussavi, 2008; Que *et al.*, 2002). The estimate of the acoustic envelope, x_{env} , was computed as the absolute value of the analytic signal, x_a , which is a complex signal consisting of a summation of the inhalation audio signal with a 90° phase shifted version of itself (HT) (Lyons, 2010). The analytic signal is calculated using the following equation;

$$x_a = x + j\hat{x} \quad (6.1)$$

where x is the original inhaler inhalation audio signal and $\hat{x}$ is the HT of the original signal.

The HT is usually most effective when applied to amplitude modulated narrow band signals. However, inhaler inhalation sounds recorded from a non-contact microphone are composed of a broad spectrum of frequencies as observed in Chapters 4 and 5 (Taylor *et al.*, 2016a; Taylor *et al.*, 2016b). Consequently, the absolute value of x_a follows high frequency changes in amplitude that distorts the envelope estimation. The absolute value of the analytic signal, x_a , was therefore low pass filtered with a cut-off frequency of 4 Hz similar to the flow signal using a second order Butterworth filter. An example of the inhalation audio signal with the estimated acoustic envelope along with the corresponding flow signal after low pass filtering is presented in Figure 6.2. Data are available from

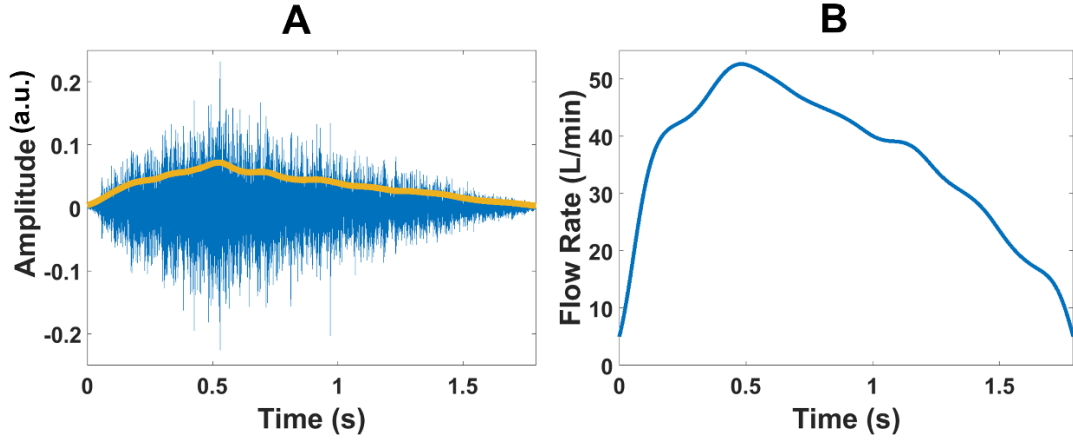


Figure 6.2. Example of inhaler inhalation audio and flow signals.

(A) Inhaler inhalation audio signal with estimated acoustic envelope and (B) corresponding flow signal.

Dryad Digital Repository (<http://datadryad.org/review?doi=doi:10.5061/dryad.8310n>).

6.2.6 Flow-sound regression model

Previous studies have reported the use of linear models to estimate flow rate using audio-based features (Taylor *et al.*, 2016a; Taylor *et al.*, 2016b; Holmes *et al.*, 2013c). However, it was also suggested in Chapter 4 that power-based features may be more strongly correlated with PIFR in the log domain. Other studies have reported that amplitude of sound and flow rate are related through a power law model (Reyes *et al.*, 2014; Yadollahi and Moussavi, 2011). In order to investigate the relationship between the inhalation acoustic envelope and its corresponding flow signal, both linear and power law regression models were employed. A power law model may be calculated as a linear regression model in a logarithmic scale. The linear and power law regression models employed can be represented as;

$$\hat{F} = y \cdot x_{env} + z \quad (6.2)$$

$$\log(\hat{F}) = a \cdot \log(x_{env}) + b \quad (6.3)$$

where $\hat{F}$ is the estimated flow signal and x_{env} is the acoustic envelope of the inhaler inhalation.

For each participant, one recording was used to calibrate a flow-sound regression model by computing the model coefficients (y and z for linear, a and b for power law) using the selected flow and audio signals. This model was then tested on the remaining 14 recordings for this participant to estimate the flow profiles from the remaining 14 audio signals. This process was repeated until each inhalation recording was used to calibrate a separate flow-sound regression model. In this way, a range of flow rates could be employed as single calibration recordings and then tested on a range of inspiratory flow rates to model real life patient inhaler use. This resulted in 210 tests (14×15 tests) being performed for each participant. Any data used to calibrate a model was not subsequently used to test the same resulting model as this may have introduced an over fitting bias. Once the estimated flow signal ($\hat{F}$) was calculated using the model coefficients, a moving average window of 200 ms was also applied to the estimated flow signal from the time point at which 80% of PIFR was reached onwards to further remove noise from the estimated flow signal. The absolute average flow estimation error (absolute error between actual flow profile and estimated flow profile) was computed at each sample point and was then averaged. The average flow estimation error ($Average_{error}$) over the entire inhalation signal was calculated using the following equation;

$$Average_{error} (\%) = \frac{1}{N} \sum_{i=1}^N \frac{|\hat{F}(i) - F(i)|}{F(i)} \times 100 \quad (6.4)$$

where $\hat{F}$ is the estimated flow rate at the i^{th} sample of the signal,

F is the actual flow rate at the i^{th} sample of the signal,

N is the length of the actual and estimated flow signals in samples.

Flow parameters that were calculated from the flow profile included PIFR, IC and the inhalation ramp time (also known as rise time) (T_r) which was pre-defined as the time taken to reach 80% of PIFR. PIFR was calculated as the peak flow rate point of the inhalation flow profile curve. The IC parameter was calculated as the area under the inhalation flow profile curve which equates to the total volume of air inhaled in litres. This was calculated using trapezoidal numerical integration of the flow and estimated flow signals. The T_r was calculated as the time at which the flow profile reached 80% of its maximum flow rate rather than the time taken to reach PIFR to avoid erroneous measurement due to small deviations when the flow profile plateaued.

Equation (6.5) details how the PIFR flow parameter estimation error was calculated. The IC and T_r estimation errors were also calculated using the same method accordingly.

$$PIFR_{error} (\%) = \frac{|\widehat{PIFR} - PIFR|}{PIFR} \quad (6.5)$$

All analyses were performed within participants and then results were averaged across participants.

In order to determine if the model coefficients remained unchanged according to calibration flow rate, a 2-sample t-test was performed to statistically compare regression model coefficients across inhalation flow ranges. These statistical tests were corrected for multiple comparisons using Bonferroni correction.

6.2.7 Effect of noise on audio-based flow estimation

As inhalers are used by patients in different environments (inside and outside of the clinic), it is important to investigate the influence of noise on audio-based flow estimation. In order to investigate the effect of noise on this method of estimating the inhalation flow profile, Gaussian white noise was added to each inhalation audio signal. The method was tested on all audio signals at signal to noise ratio (SNR) levels of 0 dB, 5 dB, 10 dB, 15 dB, 20 dB and 25 dB. The accuracy of each parameter (Average, PIFR, IC and T_r) was then calculated at each SNR level and averaged across all flow ranges and then averaged across all participants.

6.3 Results

Participant information and baseline lung function is presented in Table 6.1. A total of 300 Ellipta inhaler inhalation recordings were obtained from 20 participants in this study. Thirteen recordings were discarded due to corrupt audio and flow signals leaving 287 recordings for analysis with 3,856 flow estimation tests being performed. Table 6.2 presents the average flow parameter values across the different flow ranges. This shows that the method was tested on a wide range of PIFR, IC and T_r values. The average flow parameters for each participant are presented in Tables B1-B3 (Appendix B).

Table 6.1. Participant information and baseline lung function (mean $\pm$ standard deviation).

Parameter	Value
Age (years)	24 $\pm$ 2.5 (20-29)
Gender (M/F)	10/10
Height (cm)	171.95 $\pm$ 8.75 (158-190)
Weight (kg)	67 $\pm$ 13.18 (48-95)
BMI^a (kg/m²)	21.39 $\pm$ 2.12 (19.2-25.9)
FEV1^b (L)	3.75 $\pm$ 0.67 (2.79-5.12)
FEV1 Predicted %	97.65 $\pm$ 13.04 (80-127)
FVC^c (L)	4.68 $\pm$ 0.95 (3.38-6.73)
FEV1/FVC Ratio	0.82 $\pm$ 0.06 (0.72-0.91)
PIFR^d (L/min)	329.35 $\pm$ 93.3 (193-485)

^a BMI – body mass index

^b FEV1 – forced expiratory volume in one second

^c FVC – forced vital capacity

^d PIFR – peak inspiratory flow rate (during spirometry, not inhaler usage)

Table 6.2. Mean ($\pm$ standard deviation) of flow parameter values from recorded inhalation flow signals averaged across all participants.

Flow Range	PIFR (L/min)	IC (L)	Tr (ms)
High ($\geq$70 L/min)	109 $\pm$ 21 (70-142)	2.81 $\pm$ 0.7 (1.82-4.09)	317 $\pm$ 145 (134-597)
Medium (50-70 L/min)	60 $\pm$ 5 (52-66)	1.77 $\pm$ 0.5 (1.18-2.98)	317 $\pm$ 136 (155-770)
Low (25-50 L/min)	39 $\pm$ 4 (32-44)	1.33 $\pm$ 0.5 (0.71-2.48)	323 $\pm$ 107 (146-562)

It was observed that the power law models were superior over the linear models at estimating the inhalation flow profile using the acoustic envelope. The average flow estimation accuracy (which was calculated as $100 - \text{Average}_{\text{error}}$) was $90.89 \pm 0.9\%$ ($\pm$ standard error) for power law and $76.63 \pm 2.38\%$ for linear models. Therefore, detailed results of the power law models are discussed from this point onwards in the study. Average flow parameter estimation errors were divided according to calibration and test flow ranges. The overall $\text{Average}_{\text{error}}$ for the power law models was $9.4 \pm 0.92\%$ for High flow range, $8.65 \pm 1.67\%$ for Medium flow range and $9.29 \pm 2.44\%$ for Low flow range ($\pm$ standard error). This gave an average estimation error of $9.11 \pm 0.9\%$ across all participants. Figure 6.3 presents examples of the estimated flow signals for high, medium and low flow inhalations. Figure 6.4 shows the $\text{Average}_{\text{error}}$, $\text{PIFR}_{\text{error}}$, IC_{error} and Tr_{error} values averaged across all participants.

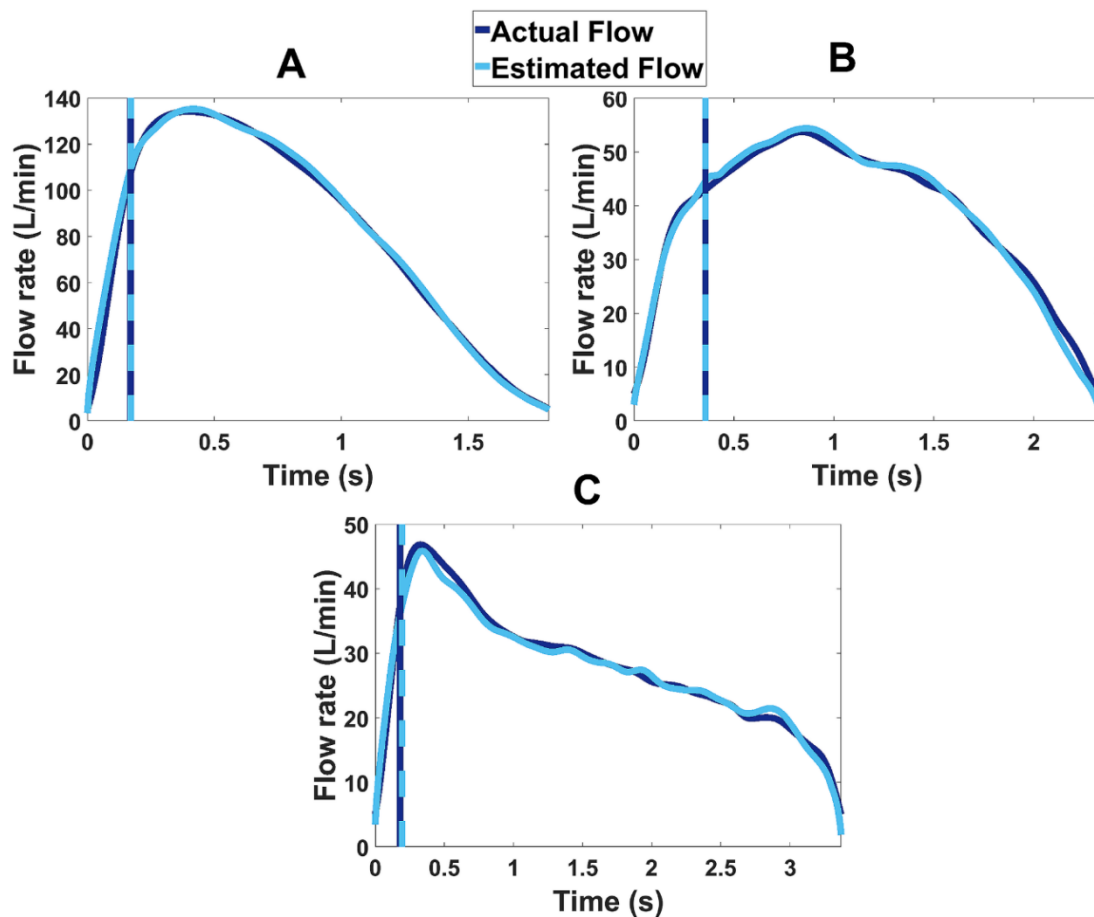


Figure 6.3. Examples of actual and estimated inhaler inhalation flow profiles.
(A) High, (B) Medium and (C) Low inhalation flow rates. The vertical lines represent the actual and estimated Tr values.

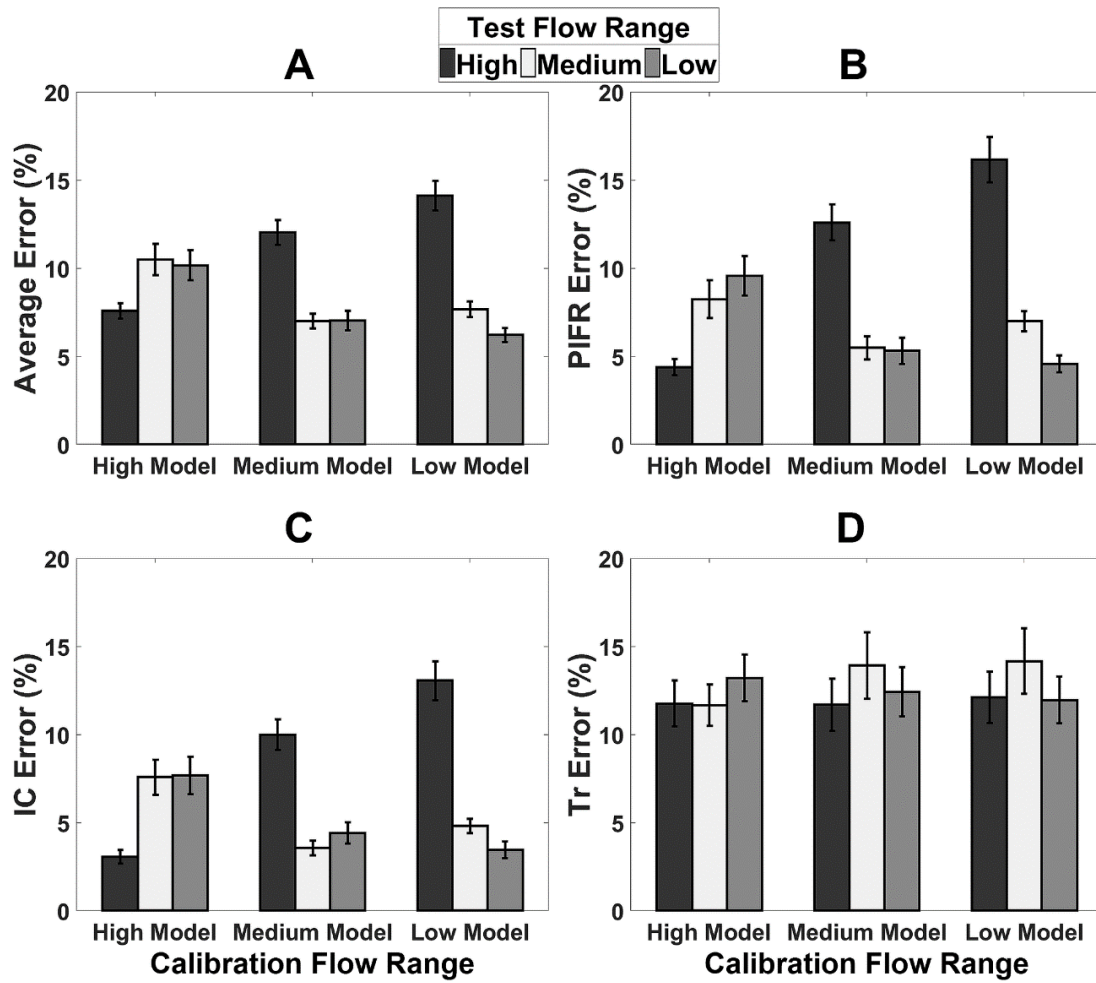


Figure 6.4. Average audio-based flow estimation errors.

(A) $Average_{error}$, (B) $PIFR_{error}$, (C) IC_{error} , and (D) Tr_{error} , (%) ($\pm$ standard error). Results are divided into models calibrated using high, medium and low flow inhalation recordings and tested on high, medium and low flow ranges.

The average flow estimation accuracy for each participant across all flow ranges is presented in Figure 6.5. The acoustic envelope of the inhalation audio signal was strongly significantly linearly correlated with the flow signal in a logarithmic scale ($p < 0.0001$). The average ($\pm$ standard error) R^2 values of the flow-sound regression models created during calibration were 0.9791 ± 0.0027 for High flow range, 0.98 ± 0.0023 for Medium flow range and 0.9778 ± 0.0019 for Low flow range ($p < 0.0001$). Although this is not a measurement of flow estimation accuracy, it is important to note the statistical correlation between the audio envelope and the flow signal.

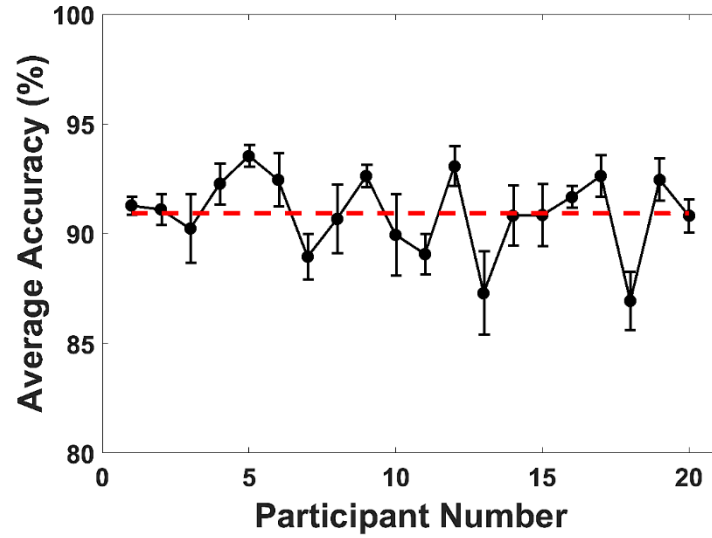


Figure 6.5. Average flow estimation accuracy ($\pm$ standard error) averaged across all flow ranges for each participant.

It was observed that the a and b model coefficients at the High flow range were statistically significantly higher than those in the Medium ($p < 0.05$ for a coefficient, $p < 0.01$ for b coefficient) and Low ($p < 0.01$ for both a and b coefficients) flow ranges. This suggests that the relationship between the flow signal and acoustic envelope may not be constant at all calibration flow rates. Figure 6.6 shows boxplots of the model coefficients across all participants in the High, Medium and Low flow ranges.

Figure 6.7 presents the average accuracy of estimating different inhalation parameters at a range of SNR levels (0-25 dB in increments of 5dB). It can be observed from Figure 6.7 that PIFR, IC and Tr achieve high accuracy above 80% even at very low SNR levels. The average flow estimation accuracy ($Average_{error}$) decreases with lower SNR levels but remains above 70% at 10 dB.

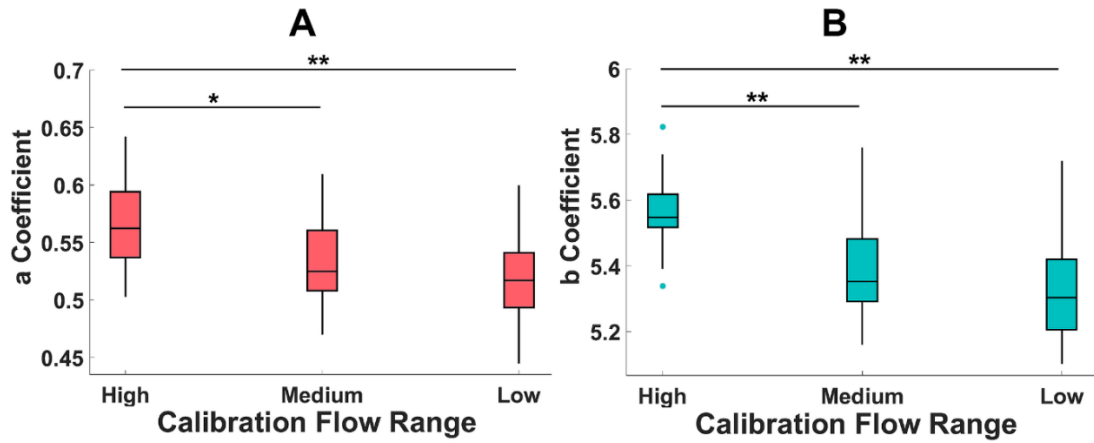


Figure 6.6. Boxplots representing the median, interquartile range and 1.5×interquartile range of regression coefficients.
 (A) *a* and (B) *b* regression coefficients where * $p < 0.05$ and ** $p < 0.01$ corrected for multiple comparisons using Bonferroni correction.

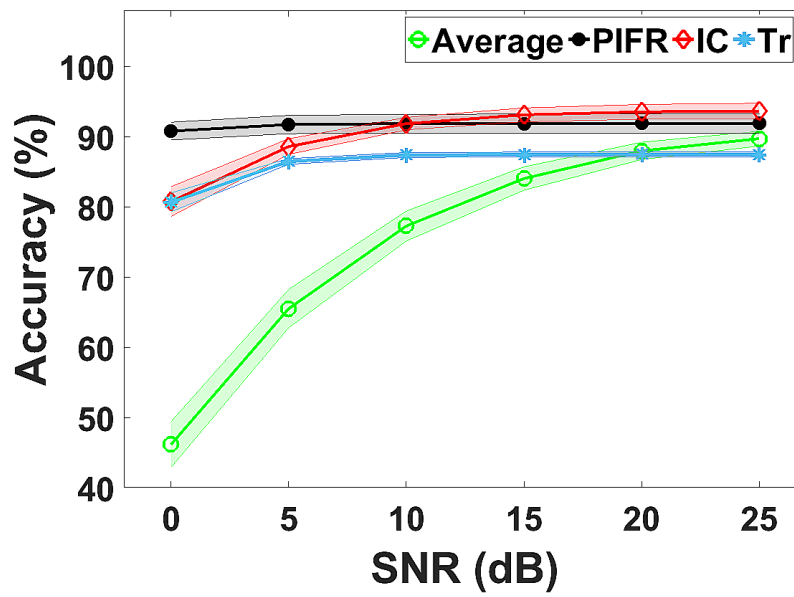


Figure 6.7. Average accuracy (%) $\pm$ standard error (shaded region) of inhalation flow profile parameter estimation across all flow rates at different SNR levels.

6.4 Discussion

It was observed that the acoustic envelope of the inhalation audio signal and its corresponding flow signal followed a power law relationship, which can be estimated as a linear model in a logarithmic scale. This agrees with previous studies that employed power and amplitude based features to estimate respiratory flow (Reyes *et al.*, 2014; Yadollahi and Moussavi, 2011). This also confirms that power-based features are more strongly significantly correlated with flow rate in the log domain as mentioned in Chapter 4. Power law models generated an average flow estimation accuracy of over 10% higher than linear models (90.89% for power law models vs. 76.63% for linear models). By estimating the acoustic envelope of the inhalation audio signal, it was possible to accurately estimate the inhaler inhalation flow profile. This may allow healthcare professionals to obtain a more comprehensive assessment of inhalation technique rather than just focusing on PIFR.

When the calibration and test recordings were of the same flow range, this generated the smallest error which would be expected. The largest error in estimating flow parameters was observed when the calibration recording was obtained from a low flow inhalation and was used to estimate a high flow inhalation. This would also be expected as one can see from Figure 6.6 that the model coefficients change at higher flow rates compared to lower flow rates. Therefore, the relationship between flow and sound may not be constant at all flow rates. In addition, the difference in model coefficients across flow ranges did not greatly impair flow estimation in inhaler inhalations in this study. The High flow range had much higher flow rates than the Medium and Low flow ranges. It was noted that the T_I values were not significantly different across flow range groups also. This may suggest that the acceleration of inhalations may have influenced the model coefficients also. Therefore, it could be argued that the model coefficients change most significantly at high flow rates with faster acceleration.

There were some limitations to this study. Healthy participants were recruited in order to investigate the accuracy of this method on a wide range of flow rates. This may not have been possible with patients suffering from impaired respiratory function. In addition, asking patients to inhale at a range of different flow rates may confuse patients on how to correctly use a DPI. Consequently, patients were not recruited for this study, however, the efficacy of this audio-based method of estimating DPI inhalation flow profiles has been presented. The airtight container may have affected inhaler inhalation audio-based

features, particularly spectral features. However, recording directly from the surface of the inhaler and not inside the airtight container, as well as using an amplitude based feature such as the acoustic envelope would minimise this effect. The airtight container also ensured accurate measurement of flow rate without the need for sensors within the inhaler device. Flow sensors placed within the inhaler may have changed the resistance within the inhaler and would affect flow measurement.

Recordings took place in a designated recording room to reduce background noise in the audio recordings which may not replicate real life clinical environments. In order to fully understand the relationship between audio and flow signals, it was essential to reduce background noise. The microphone in the INCA device was situated very close to the grill at the Ellipta mouthpiece where the inhalation sound is mostly generated. Furthermore, the SNR was high (13.9-23 dB) in low to high flow inhalations even with ambient background noise present in the recording room. This method was also tested on a range of SNR levels and generated sufficient accuracy in estimating parameters such as PIFR, IC and T_r even within lower SNR levels. This shows the robustness of this flow estimation method in noisy environments. As would be expected, the average flow estimation accuracy decreased at lower SNR levels. However, as the microphone is positioned within the device casing directly beside the inhaler mouthpiece, this should generate sufficient SNR levels even in real clinical environments. Future research will test this method in clinical and domestic environments.

Future research should also focus on the automatic detection of Ellipta inhalation sounds from noisy environments. Once the inhalation sounds are accurately detected, one can apply the methods presented in this study to accurately assess patient inhaler inhalation technique. The flow signal was used in this study to segment inhalations to investigate the relationship between the audio and flow signals. Previous studies have developed an accurate method of detecting patient inhalation sounds recorded from the INCA device attached to a Diskus DPI during inhaler use in real clinical and domestic environments (Holmes *et al.*, 2012; Holmes *et al.*, 2014a). However, there is a clinical need for further audio-based classification methods to accurately detect inhalations from Ellipta DPI as well as testing the accuracy of the presented method on estimating low, medium and high inspiratory flow rates within noisy real-life environments.

This audio-based flow estimation method could be implemented into the clinical setting by obtaining one recording of an inhaler inhalation during a patient's consultation with a healthcare professional. As the patient is trained on their inhaler, an inhalation

could be recorded using INCA and used to calibrate a model to estimate the inhaler inhalation flow profile remotely. When the patient returns for a consultation, the patient may obtain objective feedback on their inhalation technique and can be trained on how to improve their inhaler technique and their disease control as a result. Monitoring inhalation flow parameters remotely using acoustics provides a non-invasive, accurate method of monitoring inhaler user technique and potentially the respiratory health of asthma and COPD patients.

6.5 Chapter Conclusion

This study presented a method of accurately estimating the flow profile of inhaler inhalations based on the logarithmic relationship between the acoustic envelope of the inhalation sound and flow signal. Using only one inhalation recording for model calibration, an average flow estimation accuracy of over 90% was observed. This method may be employed to remotely monitor patient inhalation technique and help train patients to improve their inhaler technique by introducing more personalised treatments in respiratory medicine. Future research will investigate employing audio-based classification methods to segment inhalation sounds in noisy clinical and domestic environments. Other future research will apply the presented flow estimation method to other DPIs to remotely monitor patient adherence across a range of different inhaler devices. The clinical impact of this study lies in developing a non-invasive audio-based method of obtaining pertinent clinical information regarding inhaler inhalation technique. Furthermore, obtaining real life inhalation flow profiles can be used to test the development of new drug formulations for DPIs. Therefore, this method may be used to remotely monitor patient inhalation technique while enhancing the development of future DPI medication.

Chapter 7. Development and Validation of an Audio-Based Algorithm to Objectively Assess Patient Pressurised Metered Dose Inhaler User Technique

The studies described in this chapter investigate research questions 18-27 from Chapter 3. The studies reported in Chapter 4-6 primarily focused on the acoustic properties of inhalation sound events across a range of different inhaler devices and how audio-based features can extract pertinent clinical information from inhaler inhalation sound events such as the PIFR and IC. As thoroughly discussed in Chapter 2, there are a number of specific steps that are critical to ensure maximum drug delivery from pMDIs, unlike DPIs which are primarily dependent on the inhalation event. These critical steps include good coordination between inhalation and actuating the pMDI canister and performing a slow and steady inhalation (below 90 L/min). There is a lack of methods available to healthcare professionals to objectively assess patient pMDI user technique in clinical practice. As the pMDI is the most commonly used inhaler worldwide, there is a clinical need to develop and validate new audio-based signal processing methods to objectively assess patient pMDI user technique. Furthermore, there is a need to statistically compare audio-based methods to subjective checklists in order to investigate the clinical margin of benefit of implementing audio-based inhaler monitoring systems into clinical practice to assess patient inhaler user technique.

The pilot study presented in Section 7.1 of this Chapter focuses on analysing the acoustic properties of pMDI actuation sounds. It also reports an investigation into the use of time-frequency audio-based features to automatically detect actuation sound events during pMDI use. The study presented in Section 7.2 of this Chapter focuses on the

development and validation of an audio-based signal processing algorithm to objectively assess patient pMDI user technique. The audio-based algorithm is also statistically compared to clinical checklist assessment.

The studies presented in this chapter have resulted in the following peer-reviewed publications;

- **Taylor T E**, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2014 An acoustic method to automatically detect pressurized metered dose inhaler actuations. In: *Engineering in Medicine and Biology Society (EMBC), 2016 36th Annual International Conference of the IEEE*, Chicago, Illinois, USA.
- **Taylor T E**, Zigel Y, Egan C, Hughes F, Costello R W and Reilly R B 2018 Objective Assessment of Patient Inhaler User Technique Using an Audio-Based Classification Approach. *Scientific Reports* 8 2164.

7.1 Investigating the Use of Time-Frequency Audio-Based Features to Automatically Detect Pressurised Metered Dose Inhaler Actuations

7.1.1 Introduction

Poor actuation coordination is a common critical user technique error made by patients during pMDI use (Sanchis *et al.*, 2016). It involves the patient actuating the pMDI canister before the onset of inhalation or actuating towards the end of inhalation where insufficient inspiratory volume would inhibit optimum drug delivery to the lower airways. There is a need to identify actuations during pMDI use as they refer to the release of medication from the inhaler. Also, many pMDIs do not have dose counters within the device and so patients may find it difficult to keep track of medication intake during treatment (Sander *et al.*, 2006). As previously reported, audio-based methods have the capability to accurately detect drug preparation sounds that refer to medication release in other inhalers such as the Diskus DPI (Holmes *et al.*, 2014a). Hence, there is a need to develop an audio-based method to detect pMDI actuations to monitor the timing of medication release and the number of doses administered to the patient.

However, little is known regarding the temporal and spectral properties of actuation sounds and whether audio-based methods can be employed to automatically detect actuation sounds. As the timing between inhalation and actuation is critical, fine temporal resolution is required in order to objectively assess patient user technique. The aim of this pilot study was to analyse the temporal and spectral properties of pMDI actuation sounds and to explore the potential for employing audio-based features to automatically and accurately detect pMDI actuations during inhaler use. The hypothesis of this pilot study was that time-frequency features of actuation sound events can be employed to automatically detect the onset of actuation during pMDI use.

7.1.2 Methods

7.1.2.1 Inhaler recording setup

The study employed an Analog Devices ADMP401 MEMS omnidirectional microphone to record inhaler audio signals (Figure 7.1). The microphone was placed outside facing inwards, towards the location of the actuation site, at the lower end of the inhaler casing. The microphone was then connected to a Creative Sound Blaster [Creative Labs Ireland (Ltd.), Dublin, Ireland] sound card. The sampling rate employed was 44.1 kHz with 16 bits per sample resolution. A 0.5" force sensitive resistor (FSR) was placed on top of the inhaler canister to obtain a reference signal indicating exactly when the user actuated the inhaler canister. This reference signal was used to compare the true onset time of actuation against the detected onset time estimated by the audio-based algorithm. The FSR was connected as a feedback resistor in a buffer circuit with low resistance



Figure 7.1. pMDI recording setup.

(Left) Top-down view of the recording rig showing FSR on canister. (Right) Side view of recording setup showing microphone placement.

($R=120\Omega$) to obtain a linear force-voltage relationship as is in the manufacturer's guidelines [SparkFun Electronics, Colorado, USA]. FSR data were recorded at 1 kHz sampling rate.

7.1.2.2 Participants

Data were obtained from 15 in-patients (six male/nine female, age range 21-84) at Beaumont Hospital, Dublin, Ireland. All patients recruited were suffering from a chronic respiratory disease (asthma or COPD) and were current pMDI users. Data were also obtained from a group of five healthy participants to capture actuation events at different specific times within inhalation events.

Patient cohort recording protocol

Patients were asked to use a placebo Evohaler pMDI for three separate recordings. The first two consisted of the patient using the inhaler as they would normally on a daily basis. The patients were then informed from a healthcare professional of any user technique errors made and were then asked to use the inhaler a third time. Patient inhaler user technique was subjectively assessed by a healthcare professional. A total of 44 pMDI recordings (one recording failure instance) were obtained from the patient cohort. Figure 7.2 shows an example of a patient pMDI audio signal.

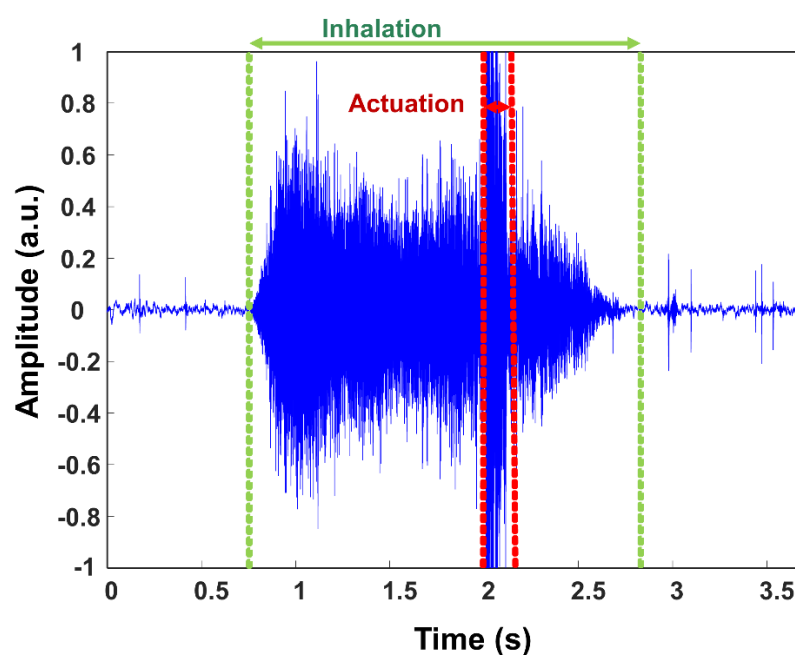


Figure 7.2. Audio signal of a patient using a pMDI.
The actuation is late into the inhalation event highlighting poor actuation coordination.

Healthy cohort recording protocol

Healthy participants were also recruited for this pilot study to record a range of specific actuation coordination manoeuvres during inhalation (both correct and incorrect user technique). Each healthy participant was trained, using a placebo Evohaler pMDI, to actuate the inhaler at three specific times during inhalation; 1s before inhalation (early actuation), 0-0.5s into an inhalation (correct actuation) and finally approximately two thirds into an inhalation (late actuation). For each actuation time, subjects were trained using a Clement-Clarke In-Check Dial to inhale at PIFR $\cong$ 30 L/min, PIFR $\cong$ 60 L/min and PIFR $>$ 90 L/min. Each actuation time was recorded three times for each PIFR giving a total of 135 recordings for five participants. All recordings were visually and aurally assessed by an independent reviewer to ensure the instructed actuation manoeuvre was performed.

7.1.2.3 Signal processing

It was hypothesised that the medication plume expelled from the inhaler canister during actuation creates an onset of high frequency power for a short time period. The signal processing was divided into two stages. Stage one consisted of time-frequency analysis of pMDI audio signals. Stage two employed a summation of high frequency content followed by a peak assessment routine.

Stage One

Wavelet transformations have been previously employed to classify between healthy subjects and subjects with respiratory diseases (Sello *et al.*, 2008). The continuous wavelet transform (CWT) was employed to highlight discontinuities in the inhaler audio signals. The CWT with scaling parameter a and time shift parameter τ is given as;

$$\mathbf{W}_f(a, \tau) = \frac{1}{\sqrt{a}} \int_{-\infty}^{+\infty} x(t) \varphi * \left(\frac{t - \tau}{a} \right) dt \quad (7.1)$$

where φ is the analysing wavelet if it verifies the admissibility condition (Sello *et al.*, 2008).

The CWT was chosen as it gives high temporal resolution at high frequencies. The Morlet wavelet, consisting of a sinusoid multiplied by a Gaussian window, was employed

as it is commonly used and its scale-frequency relationship requires less computation to define as the peak frequency is equal to the centre frequency of the wavelet. The Morlet wavelet is given as;

$$\varphi(t) = \frac{1}{\pi^{\frac{1}{4}}} (e^{i2\pi f_c t} - e^{-(i2\pi f_c)^2/2}) e^{-t^2/2} \quad (7.2)$$

where f_c is the centre frequency of the mother wavelet. Scales 2 to 1.625, corresponding to approximately 17,916 Hz to 22,050 Hz, in decrements of 0.005 were chosen to view high frequency content of the audio signal. This represents a total of 76 pseudo frequencies to utilise for time-frequency analysis of pMDI audio signals.

Stage Two

The second stage of signal processing reduced the dimensionality of the output wavelet matrix and detected high frequency power peaks that may identify actuation sound events. Each wavelet coefficient was squared to obtain all positive coefficients. All squared wavelet coefficients were then summated across all scales at each sample point. This resulted in an output signal that represented a summation of all high frequency power across high frequencies. This method is similar to that reported in previously studies (Wei, 2007). The method employed for this study can be represented as;

$$Y(\tau) = \left[\sum_{a=a_1}^m |\mathbf{w}_f(a, \tau)|^2 \right]_{\tau=\tau_1, \tau_2, \dots, \tau_N} \quad (7.3)$$

where the squared summation of wavelet coefficients from scales a_1 to m are computed for all N time points. The CWT of a pMDI audio signal and the high frequency summation output can be seen in Figure 7.3.

A peak assessment routine was then employed to detect and assess peaks above a defined threshold of 0.38. This threshold was chosen as empty canister actuations generated peaks with reduced acoustic power at 0.32 ± 0.01 hence a threshold (θ) of 0.38 ($>0.32 + 3\sigma$) was employed. It was observed that the actuation sound event was of short duration, 100-150 ms. Each detected peak in the output signal of the CWT high frequency power summation was initially flagged as a potential actuation event. Values were taken

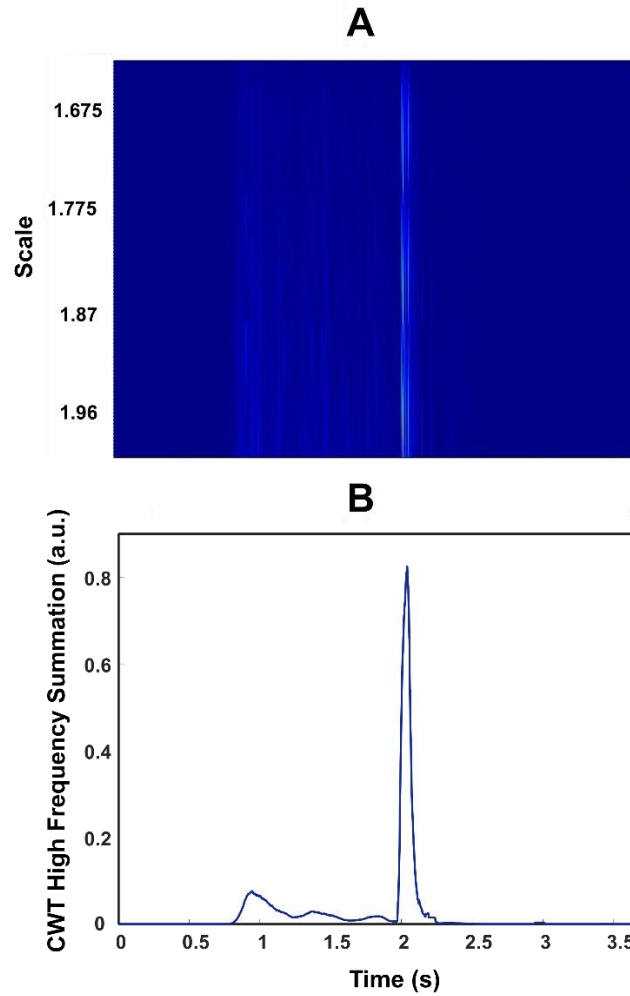


Figure 7.3. The continuous wavelet transform of a pMDI audio signal.
 (A) Continuous wavelet transform of the pMDI audio signal presented in Figure 7.2 using scales 2 to 1.625. (B) Output of high frequency summation with actuation peak at 2.04s.

± 56 ms from the maximum point of each peak to observe if the value decreased by a threshold of 25% before and after the maximum peak point. Figure 7.4 shows a flow chart of the signal processing employed to detect an actuation sound. An FSR was employed as a reference time stamp signal to combine with expert visual-aural assessment to label the onset of actuation events. An adaptive threshold of 80% of the maximum voltage triggered a logic pulse to time stamp canister actuation.

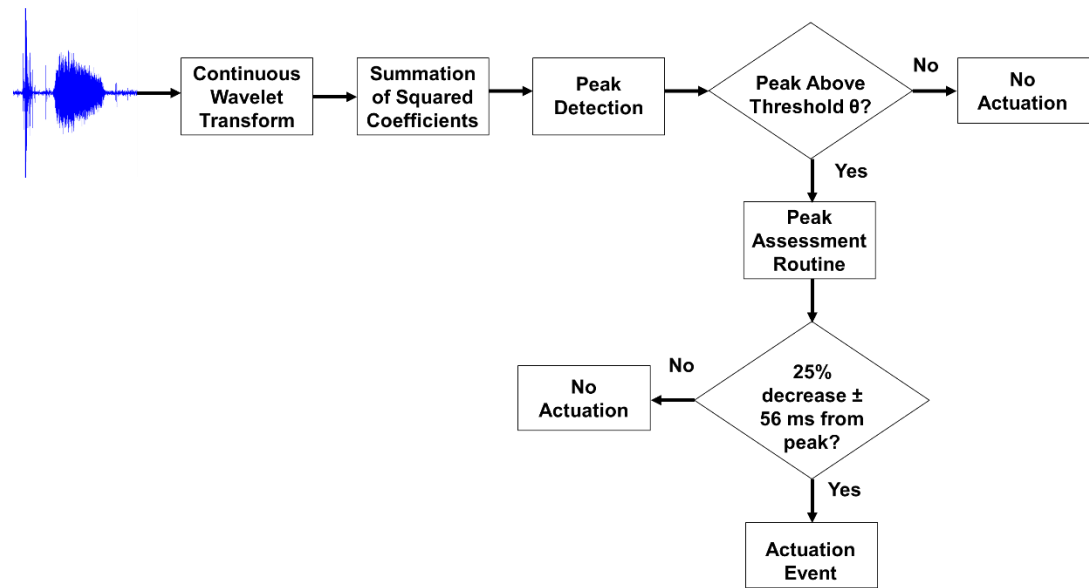


Figure 7.4. Flow chart of actuation sound event detection algorithm.

7.1.3 Results

A random selection of 20 pMDI acoustic recordings from the healthy group data was employed for algorithm training. The developed algorithm was tested on 159 test recordings obtained from in-hospital patients in a real clinical environment (n=44) and a cohort of healthy (n=115) participants. A total of 158 actuations were obtained for testing. Recordings consisted of no actuations (n=6) while others contained multiple actuations (n=4) as a result from incorrect inhaler user technique.

The algorithm was validated against the reference FSR data and visual-aural assessment. An actuation was deemed to be correctly identified if the algorithm detected the actuation within 300 ms of the onset of the FSR pulse. This was to account for the delay between the canister being actuated (FSR threshold) and the medication plume generating its maximum acoustic energy which the algorithm detects. Figure 7.5 shows an example of an early actuation audio signal with the time of actuation marked according to the audio-based detection algorithm and the corresponding FSR reference signal. The algorithm outputs the onset time of the actuation within the pMDI audio recording.

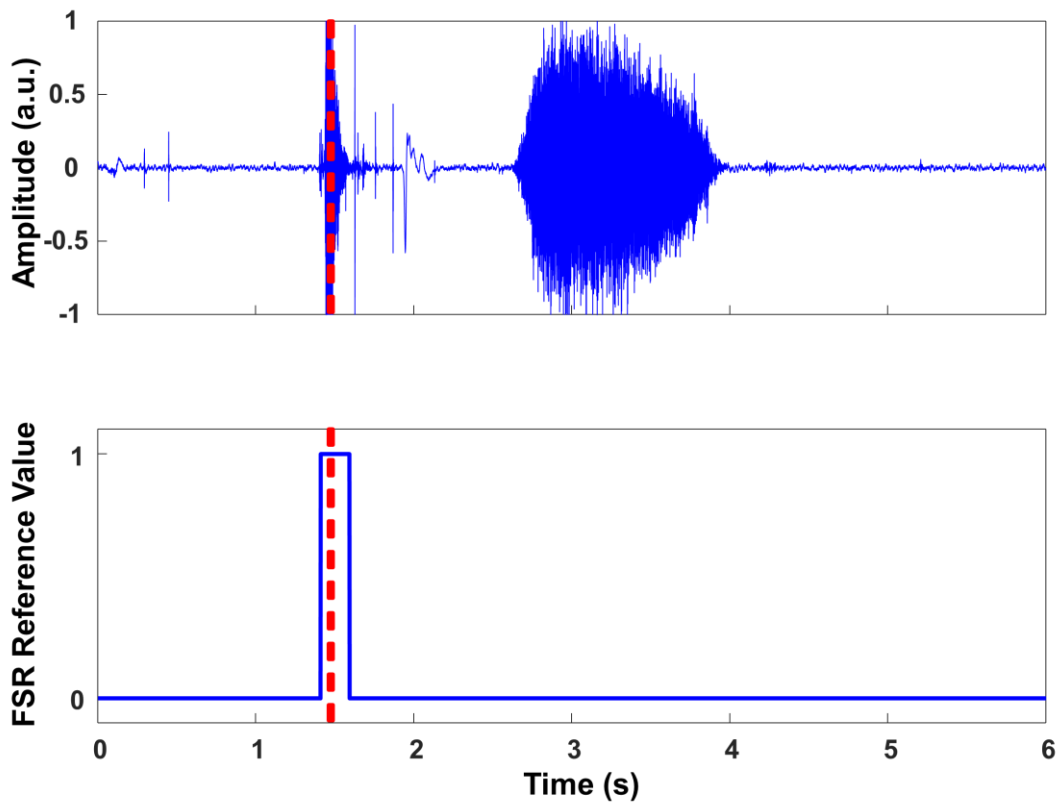


Figure 7.5. Example of a patient pMDI recording highlighting the detected actuation event.

(Top) pMDI audio signal showing the detected early actuation event (red) at 1.47s followed by an inhalation event and (bottom) the force sensitive resistor actuation reference signal (0 - no actuation, 1 - actuation event). The clinical reviewer also noted that this patient inhaled too fast (PIFR>90 L/min) in this particular example. This was based on visual/aural assessment.

Table 7.1 presents the performance of the actuation detection algorithm in terms of sensitivity (Sen) of 100%, specificity (Spe) of 99.4% and accuracy (Acc) of 99.7%. Out of the 158 actuations recorded, all 158 of them were accurately detected with only one False Positive incident.

Table 7.1. Actuation sound event detection algorithm performance results.

Total no. Recordings	Total no. Actuations	Sen (%)	Spe (%)	Acc (%)
159	158	100	99.4	99.7

7.1.4 Discussion

This pilot study investigated the acoustic properties of pMDI actuation sounds as well as developing an audio-based algorithm to automatically detect pMDI actuations in real-life clinical environments. The audio-based algorithm employed time-frequency features extracted from pMDI audio recordings in order to determine the onset of actuation sounds during inhaler use. This can give healthcare professionals information as to the number of doses administered to the patient during treatment. The results demonstrate that the audio-based features of pMDI audio recordings may be used to automatically identify actuations during inhaler use. An overall accuracy of 99.7% and a specificity of 99.4% for all actuation times is a promising result if this method is to be employed in a fully automated system for monitoring patient pMDI user technique.

If a patient incorrectly inhales too fast ($\text{PIFR} > 90 \text{ L/min}$), it can be quite challenging for a healthcare professional to accurately determine if the medication was released from the canister. However, attaching a microphone onto the inhaler may be used to detect actuation events even within inhalations with very high PIFRs as demonstrated in this pilot study. It was noted from empirical observations that pMDI actuation sounds are quite short. The CWT method was employed in this study as this approach generated high temporal resolution at high frequencies. One of the challenges in this study was detecting actuations within high PIFRs as it was noted that patients tend to inhale too fast when using the pMDI. This involves detecting a very short actuation sound within a loud inhalation sound. Wavelet scales 2 to 1.625 frequencies contain unique acoustic information of an actuation sound which is not as prominent in inhalations. Such low scales were examined to separate actuations from inhalation sounds with very high PIFRs. Inhalation sounds generated some power at high frequencies also, even within the actuation sound frequency bands of interest. It was for this reason that a summation of all squared coefficients across all selected scales at each sample point was employed to distinguish an actuation sound within inhalations containing high frequency.

It was noted upon visual and aural assessment of the patient pMDI audio signals combined with the actuation event detection that 87% ($n=13$) of patients had poor actuation coordination based on the initial two recordings (at least one occurrence of poor actuation coordination in recordings 1 and 2). However, this reduced to 53% ($n=8$) after tuition in the third recording. This demonstrates that an audio-based pMDI monitoring system may be of clinical benefit to patients and healthcare professionals. It also

highlights the inability of many patients to control their disease due to persistent inhaler misuse. It was noted that the most common technique error among patients was early actuation with 47% (n=7) of patients actuating too early before inhaling. While breath actuated pMDIs have been reported (Virchow *et al.*, 2008) which release the drug once the user reaches a PIFR of ~20 L/min, their use is not mainstream. A non-invasive portable monitoring system for pMDIs may therefore present clinically important information to patients regarding their own inhaler use. There is a need to further investigate the use of additional audio-based features to automatically detect inhalation sounds as well as actuation sounds. It was noted from empirical observations in this study that patients also tend to inhale too fast during pMDI use. Therefore, there is a need to develop an audio-based signal processing algorithm that can objectively assess patients' actuation coordination and inhalation flow rate during pMDI use.

7.2 An Audio-Based Signal Processing Algorithm to Objectively Assess Patient Pressurised Metered Dose Inhaler User Technique

7.2.1 Introduction

Two of the most common critical errors patients make while using pMDIs include poor actuation coordination and inhaling too fast with a PIFR of over 90 L/min (Melani *et al.*, 2011; Sanchis *et al.*, 2016; Jha *et al.*, 2017; Price *et al.*, 2017). Studies have reported that 45% of patients have poor actuation coordination while using a pMDI (Sanchis *et al.*, 2016). Furthermore, it has been reported that 47.2% of patients inhale too fast (PIFR>90 L/min) when using a pMDI (Price *et al.*, 2017).

Patient inhaler user technique is assessed most commonly using checklists based on visual/aural assessment by a healthcare professional (Batterink *et al.*, 2012; Ozturk *et al.*, 2015). However, this method of assessment is subjective, it gives equal rating to all errors, is prone to overestimate patient performance and cannot be used to monitor how patients use their inhaler outside of clinical visits (Pritchard and Nicholls, 2015; Sulaiman *et al.*, 2017). Inhaler training devices have been reported to improve patient inhaler user technique (Ammari and Chrystyn, 2013; Azouz *et al.*, 2014). Devices such as the In-Check Flo-Tone [Clement-Clarke International Ltd, Harlow, UK] can give patients an

audible signal once they generate the required inhalation flow rate and has been reported to improve patient inhalation technique in the pMDI (Ammari *et al.*, 2017). However, many training devices, such as the Flo-Tone, cannot objectively monitor both actuation coordination and inhalation flow rate.

Audio-based methods, using the INCA system, have presented promising opportunities to remotely monitor patient inhaler adherence (both time of use and user technique) and quantify drug delivery in DPIs (Holmes *et al.*, 2014a; D'Arcy *et al.*, 2014; Killane *et al.*, 2016; Sulaiman *et al.*, 2016d; Sulaiman *et al.*, 2016e). This has led to more clinically accurate measures of DPI use that reflect changes in patients' health over the course of treatment (Sulaiman *et al.*, 2015; Sulaiman *et al.*, 2016d). Recent studies have reported the use of audio-based methods to automatically detect and classify events associated with pMDI use such as actuation (drug release) and inhalation events (Taylor *et al.*, 2014; Kikidis *et al.*, 2015; Lalos *et al.*, 2016; Nousias *et al.*, 2016). However, these studies mostly recruited either small patient cohorts or small cohorts of healthy participants and did not objectively detect the presence of critical user technique errors such as poor actuation coordination and inhaling too fast during pMDI use. There may be challenges, however, in accurately estimating the inhalation flow rate from pMDIs using audio-methods due to the limited acoustic energy generated in pMDIs during inhalation (as reported in the studies described in Chapter 4) (Taylor *et al.*, 2016b).

The aim of this study was to develop an audio-based signal processing algorithm to objectively assess pMDI user technique using patient recordings from the INCA audio recording device. It was hypothesised that audio-based methods may be employed in clinical practice to objectively detect the presence of two of the most common critical errors during pMDI use: poor actuation coordination and inhaling too fast (above 90 L/min). Since the Flo-Tone device can generate an audible signal during pMDI inhalation, the unique characteristic sound of the device was exploited to automatically classify between three inhaler sound events (inhalation/actuation/exhalation). Then, from the detected inhalation sound event, two flow parameters were estimated: PIFR and volume (IC). The accurate estimation of these parameters would be of significant clinical benefit to both patients and healthcare professionals by providing more accurate assessment of patient inhaler user technique.

7.2.2 Methods

In order to develop an audio-based method to objectively assess patient pMDI user technique, the approach of this study was divided into three stages. Stage 1 aimed to develop an audio-based algorithm to automatically detect and classify inhaler sound events (actuation, inhalation and exhalation sounds) from asthma and COPD patient pMDI audio recordings. This would allow healthcare professionals to objectively assess patients' coordination between actuation and inhalation. Stage 2 aimed to develop an audio-based model to accurately estimate the PIFR and volume of the detected inhalation event. This would allow healthcare professionals to objectively assess if patients perform a "slow" and "deep" inhalation as required. Stage 3 involved combining Stages 1 and 2 (objectively assessing the sequence of inhaler sound events and then estimating PIFR and volume from the detected inhalation events). A statistical comparison between the presented objective audio-based method of assessing patient pMDI user technique and the subjective clinical visual/aural assessment was then performed.

7.2.2.1 Inhaler audio recording setup

In this study, an In-Check Flo-Tone training device was attached to the mouthpiece of a placebo Evohaler pMDI as recommended by the manufacturer (Figure 7.6B). The Flo-Tone is an add-on mouthpiece for a pMDI with a reed situated on top that starts to generate an audible sound when the patient reaches an inspiratory flow rate of 30-60 L/min (Ammari *et al.*, 2017). The sound is harmonic with a fixed fundamental frequency (pitch) of approximately 540 Hz. The Flo-Tone sound becomes louder as the flow rate of inhalation increases. The INCA device was attached to the back of the pMDI to record inhaler audio signals as shown in Figure 7.6B. Audio signals were recorded at 48 kHz sampling rate with 16 bits per sample resolution.

7.2.2.2 Stage 1: Automatic classification of inhaler sound events

Patient recruitment

In this study, 62 patients (19 male/43 female, age range: 17-82) with asthma (n=30), COPD (n=27) and both asthma and COPD (n=5) were recruited from both in-patient wards and out-patient respiratory clinics at Beaumont Hospital, Dublin, Ireland. This study was approved by the Beaumont Hospital Ethics (Medical Research) Committee (13/53). Written consent was obtained from each patient.

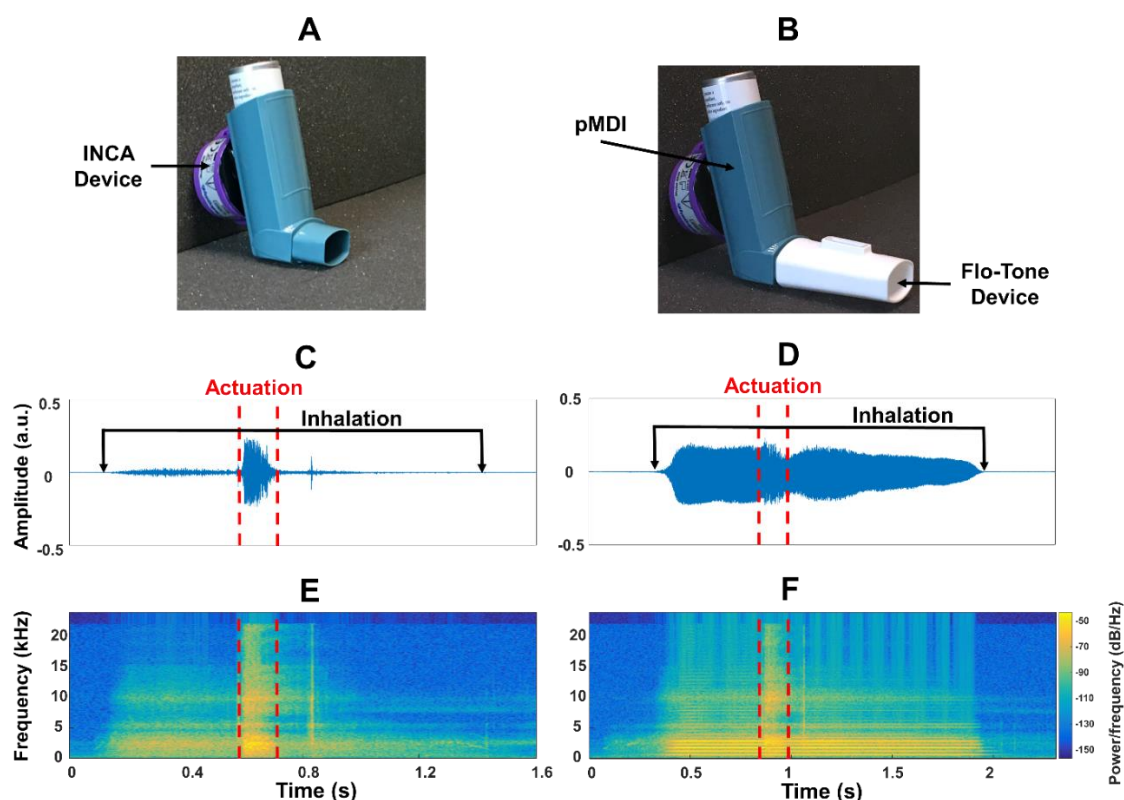


Figure 7.6. Inhaler audio recording setup. Evohaler pMDI with the Flo-Tone attached to the mouthpiece.

(A) pMDI with the INCA audio recording device attached to the back of the inhaler. (B) pMDI with the INCA device attached to the back of the inhaler with the Flo-Tone attached to the inhaler mouthpiece. (C) Time domain signal and (E) spectrogram of pMDI audio recording containing an inhalation (approximately 60 L/min PIFR) and an actuation event. (D) Time domain signal and (F) spectrogram of pMDI audio recording containing an inhalation (approximately 60 L/min PIFR) and an actuation event with the Flo-Tone attached to the inhaler mouthpiece. The intensity levels of pMDI inhalation sounds, with the Flo-Tone attached to the inhaler mouthpiece, is approximately 62dBA at 60 L/min. However, without the Flo-Tone attached to the inhaler mouthpiece, the inhalation sounds are much more quiet (~35dBA at 60 L/min). The inhaler audio signal was obtained from the INCA device and input to a Creative Sound Blaster external sound card [Creative Labs Ireland (Ltd.), Dublin, Ireland] which was connected to a data acquisition laptop. Audio signals were sampled at 48 kHz with 16 bits per sample resolution. A toggle switch was wired to the INCA device to manually activate/deactivate the device for recording audio data. The INCA device uses a Knowles SPU0414HR5H-SB microelectromechanical systems (MEMS) microphone [Knowles Acoustics, Illinois, USA] to record audio signals. The device usually records inhaler audio data at 8 kHz sampling rate with 8 bits per sample resolution (Holmes et al., 2014a; D'Arcy et al., 2014). However, for this study a higher sampling rate and bit resolution was implemented.

Patient recording protocol

All asthma and COPD patients were asked to use the placebo pMDI with the INCA and Flo-Tone attached for a total of four recordings under the supervision of an expert clinical reviewer. For the first two recordings, patients were asked to use the inhaler as they normally would (i.e. patients did not receive any tuition regarding inhaler user technique from the expert clinical reviewer for the first two recordings). Fifty-seven of the patients recruited were current or previous pMDI users, while the remaining five had used other inhaler devices during treatment. The five patients who had not previously used a pMDI were instructed how to use the inhaler correctly before the first recording and not before the second recording. Patients were then given feedback on their user technique before recording three and before recording four. This was to investigate the effect of tuition from an expert clinical reviewer on patient inhaler user technique. The feedback given to patients from the expert clinical reviewer was based on visual/aural assessment using a checklist method. This checklist method was used to replicate current clinical inhaler user technique assessment. The pMDI user technique checklist that was employed in this study incorporates both manufacturer's guidelines for using the pMDI and the Flo-Tone device and is available in Appendix C (Figure C1). A total of 32 Flo-Tone devices were employed and were randomly allocated across the 62 patients recruited. Flo-Tone devices were sterilised after each patient to prevent spread of infection. Each patient used a different pMDI device to account for variability in the inhaler sounds across devices.

The audio-based algorithm in Stage 1 to automatically classify inhaler sound events was composed of two phases: training and testing (a block diagram of the inhaler sound event classification algorithm is presented in Figure 7.7A). The patient dataset was divided using a hold-out approach into training set (31 patients) and testing set (31 patients). The training and testing sets were divided in such a way to ensure that patients' age was not significantly different between training and testing sets to eliminate any bias ($p=0.9$). This was done also as the age between the asthma and COPD patient cohorts was significantly different in this study (asthma age (48 ± 16 years) and COPD age (70 ± 7 years), $p<0.001$). This also eliminated any bias between the training and testing sets regarding respiratory disease type.

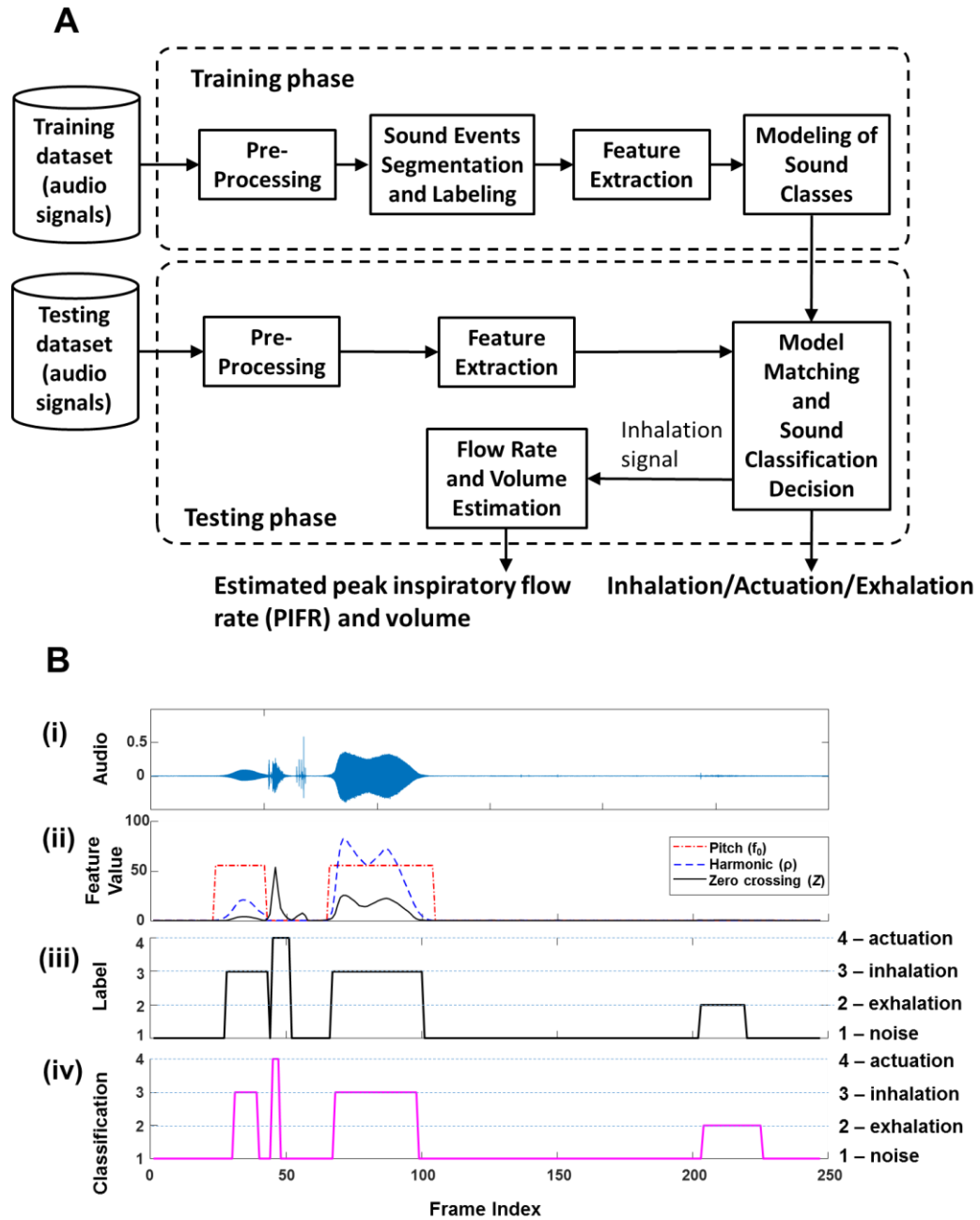


Figure 7.7. Overview of audio-based classification of inhaler sound events from patient audio recording.

(A) Block diagram of the audio-based inhaler sound event classification algorithm. The audio-based signal processing algorithm is composed of two phases: training and testing. In the training phase, the digital audio signal undergoes pre-processing which contains a band pass filter to reduce background noise; manual sound events segmentation to label the different sound events (actuation/inhalation/exhalation/noise) for the training process; audio-based feature extraction; and classifier training (sound models estimation). In the testing phase, the inhaler audio signal undergoes similar pre-processing and feature extraction, as in the training phase; frame-by-frame sound model matching and classification. The detected inhalation segments then undergo flow rate and volume estimation. (B) Example of inhaler sound event classification using patient recording. (B) (i) Audio time domain signal of asthma patient using a pMDI, (ii) illustration of a set of audio-based feature values that are employed to automatically detect and classify inhaler sound events, (iii) the manually labelled classes within the inhaler audio signal including (noise-1/exhalation-2/inhalation-3/actuation-4) and (iv) classification result from the audio-based algorithm.

Audio signal pre-processing

In both training and testing phases, the inhaler audio signal was band pass filtered between 140-22,000 Hz to emphasise the relevant inhaler sound events (actuation, inhalation and exhalation) and reduce background noise. In the training phase, each signal underwent sound event segmentation (labelling) which consisted of labelling each inhaler sound event (actuation, inhalation and exhalation) for the training process. This was performed through an initial automatic sound event segmentation process using a graphical user interface (GUI) which was over read by two independent reviewers. This was carried out to label each inhaler sound event for the training process and for the evaluation of the inhaler sound event classification algorithm in the testing phase. Figure C2 presents the GUI employed in this study (Appendix C). Inhaler audio signals were divided into frames of 40 ms duration with 20 ms overlap between adjacent frames giving a frame rate of 20 ms. The DC offset was removed from each frame.

Feature extraction

Thirty audio-based features from time and spectral domains were extracted from each frame. The full list of the features is presented in Table C1 (Appendix C). Among the extracted features included: Twelve mel-frequency cepstral coefficients (MFCCs), 10 linear predictive coding (LPC) coefficients, energy, zero-crossing rate and a high frequency power (over 15 kHz) feature estimated using the continuous wavelet transform (as previously described in Section 7.1 of Chapter 7) (Taylor *et al.*, 2014). Since the Flo-Tone device generates a harmonic sound during inhalation, a harmonic feature was also extracted. This harmonic feature was calculated as the peak value of the frame's autocorrelation function, searched in the range of 500-600 Hz.

Inhaler sound classification

In this study, the classification approach was frame-by-frame. A quadratic discriminant analysis (QDA) classification method was employed to classify each audio frame. This method was compared later to an artificial neural network (ANN) classifier. In the training phase, the classifier model was trained (in QDA: the mean vectors and the covariance matrices (McMenamin and Pessoa, 2015)) from the training feature set of each of the three inhaler sound classes (actuation, inhalation, and exhalation).

In the testing phase, each frame was classified individually as one of four sound classes: actuation, inhalation, exhalation, or noise. Adjacent frames from the same class were concatenated together as one inhaler sound event segment (actuation, inhalation, or exhalation). After pre-processing and feature extraction, the testing process (model matching and sound classification module, Figure 7.7A) was performed in four main steps: 1) noise estimation, 2) model adaptation, 3) frame-by-frame classification, 4) formation of sound events by concatenation of adjacent frames.

1) Noise estimation:

Since the audio signals were recorded in different clinical environments, the background noise was different for each signal. The background noise was estimated using the feature vectors from the frames containing the lowest (40%) energy values.

2) Model adaptation:

To account for the variability in the sounds across different Flo-Tone devices, adaptation of the inhalation class model was performed. This was done by *initial* frame-by-frame classification by finding the minimum Euclidian distance between a frame feature vector $\mathbf{x}$ and each class model mean vector $\boldsymbol{\mu}_\omega$ ($\omega = 1, \dots, 4$). This was calculated as;

$$\omega^*(\mathbf{x}) = \underset{\omega=1,\dots,4}{\operatorname{argmin}} \left[\sqrt{(\mathbf{x} - \boldsymbol{\mu}_\omega)^T (\mathbf{x} - \boldsymbol{\mu}_\omega)} \right] \quad (7.4)$$

where $\omega^*(\mathbf{x})$ is the chosen class for the given frame.

In this approach, the classified inhalation frames were used to adapt the mean vector of the inhalation class model. This was done by taking the average of the mean vectors of the inhalation class model and the initial classified inhalation frames. It was found that this simple process is quite efficient in terms of computation complexity and accuracy.

3) Frame-by-frame classification:

A QDA classification method was employed in Stage 1 to classify each audio frame. Each frame was assigned to the class determined by a maximum probability score, as given by;

$$\omega^* = \underset{\omega=1,\dots,4}{\operatorname{argmax}} \left[\frac{1}{\sqrt{2\pi|\mathbf{\Sigma}_\omega|}} \exp \left(-\frac{1}{2} (\mathbf{x} - \mathbf{\mu}_\omega)^T \mathbf{\Sigma}_\omega^{-1} (\mathbf{x} - \mathbf{\mu}_\omega) \right) P(\omega) \right] \quad (7.5)$$

where ω^* is the chosen class of the frame, $\mathbf{\mu}_\omega$ the mean feature vector of class ω , $\mathbf{\Sigma}_\omega$ is the covariance matrix of class ω , and $\mathbf{\Sigma}_\omega^{-1}$ its inverse. The prior probabilities of each class, $P(\omega)$ were determined by their frequency in the training dataset. The QDA as a classifier model was chosen as the feature distribution of actuation, inhalation and exhalation classes were approximately Gaussian. An example of distribution of features in the feature space is shown in Figure 7.8A.

Once each frame was classified, a median filter (order of five) was applied to the resulting classification output to reduce the occurrence of noise (class 1) being classified as one of the other three inhaler sound classes (class-2 exhalation, class-3 inhalation, class-4 actuation).

4) Formation of sound events by concatenation of adjacent frames:

Adjacent frames from the same class were concatenated to form an inhaler sound event (actuation, inhalation, and exhalation). A duration rule was set to a minimum of five frames (100 ms) per class (for inhalation and exhalation) to reduce false positive occurrences of inhalation and exhalation sound events.

Feature selection

A sequential forward feature selection approach was employed to select the optimum set of audio-based features to classify inhaler sound events. This method of feature selection is commonly used in classification methods (Jain *et al.*, 2000; Bishop, 2006; Dafna *et al.*, 2013). The criterion used for feature selection was a weighted performance measure which accounted for the average sensitivity and positive predictive values for actuation, inhalation and exhalation sound event classification. The weighted performance measure that was employed for feature selection was calculated as;

$$J(X) = w^A(S_X^A + P_X^A) + w^I(S_X^I + P_X^I) + w^E(S_X^E + P_X^E) \quad (7.6)$$

S_X^A, S_X^I, S_X^E are the sensitivity measures of actuation, inhalation and exhalation sound event classification for the subset of features X . P_X^A, P_X^I, P_X^E are the positive predictive values,

w^A , w^I , and w^E are the weights assigned to actuation ($w^A = 0.2$), inhalation ($w^I = 0.2$) and exhalation ($w^E = 0.1$) sensitivity and positive predictive value measures.

Figure 7.8A illustrates a three dimensional projection of a subset of the employed audio-based feature space highlighting three distinct inhaler sound classes (inhalation, actuation and exhalation). Figure 7.8B presents the results of the feature selection process. Similar approaches, including feature selection, were then applied to a feed-forward, three hidden layer ANN to compare against the QDA classifier model.

7.2.2.3 Stage 2: Audio-based measurement of inhalation flow parameters

pMDI flow estimation participants

An audio-based flow estimation model was developed to accurately estimate pertinent clinical measures of patient inhalation technique, such as the PIFR and volume, from inhalation audio signals. Ten healthy participants (six male/four female, age range (21-29)) were recruited to record a dataset of inhalation audio signals. Baseline spirometry was performed on all participants according to ATS/ERS standards to confirm all participants had normal lung function (Miller *et al.*, 2005). Healthy participants were recruited for this stage of the study only as numerous inhalation recordings were required from each participant at a wide range of inspiratory flow rates to design and validate the audio-based flow estimation model. This may not have been feasible with asthma and COPD patients.

pMDI flow estimation experimental setup

In order to develop audio-based models to estimate inhalation flow parameters from the pMDI, audio signals and PIFR/volume measurements of inhalations were required. The top of the pMDI (where the airflow enters the inhaler during inhalation) was fixed inside an airtight container (Figure C3 in Appendix C). A Pneumotrac 68000 pneumotachograph spirometer [Vitalograph Ltd., Co. Clare, Ireland] was connected to the airtight container. This ensured that the airflow passed through the spirometer during inhalation and allowed for objective measurement of PIFR and volume from the pMDI. This method of measuring PIFR and volume through inhalers has been employed in

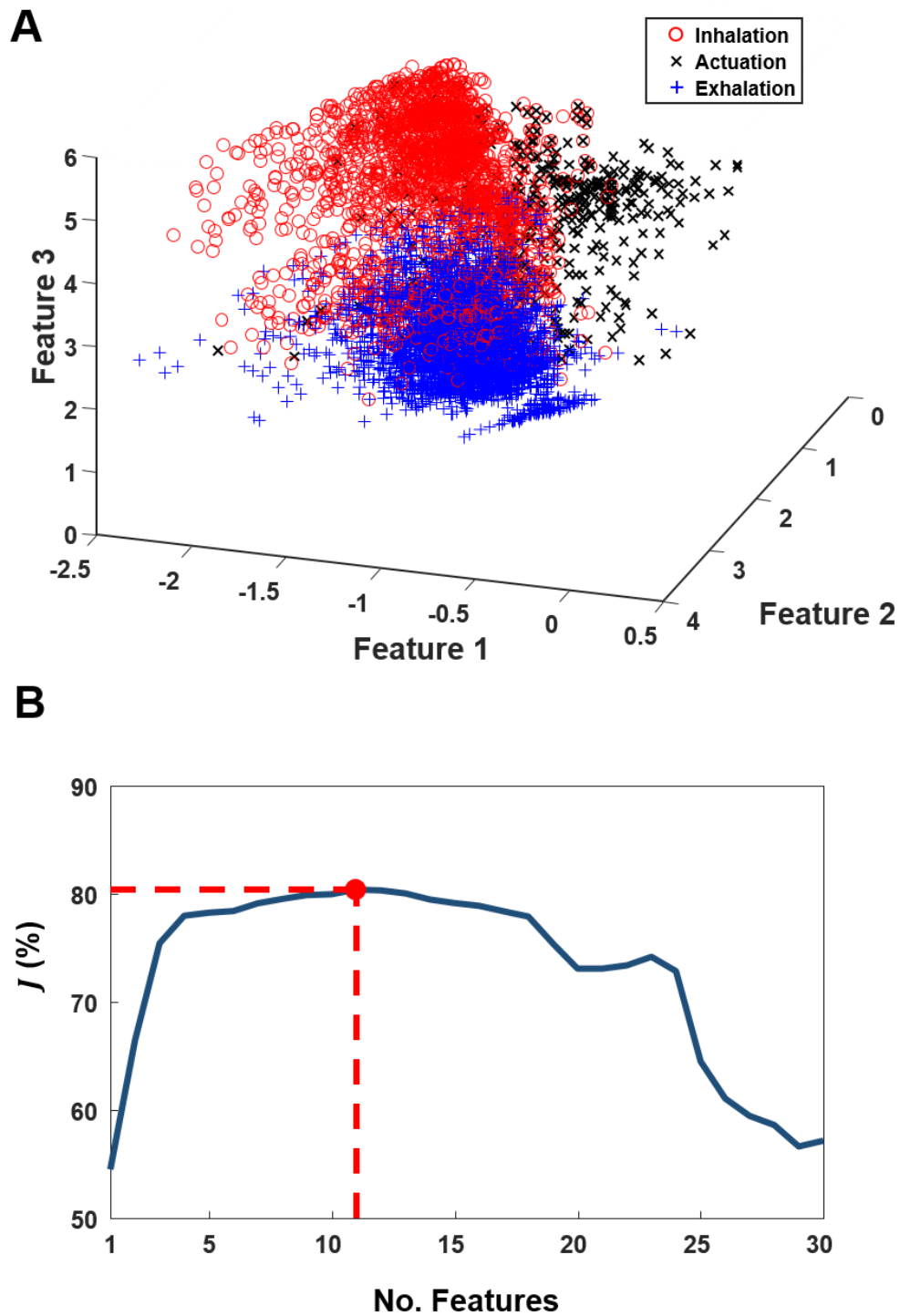


Figure 7.8. Feature projection visualisation and feature selection results.
 (A) Feature vector values of three classes (inhalation/actuation/exhalation) in a three dimensional projected feature space. Feature 1 is LPC1 (a_1), Feature 2 is LPC2 (a_2) and Feature 3 is entropy (H). (B) Forward feature selection results highlighting 11 selected features which generated the highest performance measure ($J=80.38\%$).

previous audio-based inhaler flow estimation studies (Taylor *et al.*, 2016a; Taylor *et al.*, 2016b; Holmes *et al.*, 2013c). An illustration of the pMDI flow estimation experimental setup is shown in Figure C3 (Appendix C).

During inhalation, airflow also passes through the reed of the Flo-Tone which is not placed inside the airtight container. However, this had minimal effect on the inhalation PIFR measurements from the spirometer (average inhaler inhalation PIFR measurement using the spirometer generated an accuracy over 95%). Details of an *in-vitro* experiment that compared the PIFR of pMDI inhalations measured at the spirometer and the PIFR measured at the mouthpiece of the Flo-Tone is described in Appendix C (Figure C4 and Figure C5 in Appendix C).

pMDI flow estimation recording protocol

Each participant was asked to exhale to full residual capacity away from the inhaler before sealing their lips tightly around the Flo-Tone mouthpiece. Participants were then asked to perform an inhalation manoeuvre. Each participant used a different Flo-Tone device to account for any variability in inhalation sounds across devices and to avoid any bias in the audio-based flow estimation model. Each participant performed 16 separate inhalation recordings in total. Participants were first asked to perform four separate inhalation recordings within the inspiratory flow range of 180-240 L/min. This was followed by four separate inhalation recordings within each of the following flow ranges; 120-180 L/min, 60-120 L/min and <60 L/min respectively. The PIFR of each inhalation was checked using the reference PIFR values from the spirometer and was presented on a screen at the end of each inhalation to give participants feedback on their inspiratory flow rate. This was used to guide participants towards their target PIFR for each inhalation recording. The four inspiratory flow ranges were chosen to simulate both correct and incorrect patient inhalation technique. Recordings took place in a designated recording room which was not soundproof and did not have any acoustic materials installed to reduce background noise. However, the signal to noise ratio (SNR) of the recordings was deemed suitable to investigate the relationship between audio-based features of the Flo-Tone inhalation signal and PIFR/IC measures (SNR= 9.5 dB for low flow inhalation recordings, SNR= 15.6 dB for high flow inhalation recordings).

Flow estimation audio signal processing

Inhalation audio signals were decimated by a factor of four and were then band pass filtered between 200-5000 Hz. The inhalation audio signals were divided into frames of 50 ms duration with an overlap of 25 ms. A Hanning window was applied to each frame to reduce spectral leakage. Three audio-based features were extracted from each audio frame. The energy (E) of the inhalation audio signal was obtained by calculating the root mean square. The energy feature was calculated using the *RMS* equation (4.5) previously employed in Chapter 4 and Chapter 5.

The power of the fundamental frequency (P_{f_0}) was then estimated from the PSD of the inhalation audio signal. The fundamental frequency of Flo-Tone inhalation sounds may vary across Flo-Tone devices (approximate range of 520-570 Hz). Therefore, an autocorrelation method was first employed to determine the fundamental frequency of each inhalation audio signal. The total power of the fundamental frequency and first harmonic ($P_{f_0f_1}$) was also estimated from the inhalation PSD estimate. Only f_0 and f_1 were considered to eliminate the effect of higher frequencies contained within actuation sounds if the patient were to actuate during inhalation in real life scenarios during inhaler use.

The three audio-based features (E , P_{f_0} and $P_{f_0f_1}$) were extracted from each frame. The frame with maximum f_0 power (P_{f_0}) was selected from each inhalation audio signal. It was observed that this frame was unaffected by the presence of actuation sounds in comparison to the frame of maximum energy (E). Figure C6 (Appendix C) highlights how selecting the frame of maximum energy in a real life patient pMDI audio recordings may influence flow rate estimation.

Flow estimation statistical analyses

Data were divided, using a hold-out approach, into a design dataset (five participants, 80 inhalation audio recordings) which was used to develop the audio-based flow-estimation models and validation dataset (five participants, 76 inhalation audio recordings) to validate the flow estimation models. Design and validation datasets contained different participants to eliminate any bias or over-fitting in the flow estimation models. The relationship between audio-based features and PIFR was first investigated. Using the design dataset, the relationship between audio-based features and PIFR was modelled using both linear and power law (logarithmic) regression models (as previously employed in Chapter 6).

In order to estimate the volume of inhalations, the PIFR estimation model was applied to each frame of inhalation audio signals to estimate the inhalation flow profile (flow rate vs time). The volume was estimated as the area under the curve of the flow profile and was calculated using trapezoidal numerical integration.

To observe the performance of the flow estimation models within noisy environments and within the presence of actuation sounds, white Gaussian noise was added to each inhalation signal from -10 dB to 25 dB in increments of 5 dB. Gaussian white noise was selected to model the spectral content of an inhaler actuation sound which also consists of a flat-like broad band spectrum of frequencies (see Figure 7.6). Actuation sounds are more prominent than background noise in the pMDI audio signals as shown in Figure 7.6 and so may have the most detrimental effect on flow estimation from the inhalation audio signal. The accuracy of PIFR and volume estimation was assessed at each SNR level using the following equation;

$$Accuracy (\%) = 100 - \frac{|\hat{F} - F|}{F} \quad (7.7)$$

where $\hat{F}$ and F are the estimated and actual flow rate respectively.

7.2.2.4 Stage 3: Assessment of patient inhaler user technique

The trained classification and flow estimation models were then applied to the full patient dataset to assess inhaler user technique. To determine the level of agreement between the subjective checklist (clinical reviewer checklist) and the objective audio-based algorithm in assessing patients' actuation coordination and inhalation PIFR, the Cohen's kappa statistic was computed for each critical error for each of the following; checklist vs manually labelled audio events, checklist vs detected audio events (according to the algorithm) and manually labelled audio events vs detected audio events. Cohen's kappa is measure of agreement between two raters with respect to a dichotomous outcome while taking into account the prior probability of a specific outcome occurring (Blackman and Koval, 2000; Redmond and Heneghan, 2006). In order to further investigate the effect of tuition from the clinical expert reviewer on patients' inhalation technique, a Wilcoxon signed rank test was performed comparing the average estimated PIFR and volume of patients' inhalations before (recordings 1 and 2) and after tuition (recordings 3 and 4). Finally, the percentage of patients who had poor actuation coordination or inhaled too

fast (PIFR>90 Lmin) on at least one occasion before and after tuition was computed based on the checklist and the labelled and detected audio events.

7.2.3 Results

A total of 247 inhaler audio recordings were obtained from the 62 asthma and COPD patients recruited in this study. One patient could only complete three recordings while all other patients performed four recordings each. The training dataset consisted of 90 inhalation sound events (4,832 frames), 114 actuation sound events (808 frames) and 109 exhalation sound events (4,902 frames). The testing dataset consisted of 104 inhalation sound events (5,500 frames), 115 actuation sound events (599 frames) and 130 exhalation sound events (6,824 frames).

7.2.3.1 Stage 1: Automatic classification of inhaler sound events

The forward feature selection process selected 11 features to be employed in the inhaler sound event classification algorithm. The features included MFCCs, entropy, Harmonic, Skewness, Kurtosis, and LPCs. The full list of features selected is presented in Table C1 (Appendix C).

The results of sound event classification using the QDA and ANN classifiers are presented in Table 7.2. It was observed that the sensitivity and positive predictive values of inhalation and actuation sound event classification using the QDA was over 90% (sensitivity of 90% and 92.11% for inhalation and actuation detection respectively, positive predictive values of 92.13% and 94.59% for inhalation and actuation detection respectively). Frame-by-frame accuracy for the QDA was 88.2%. The ANN generated high sensitivity values for, inhalation, actuation and exhalation detection (sensitivity of 85.38%, 91.23% and 84.62% for inhalation, actuation and exhalation detection respectively). However, the positive predictive values generated from the ANN were lower compared to the QDA (positive predictive values of 84.09%, 59.09% and 12.82% for inhalation, actuation and exhalation detection respectively). Frame-by-frame accuracy for the ANN was 65.56%. Further results from this analysis are presented in Tables C2-C5 (Appendix C). Figure 7.7B shows an example of a patient pMDI audio signal with examples of some audio-based features along with the labelled and classified signals.

Table 7.2. Performance measures of quadratic discriminant analysis and artificial neural network classification on patient inhaler audio testing dataset.

Performance Measure	Symbol	QDA Result (%)	ANN Result (%)
Weighted performance measure	J	80.22	73.70
Accuracy (frame-by-frame)	Acc	88.2	65.56
Sensitivity of inhalation detection	S^I	90	85.38
Positive predictive value of inhalation detection	P^I	92.13	84.09
Sensitivity of actuation detection	S^A	92.11	91.23
Positive predictive value of actuation detection	P^A	94.59	59.09
Sensitivity of exhalation detection	S^E	40.77	84.62
Positive predictive value of exhalation detection	P^E	23.77	12.82

7.2.3.2 Stage 2: Audio-based measurement of inhalation flow parameters

A total of 156 inhalation audio recordings were obtained for the flow estimation phase of this study. One participant could not reach the highest inspiratory flow range; therefore 12 recordings were obtained from this participant. Sixteen recordings were obtained from all other participants each. All three audio-based features (E , P_{f0} and P_{f0f1}) were statistically significantly correlated with PIFR using both linear and power law models ($p < 0.0001$). It was observed that P_{f0f1} generated the strongest statistically significant correlation with PIFR using a power law model ($R^2 = 0.90$ $p < 0.0001$). The resulting flow estimation model using the P_{f0f1} power law model is given as;

$$\log(\hat{F}) = 0.3183 \cdot \log(P_{f0f1}) + 7.5061 \quad (7.8)$$

Table C6 (Appendix C) presents the R^2 values obtained from the regression models using each audio-based feature in the linear and power law models. Figure 7.9A shows the PSD estimates of three inhalation sounds at different flow rates showing the increase in harmonic power with an increase in PIFR. In addition, Figure 7.9B illustrates the power law relationship between PIFR and P_{f0f1} .

The accuracy measures of PIFR and volume estimation for all three audio-based features using power law models across a range of SNR levels are presented in Figure 7.10.

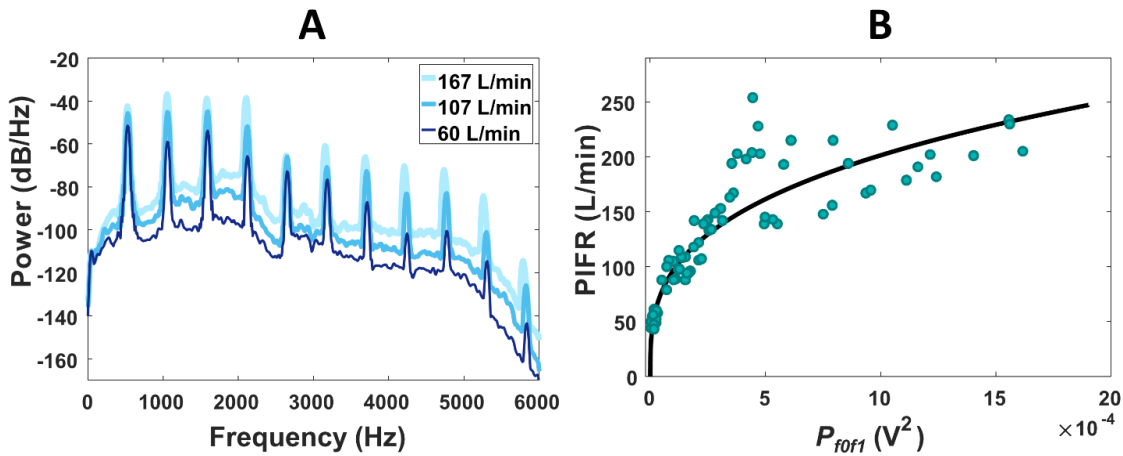


Figure 7.9. The relationship between PIFR and P_{f0f1} .

(A) Three PSD estimates of Flo-Tone pMDI inhalation sounds at different inhalation flow rates. (B) Power law relationship between PIFR and P_{f0f1} audio-based feature of pMDI Flo-Tone inhalation sounds ($R^2=0.90$, $p<0.0001$). The plot consists of the observed P_{f0f1} values of inhalations (green data points) and the calculated regression line (thick black line).

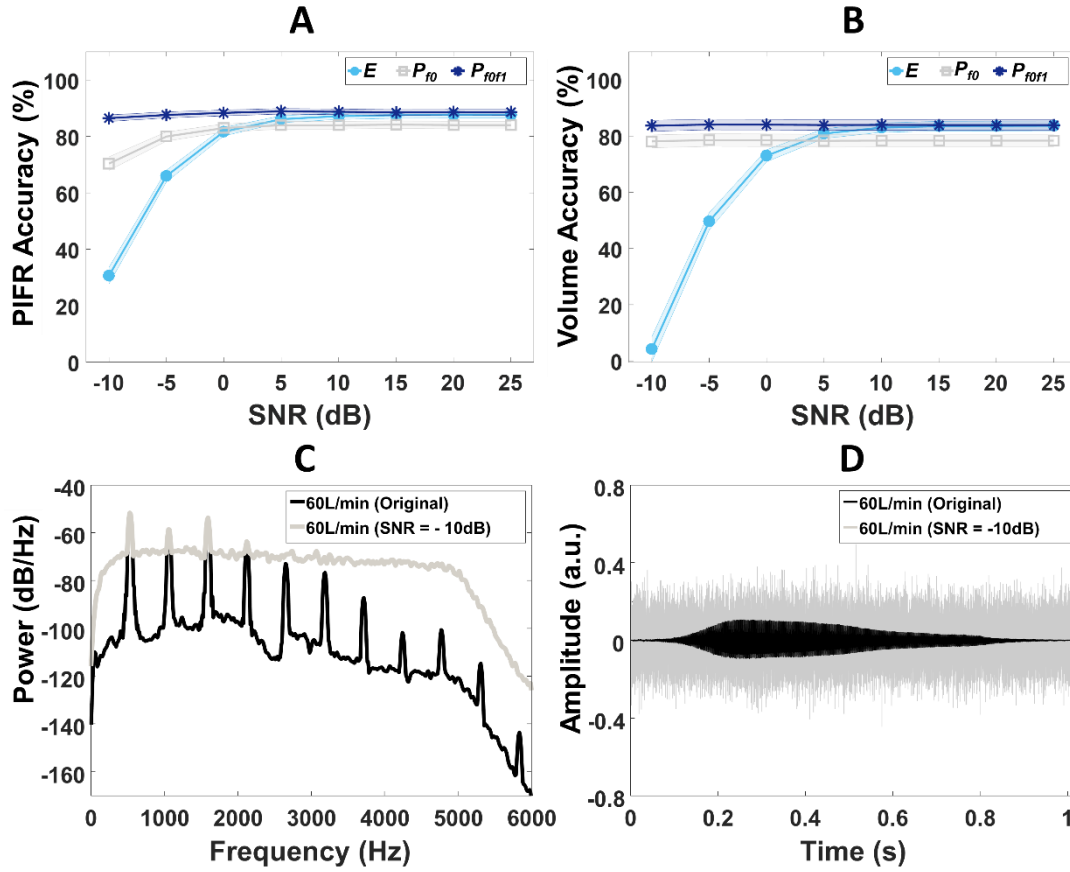


Figure 7.10. Audio-based inhaler inhalation flow estimation performance within different SNR levels.

Average $\pm$ standard error (shaded region) of (A) PIFR and (B) volume estimation accuracy for three audio-based features (E , P_{f0} and P_{f0f1}) using power law regression models across different SNR levels. (C) PSD estimates and (D) time domain signals of an original inhalation Flo-Tone pMDI audio recording at 60 L/min along with the same audio signal at SNR= -10 dB.

The harmonic power features (P_{f0} and P_{f0f1}) generated high accuracy consistently compared to the energy (E) feature even within lower SNR levels, particularly below 0 dB. The P_{f0f1} feature generated the highest accuracy across all SNR levels in both PIFR and volume estimation as shown in Figure 7.10. Figure 7.10 also highlights how energy based features from the time domain signal may not perform well within low SNR levels compared to harmonic features. The average ($\pm$ standard error) PIFR and volume estimation accuracy using a power law regression model was $88.2 \pm 0.28\%$ and $83.94 \pm 0.05\%$ respectively using the P_{f0f1} feature across all SNR levels. Accuracy reduced to $68.26 \pm 0.19\%$ for PIFR estimation and $61.83 \pm 0.01\%$ for volume estimation using the P_{f0f1} linear model. The accuracy measures of pMDI flow estimation using linear models within different SNR levels are presented in Appendix C (Figure C7).

The Bland Altman plot presented in Figure 7.11 shows high level of agreement between the audio-based (estimated) and spirometer (reference) PIFR and volume measures. The reference and estimated values for PIFR and volume were strongly statistically significantly linearly correlated ($R^2=0.88$ for PIFR and $R^2=0.90$ for volume $p<0.001$). The mean bias between the estimated and reference PIFR and volume measurements was 2.6 L/min and 0.12 L respectively. This highlights the reliability of using this audio-based method to assess patient inhalation technique in clinical applications.

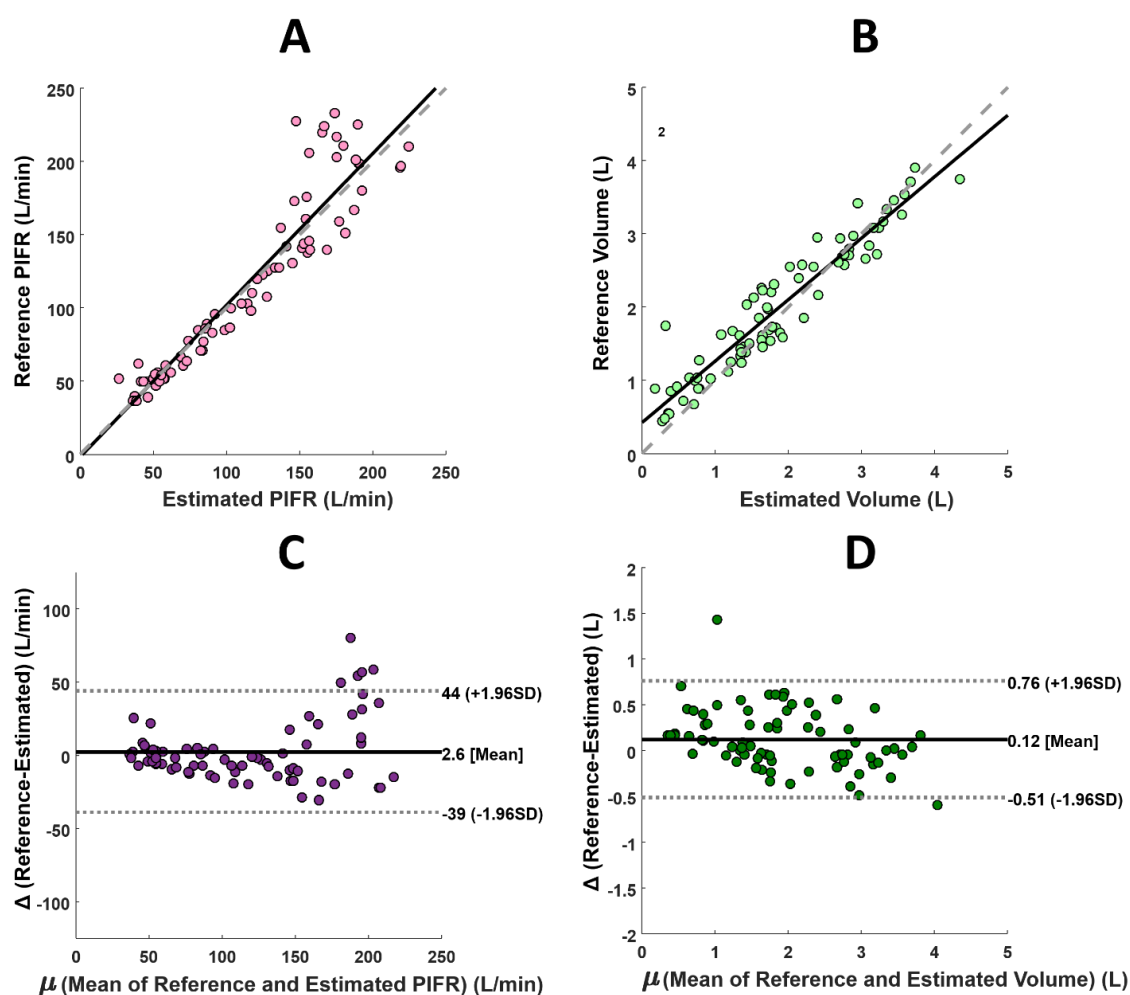


Figure 7.11. Bland Altman plot showing the relationship between the reference and estimated PIFR and volume measures.

7.2.3.3 Stage 3: Assessment of patient inhaler user technique

Table 7.3 presents the Cohen's kappa agreement rating between the checklist, labelled audio and detected audio (algorithm). All Cohen's kappa statistics (κ) were statistically significant ($p < 0.0001$). Both the labelled and detected audio (algorithm) analyses generated moderate agreement with the checklist method for actuation coordination assessment (moderate agreement being defined as $0.4 \leq \kappa < 0.6$ (Blackman and Koval, 2000)). Both the labelled and detected audio analyses generated fair agreement with the checklist method for assessing PIFR (fair agreement being defined as $0.2 \leq \kappa < 0.4$ (Blackman and Koval, 2000)). The labelled and detected analyses audio generated substantial to almost perfect agreement with each other for both actuation coordination and PIFR assessment (substantial to almost perfect agreement being defined as $0.6 \leq \kappa < 1$ (Blackman and Koval, 2000)).

It was also observed, using the audio-based algorithm, that the average PIFR and volume of patient pMDI inhalations significantly decreased after tuition (PIFR: $p = 0.001$, volume: $p = 0.002$). Details of the Wilcoxon signed rank test results comparing the average PIFR and volume before and after tuition are given in Appendix C (Table C7 and Table C8).

According to the checklist assessment, 90% of patients had poor actuation coordination before tuition and this reduced to 84% after tuition. According to the audio-based algorithm, 85% of patients had poor actuation coordination before tuition and this

Table 7.3. Cohen's kappa statistic (κ) measuring level of agreement between the inhaler user technique checklist, labelled inhaler audio events and detected inhaler audio events according to the audio-based algorithm.

		Assessment Comparison		
		<i>Checklist vs. Labelled Audio</i>	<i>Checklist vs. Detected Audio</i>	<i>Labelled Audio vs. Detected Audio</i>
Critical User Technique Error	Poor Actuation Coordination	0.49	0.40	0.68
	Inhaling Too Fast	0.36	0.38	0.83

only reduced to 82% after tuition. Regarding PIFR, it was observed using the checklist, that 79% of patients had inhaled too fast before tuition and this reduced to 56% after tuition. However, according to the audio-based algorithm, 89% of patients had inhaled too fast before tuition and this only reduced to 84% after tuition. Full table of results including the labelled audio data is available in the Appendix C (Table C9). Figure 7.12 presents an example of a patient's pMDI audio recordings before and after receiving tuition from the clinical reviewer. It is evident that the audio-based method can highlight how patient inhalation technique improves after receiving tuition.

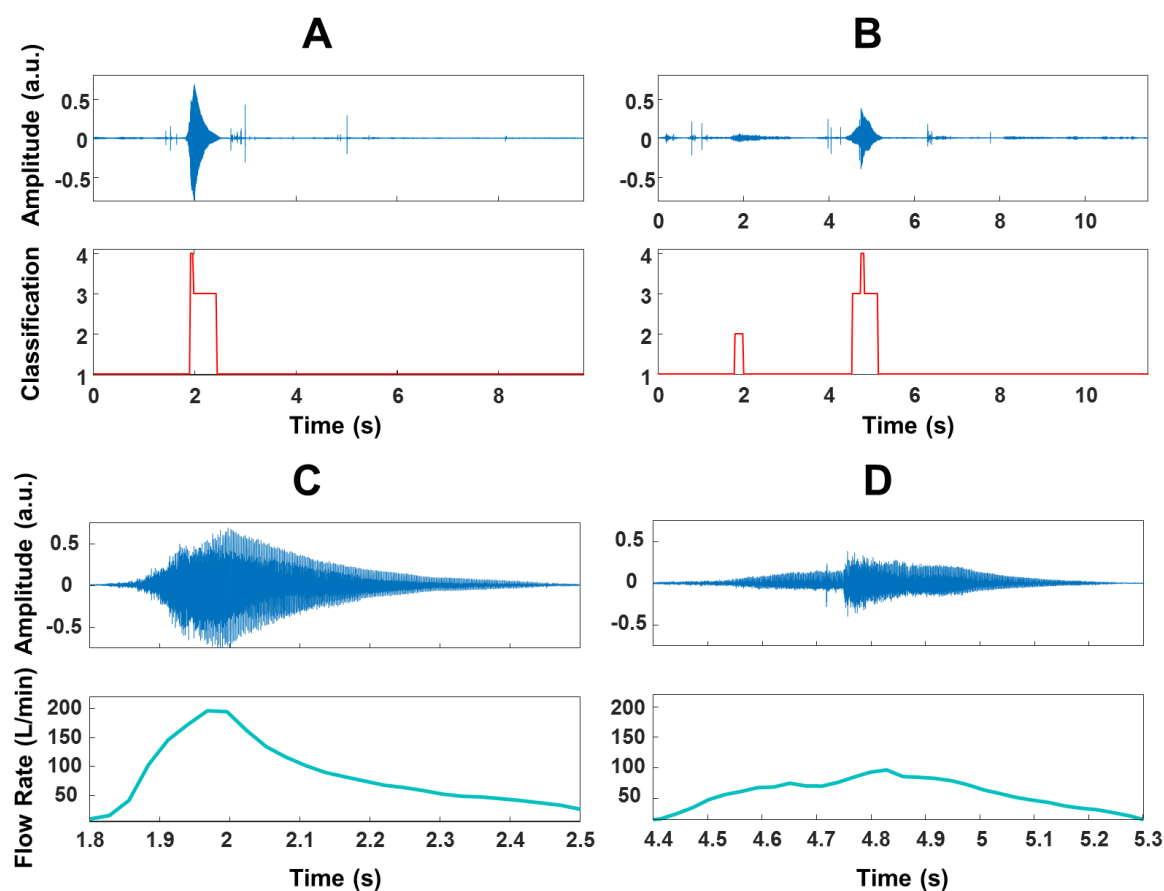


Figure 7.12. Example of patient inhaler audio signals before and after tuition regarding user technique from a clinical reviewer.

Classification event labels are as previously described in Figure 7.7 (1 – noise, 2- exhalation, 3 – inhalation, 4 - actuation). The audio time domain signal and classification label result for one patient (A) before and (B) after receiving tuition regarding user technique from the clinical reviewer. (C) Inhalation audio signal of panel (A) with its corresponding estimated flow signal. (D) Inhalation audio signal of panel (B) with its corresponding estimated flow signal. It is evident from the estimated inhalation flow signal in panel (C) that the patient inhaled too fast (approximately 200 L/min). After tuition, it is evident from the estimated inhalation flow signal presented in (D) that the patient decreased their PIFR (just under 90 L/min) which would consequently increase drug deposition in the lower airways. Additionally, it can be observed in (D) that the patient first generates the Flo-Tone sound before actuating the inhaler which is recommended according to the checklist. It is also evident that the actuation sound events that are present within both the inhalation audio signals in (C) and (D) do not affect the estimated inhalation flow signals.

7.2.4 Discussion

In this study, an audio-based method to objectively assess patient pMDI user technique has been presented. This method accurately detected the presence of two of the most common critical pMDI user technique errors; poor actuation coordination and inhaling too fast ($\text{PIFR} > 90 \text{ L/min}$). The method was trained and tested using inhaler audio recordings obtained from patients with chronic respiratory diseases in real life clinical environments. By attaching a Flo-Tone device to the mouthpiece of a pMDI, it enhanced the inhalation audio signal by generating a harmonic sound which could be used to accurately detect inhalation events as well as estimate the PIFR and volume of patient inhalations.

The QDA method detected actuation and inhalation sound events with high levels of sensitivity and positive predictive values (sensitivity of 90% and 92.11% for inhalation and actuation detection respectively, positive predictive values of 92.13% and 94.59% for inhalation and actuation detection respectively); this generated a total (frame-by-frame) accuracy of 88.2%. An ANN approach was also compared to the QDA method in this study. It was observed that the ANN generated high sensitivity values of inhalation and actuation (sensitivity of 85.38% and 91.23% for inhalation and actuation detection respectively), however, at the cost of positive predictive values (positive predictive values of 84.09% and 59.09% for inhalation and actuation detection respectively); this generated a total (frame-by-frame) accuracy of 65.56%. The QDA method offers a more accurate and less computationally complex method of detecting inhaler sound events. The audio-based flow estimation model estimated PIFR and volume of inhaler inhalations with an accuracy of $88.2 \pm 0.28\%$ and $83.94 \pm 0.05\%$ respectively across a range of SNR levels. This suggests that the estimation of inhalation PIFR and volume using the presented audio-based methods is unaffected by loud background noise or actuation sounds.

Using this audio-based method, it was observed that 97% (60/62 patients) of patients made at least one critical error before tuition and 89% (55/62 patients) of patients still made at least one critical error after tuition. This coincides with the literature that has reported that patients are more likely to make critical errors when using the pMDI as opposed to any other inhaler (Batterink *et al.*, 2012; Sanchis *et al.*, 2016). It was also observed that 82% of patients had poor actuation coordination and 84% of patients inhaled too fast ($\text{PIFR} > 90 \text{ L/min}$) even after tuition (according to the algorithm) (further

details are presented in Table C9 in Appendix C). This is an alarming sign of the prevalence of poor inhaler adherence in respiratory medicine.

The fair to moderate agreement (according to the Cohen's kappa statistic) between the subjective visual checklist assessment and the objective audio-based algorithm ($\kappa=0.4$ for actuation coordination assessment and $\kappa=0.38$ for PIFR assessment) highlights the potential inaccuracy of checklist methods in assessing patient inhaler user technique. Although the Flo-Tone can give healthcare professionals and patients an audible signal during inhalation, it can still be challenging to determine at exactly what flow rate the patient inhales at during inhaler use. Therefore, there is an urgent clinical need to introduce objective measures of inhalation technique into clinical practice to improve the clinical efficacy of treatment in respiratory medicine.

All of the patients recruited in this study had no previous experience with using the Flo-Tone device which could have affected their inhaler user technique during recording. Each patient was allowed to inhale through the Flo-Tone to hear the reed sound before recordings took place (without feedback on their user technique). Therefore, the effect of the application of Flo-Tone should have been minimal as they were instructed to use the inhaler as normal. Although the inhalation and actuation detection sensitivity was over 90% for the QDA model, the sensitivity for classifying exhalation sound events was moderate (40.77%). The main reason for this was that many patients either did not exhale to full residual capacity prior to inhalation or they exhaled at a distance from the recording device after inhalation. Thus, making it challenging to determine the duration of patients' breath holding after inhalation. Future research will further investigate methods to improve the detection of exhalation events during inhaler use. There is a consensus in the literature, however, that there is a lack of objective evidence that reports the long term clinical benefit of breath holding after inhalation during inhaler use. It is difficult to quantify the clinical benefit of the breath hold event during pMDI use as there are many critical events that significantly affect the delivered dose to the patient (Levy *et al.*, 2016). Two of the most significant events are the coordination between actuation and inhalation and the flow rate of inhalation which the presented audio-based algorithm can accurately and objectively assess. The shaking of the inhaler may be important also depending on the medication formulation (Melani *et al.*, 2011; Hatley *et al.*, 2017); however, this may be easily detectable in future audio-based monitoring systems through the use of an additional gyroscope sensor for example.

The analysis of critical inhaler user technique errors occurred within a very short time frame of approximately 15-20 minutes per patient. Therefore, a significant improvement in inhaler user technique may not have been achieved by some patients in such a short time frame. However, currently most patients only receive subjective feedback on their user technique during clinical consultation. This study highlights the need for repetitive objective feedback not just at clinical consultation but also remotely during the course of treatment in order for patients to receive maximum clinical benefit from their inhaler medication.

Some patients who have poor actuation coordination may be instructed to use a spacer or valve holding chamber (VHC) when using a pMDI. This can remove the challenge of actuation coordination and increase drug delivery to the lungs (Roche and Dekhuijzen, 2016). The audio-based method presented in this study was not tested on recordings of inhaler use with spacers or VHCs. Future research will investigate the performance of this audio-based method on assessing inhaler user technique with the use of spacers and VHCs. This method could, however, highlight those who have poor actuation coordination and may assist healthcare professionals in advising patients to use spacers or VHCs. Furthermore, this method was tested on patients who closed their lips around the mouthpiece (as recommended by the manufacturer of the Evohaler and the manufacturer of the Flo-Tone device). If patients position the pMDI at a distance from their mouth during inhalation, this may affect the sensitivity of the audio-based method. In addition, as this study solely focused on the Evohaler placebo pMDI, it may be of interest to test this method on other pMDI medications that generate lower/higher velocity actuation plumes. By using the presented audio-based approach in future research, it may be possible to detect other sound events such as sounds associated with patients who may struggle to actuate the pMDI canister due to inadequate hand strength. This may assist healthcare professionals in selecting a more suitable inhaler for these specific patients if required.

The application of the Flo-Tone increases the sound intensity of an inhalation event. This enhancement of inhalation sounds serves as an advantage for audio-based algorithmic development but may not be ideal in certain environments. Future audio-based studies may employ an ultrasonic acoustic device that generates inaudible harmonic sounds that may be used to assess inhalation technique. However, the effect of giving the patient audible feedback regarding their inhalation flow rate would be removed in this case.

Although the audio-based method detected that 84% of patients inhaled too fast (PIFR>90 L/min) even after tuition from an expert clinical reviewer, there was a statistically significant decrease in PIFR after tuition ($p=0.001$). This shows the positive clinical effect of tuition on inhalation technique. Interestingly, there was also a statistically significant decrease in inhalation volume after tuition ($p=0.002$). Patients are instructed to inhale to full capacity volume when using their inhaler, hence, there should be no significant decrease in inhalation volume regardless of the patient's PIFR. Patients decreasing their inhalation volume during inhaler use is another user technique error that needs to be monitored in clinical practice. Inhalation volume was not included in the Cohen's kappa analysis to determine if patient's inhaler inhalation volume was sufficient as baseline lung volume capacity values were not obtained from patients prior to recording. This would have required additional spirometry lung function tests which were not available for this study given the limited time available with each patient.

The algorithm presented in this study has value for future studies for the remote monitoring of patient inhaler use and to quantify the clinical effects of specific user technique errors. Moreover, providing patients with objective feedback regarding their adherence to inhaler medication using this audio-based method could significantly improve their clinical outcomes from treatment. It could also help healthcare professionals differentiate if respiratory health improvement during treatment is due to changes in medication or an improvement in user technique. New objective measures of patient user technique may help healthcare professionals further investigate the clinical effects of co-morbidities such as cognitive impairment on patients' adherence to inhaler use (Baird *et al.*, 2017; Moran *et al.*, 2017). Improving patient inhaler user technique, using audio-based methods, could improve the efficacy of inhaler medication, assist healthcare professionals to select suitable inhalers for patients and improve patient clinical outcomes in respiratory medicine.

7.3 Chapter Conclusion

One of the main goals in treating chronic respiratory diseases is ensuring that patients receive the required doses of medication over the course of treatment. This has proven to be quite a challenge in respiratory medicine as many patients do not use their inhaler with the correct user technique. The studies described in this Chapter presented a novel audio-based method which can accurately assess how patients use a pMDI, the most commonly

used inhaler worldwide. By attaching a Flo-Tone device to the mouthpiece of a pMDI, it greatly enhanced inhalation audio signals. The audio-based method detected critical inhaler events such as inhalations and actuations. Moreover, the algorithm accurately estimated the PIFR and volume of inhalations during inhaler use. This information can be used to objectively determine the presence of critical user technique errors which may limit the amount of drug delivered to the patient. According to the audio-based algorithm, many patients have poor actuation coordination and also inhale too fast ($\text{PIFR} > 90 \text{ L/min}$) when using a pMDI. The audio-based method provided a more clinically accurate assessment of patient inhaler user technique than checklist-based assessment. The studies described in this Chapter highlight the potential for audio-based inhaler monitoring systems to objectively monitor patient inhaler user technique and enhance the clinical efficacy of inhaler medication in the treatment of chronic respiratory diseases.

Chapter 8. General Discussion

8.1 Thesis Summary

Monitoring inhaler adherence is most effective when it is objectively measured and does not rely on subjective estimations from the patient or healthcare professional (Bender *et al.*, 1997). The studies detailed in this thesis aimed to develop audio-based signal processing methods to objectively assess patient inhaler user technique. Audio-based inhaler monitoring systems show promising opportunities to objectively monitor inhaler temporal (when) and user technique (how) adherence, inhaler drug delivery and patients' respiratory health non-invasively. The novelty of this thesis lies in developing audio signal processing methods that can detect the sequence of inhaler sound events and also estimate the PIFR and IC of inhaler inhalations. These methods can therefore obtain pertinent clinical information regarding the efficacy of patient inhaler use. Remote monitoring of inhaler use on a day-to-day basis can assist healthcare professionals in assessing patients' respiratory condition over time, identifying poor adherers and those at risk of adverse clinical outcomes. Along with intuitive feedback, such audio-based systems can assist health professionals in selecting suitable inhalers, therapy and dosage, leading to more personalised inhaler therapy and enhancing the clinical outcomes of treatment.

In order to significantly improve audio-based methods of monitoring patient inhaler adherence, a number of studies were carried out as described in Chapters 4-7. Previous audio-based analysis of patient inhaler use primarily focused on the Diskus inhaler (Holmes *et al.*, 2014a). Furthermore, the data acquisition device used in previous studies to record inhaler audio signals was the INCA device. As the sampling rate and bit resolution of INCA audio recordings are relatively low (8 kHz sampling rate with 8 bits per sample resolution) this resulted in lower quality of audio signals. Therefore, the

studies performed in this thesis aimed to provide objective measures of inhaler user technique by extracting a range of audio-based features from audio recordings of the pMDI and other DPIs using higher quality audio recordings (44.1 - 48 kHz sampling rate, 16 bits per sample resolution). The methods presented in this thesis provided more scientific depth to the existing literature on audio-based inhaler monitoring systems. This was achieved by extracting a number of temporal and spectral audio-based features from inhaler audio signals recorded using microphones attached and distant to a range of inhaler devices. All thesis aims were examined by the studies and are further outlined within this General Discussion Chapter.

8.2 Main Findings of the Thesis

The studies detailed in this thesis demonstrate that audio-based signal processing methods can provide objective measures of patient inhaler user technique. This finding was established from carrying out a number of studies that probed different aspects of inhaler user technique and investigated the use of audio-based methods in analysing events crucial for successful inhaler use. The importance of the research findings and the lessons learnt from this research will now be critically discussed in relation to the research questions previously posed in Chapter 3. Interpretation of the main findings will also be discussed in the light of the previous literature as detailed in Chapter 2.

Non-contact methods may be employed to objectively measure peak inspiratory flow rate in a range of different inhaler devices (research questions 1-2)

As previously discussed in Chapter 2, the inhalation event is the most critical event during inhaler use. Drug delivery from inhalers is directly dependent on the PIFR of inhalation. Although previous studies have reported the use of audio-based methods to estimate PIFR in the Diskus using the INCA device, there was a need to investigate the correlation between PIFR and inhalation audio-based features in other DPIs and pMDIs. The results reported in the study described in Section 4.1.3 of Chapter 4 provide evidence to suggest that non-contact audio-based methods (using a microphone distant to the inhaler device) can be employed to estimate PIFR in a range of inhaler devices, particularly DPIs (Diskus and Turbuhaler) (Taylor *et al.*, 2016b). For the first time, it was reported that spectral features, such as the median frequency of the inhalation audio signal (F_{50}), are strongly significantly linearly correlated with PIFR ($R^2=0.85$, $p<0.001$ for the

Diskus). Therefore, non-contact audio-based methods, which may be employed in a wearable smart device, may offer healthcare professionals objective measures of inhalation technique.

The position of peak frequencies of the power spectral density of inhaler inhalation sounds remain unchanged regardless of flow rate at an intra-subject level (research questions 3-4)

The study presented in Section 4.1 Chapter 4 highlighted an interesting acoustic property of inhaler inhalation sounds in that the position of the peak frequencies of the PSD of inhalation sounds remain unchanged regardless of flow rate at an intra-subject level. This property was observed in the Diskus DPI, Turbuhaler DPI and the Evohaler pMDI. Although the profile of the PSD remains consistent, the quartile frequencies (F_{25} , F_{50} and F_{75}) linearly increase with flow rate making the higher frequencies of the spectrum becoming more emphasised. Interestingly, the coefficient of variation for spectral features across flow rates was approximately 20%. These properties of inhaler inhalation sounds are important to note for future algorithmic development in audio-based inhaler monitoring. The repeatability of the inhalation PSD at an intra-subject level in Chapter 4 was observed over a short time period. However, this finding offers a baseline to monitor changes in the PSD of inhalations sounds longitudinally. It has yet to be reported whether changes in the PSD of inhaler inhalation sounds over the course of treatment highlight physiological changes in respiratory function.

Audio-based features of inhaler inhalation sounds vary across inhaler devices (research questions 5-6)

It is evident from the results reported in Sections 4.1.3 and 4.2.3 of Chapter 4 that audio-based features of inhalation sounds are significantly different across inhaler devices. The ANOVA analysis which statistically compared inhalation audio-based features across inhaler devices supported this finding ($p < 0.001$). The mechanical design and airflow resistance of inhaler devices directly influences audio-based features of inhalation sounds. This is evident from the differences observed in audio-based features of inhalation sounds presented in Figure 4.2 and Figure 4.6. It was also noted that the user may have some influence on inhalation audio-based features also. Therefore, a generalised audio-based inhaler monitoring system (which accounts for a range of inhaler devices) should not be recommended as each inhaler device has specific acoustic

properties that will significantly influence the automatic classification of inhaler sounds and the estimation of inhalation flow rate.

The turbulent energy generated within the inhaler device during an inhalation event has a direct influence on the performance of audio-based methods to estimate PIFR. It is evident that as pMDIs have very low airflow resistance, they generate minimal turbulent energy and hence minimal acoustic energy during inhalations at the clinically effective flow range (<90 L/min). This may result in much lower SNR levels being observed compared to DPI inhalation sounds. This poses a significant challenge if audio-based systems are to be implemented into clinical applications to monitor pMDI user technique.

Complexity features such as the Shannon entropy may be used to estimate the peak inspiratory flow rate of inhaler inhalations (research question 7)

For the first time, the relationship between PIFR and the Shannon entropy of inhaler inhalation sounds was investigated. It was observed in Section 5.1.3 of Chapter 5 that the Shannon entropy is strongly significantly linearly correlated with PIFR ($R^2=0.82$ $p<0.001$). It may therefore be employed to estimate PIFR in future audio-based inhaler monitoring systems. The Shannon entropy generated the strongest correlation with PIFR compared to spectral and power/amplitude based features. It is a temporal feature that is energy independent; however, it is related to amplitude through the logarithm of the amplitude range of the time domain audio signal (Yadollahi and Moussavi, 2007). As the inhaler audio recordings were obtained in real clinical settings, it may suggest that complexity-based features, such as the Shannon entropy, may be less susceptible to background noise. It was reported that spectral features were significantly different across users therefore may not be suitable to estimate flow rate using generalised models.

Non-contact inhaler inhalation sounds generate less variability than tracheal sounds (research questions 8-10)

It was observed in Section 5.1.3 of Chapter 5 that there may exist some variability in non-contact audio-based features of inhaler inhalation sounds across users (Taylor *et al.*, 2016a). The PSD of inhalations was significantly influenced by the user which may suggest that spectral features may not be suitable to estimate inhalation flow rate using a generalised approach. The fact that the microphone was placed distant to the inhaler and was not physically attached to the inhaler (like the INCA device), may have introduced more of an influence from the user's human breath sound. Also, the position of the

microphone may have been more sensitive to the user's mouth seal around the inhaler mouthpiece which may explain some of the variability observed in the non-contact recordings. However, it was clearly evident that inhalation sounds recorded using non-contact methods generated much less variability than sounds recorded using a tracheal microphone. The results from the studies presented in Section 4.2 of Chapter 4 and Section 5.1 of Chapter 5 suggest that tracheal contact microphones are not suitable for monitoring inhaler inhalations longitudinally as they are significantly influenced by the user more so than non-contact methods.

Changes in dry powder inhaler inhalation audio-based features may highlight the onset of an asthma exacerbation and the positive response to inhaler medication (research questions 11-12)

It is unknown whether asthma patient's inhaler PIFR changes over the course of treatment and whether these changes relate to clinical outcomes. According to the literature, PIFR significantly changes in COPD patients during the acute and recovery phase of an exacerbation (Broeders *et al.*, 2004). The PIFR of DPI inhalations may be of interest to monitor changes in lung function as DPIs require a forced inhalation manoeuvre to administer the medication to the patient. Therefore, if the PIFR was to change significantly over time, this may highlight that the patient cannot generate sufficient inspiratory force due to the onset of an adverse event such as an asthma attack.

In order to investigate the relationship between changes in inhalation audio-based features, PIFR and lung function, eight patients undertook a bronchial challenge test to induce an asthma exacerbation (study described Section 5.2 of Chapter 5 (McCartan *et al.*, 2016)). Patients performed inhalations at each stage of the BCT. It was observed that both audio-based features and PIFR of Diskus DPI inhalations decreased with lung function (FEV1) during an induced exacerbation. Although more data from a larger patient cohort is required to confirm these findings, the preliminary results show promising opportunities for audio-based inhaler monitoring systems to detect changes in lung function before the onset of an exacerbation. Interestingly, after patients were administered a bronchodilator, the audio-based features and PIFR of inhalations increased showing the positive response to inhaler medication. These findings were not observed in patients who were not responsive to the BCT (FEV1 did not decrease by 20% of baseline). Hence, the discriminant and predictive validity of audio-based monitoring tools show their potential for the prediction of clinical outcomes.

The acoustic envelope (amplitude envelope) of inhalation sounds may be employed to estimate the inhalation flow profile from the Ellipta dry powder inhaler using only one inhalation recording for calibration (research questions 13-17)

The study presented in Chapter 6 presented a novel audio-based method of estimating the DPI inhalation flow profile using the amplitude envelope of the inhalation audio signal (Taylor *et al.*, 2018a). This study was also the first study to successfully investigate the relationship between inhalation audio-based features and flow rate in the Ellipta DPI. As discussed in Chapter 2, the inhalation flow profile can provide pertinent clinical information regarding inhalation technique in DPIs including the PIFR, IC and the inhalation ramp time (Dorosz *et al.*, 2016). Moreover, the inhalation flow profile is known to change according to disease type and severity (Hamilton *et al.*, 2015). Therefore, it was of interest to investigate the use of audio-based features to estimate the inhalation flow profile. The results presented in Section 6.3 of Chapter 6 demonstrated that the amplitude envelope of the inhalation audio signal is strongly statistically significantly correlated with corresponding inhalation flow signal through a logarithmic relationship (power law) ($R^2 > 0.97$ $p < 0.0001$ across low, medium and high flow rates). The method was trained and tested across a wide range of inspiratory flow rates generating an average flow estimation accuracy of over 90%. Interestingly, the power law flow estimation model relationship outperformed the linear model by over 10% in terms of flow estimation accuracy. This finding agrees with the results of Chapter 4 and Chapter 5 in that amplitude and power audio-based features generate stronger correlations with flow rate in the log domain as opposed to the linear domain. This also agrees with the literature in audio-based flow estimation (Reyes *et al.*, 2014; Reljin *et al.*, 2015; Taylor *et al.*, 2016b; Taylor *et al.*, 2016a).

Furthermore, this novel audio-based method only requires one inhalation recording at any flow inspiratory flow rate to calibrate an accurate model to estimate inhalation flow profile. This offers an alternative method of developing audio-based flow estimation models for future clinical applications. The inhalation recording required to calibrate the flow estimation may be obtained during clinical consultation and would not require repeated inhalation manoeuvres from the patient which poses a significant clinical advantage if this method is to be introduced into clinical practice. The PIFR, IC and ramp time estimation accuracy was above 80% even at an SNR of 0 dB highlighting sufficient reliability if this were to be implemented into real clinical applications.

Time-frequency audio-based features can be employed to automatically detect pressurised metered dose inhaler actuations during inhaler use (research question 18)

The study described in Section 7.1 of Chapter 7 investigated the use of time-frequency features to detect pMDI actuations (Taylor *et al.*, 2014). It was observed that pMDI actuation sounds contain unique acoustic properties which can differentiate them from other inhaler sound events such as inhalations or exhalations. Actuations are quite short in duration (100-150 ms) and contain acoustic power at high frequencies (over 15 kHz). The CWT was employed to compute a summation of high frequency power in order to automatically detect actuation sounds during inhaler use. The CWT offers high temporal resolution at high frequencies which suited this analysis. An audio-based algorithm was developed and tested on a cohort of pMDI audio recordings from patients and healthy participants. The algorithm generated an accuracy of 99.7% highlighting that the CWT based feature may be employed to monitor medication usage from pMDIs.

An audio-based algorithm was developed and validated to detect pressurised metered dose inhaler sound events with high levels of accuracy and sensitivity (research questions 19-23)

It was discussed in Section 2.8 of Chapter 2 that recent studies (that were published after Section 7.1 of Chapter 7) have employed audio-based methods to automatically detect pMDI sound events such as actuations and inhalations (Lalos *et al.*, 2016; Kikidis *et al.*, 2015). However these studies only recruited very small cohorts of healthy participants and did not estimate PIFR or IC from pMDI inhalations. Moreover, these studies did not analyse actuations during inhalation events but rather actuation sounds when the pMDI was actuated into open air. This does not provide healthcare professionals with the information required to make informed clinical decisions on patient user technique adherence.

The study described in Section 7.2 of Chapter 7 developed and validated an audio-based algorithm to objectively detect pMDI sound events including actuations, inhalations and exhalations (Taylor *et al.*, 2018c). The study employed a QDA method to classify each inhaler sound event in order to assess patient user technique. Using a set of 11 selected audio-based features (which included MFCC, entropy, harmonic and LPC features), the method was tested on 124 pMDI audio recordings from 31 asthma and COPD patients. The method generated a total accuracy of 88.2% and could detect both

inhalation and actuation sound events with a sensitivity and positive predictive value of over 90%. This suggested that the enhanced pMDI inhalation audio signal from the Flo-Tone device improves the detection of pMDI inhalation sounds. Interestingly, the 11th and 12th MFCCs were selected during the feature selection process. This may suggest that these MFCCs contain information regarding the pitch of the harmonic Flo-Tone inhalation sound. The CWT time-frequency feature described in Section 7.1 of Chapter 7 was not selected during the feature selection process. This is most likely due to this feature only focusing on higher frequencies (>15 kHz). Although it is suitable for actuation sound event detection, it may not generate high performance measures for detecting inhalation sounds. It was also observed that the ANN method did not generate positive predictive values to the same level as the QDA. However, future research will test different designs of ANNs to improve these performance measures. The study showed that, for the first time, audio-based methods can provide healthcare professionals with pertinent information regarding pMDI user technique. More specifically, the algorithm can accurately detect the sequence of pMDI sound events and also estimate inhalation flow rate from the detected inhalation sounds events. This study posed as a major step forward in audio-based inhaler monitoring systems as the pMDI is the most commonly used inhaler worldwide.

The acoustic properties of the Flo-Tone device greatly enhance audio-based estimation of peak inspiratory flow rate and volume of pressurised metered dose inhaler inhalations (research questions 24-25)

It was reported in Chapter 4 that pMDI inhalation sounds generate minimal acoustic energy in comparison to DPI inhalation sounds. This makes it challenging to objectively estimate PIFR in pMDIs. In the study described in Section 7.2 of Chapter 7, an audio-based flow estimation model was developed to estimate the PIFR and IC of sounds generated during pMDI inhalation. A Flo-Tone device was attached to the mouthpiece of a pMDI in order to increase the intensity of the sound generated during inhalation without affecting the pMDI resistance. The Flo-Tone starts to generate an audible harmonic signal when the patient generates an inspiratory flow rate of 40-60 L/min. The sound has a fixed fundamental frequency of approximately 540 Hz. It was observed that the P_{f0f1} audio-based feature (summation of power of the fundamental frequency and first harmonic) of the Flo-Tone inhalation sound generated a strong statistically significant correlation with PIFR through a power law relationship ($R^2=0.90$, $p<0.0001$). The PIFR and IC estimation

using the P_{f0f1} feature was observed to be highly consistent across a range of SNR levels (PIFR and IC accuracy greater than 80% at SNR= -10 dB). This provides evidence to suggest that this audio-based method of estimating PIFR and IC is less susceptible to noise even within noisy clinical environments. Furthermore, as actuation sounds generate power at high frequencies (much higher than the first harmonic of the Flo-Tone), P_{f0f1} is a reliable feature to accurately estimate PIFR and IC even when an actuation occurs within an inhalation event which is to be expected during real patient inhaler use. This novel method of objectively assessing patients' PIFR and IC during pMDI use may help to significantly improve how patients are trained to use their inhaler.

Many asthma and COPD patients do not use pressurised metered dose inhalers with correct user correct technique (research questions 26-27)

Section 2.1 of Chapter 2 discussed the prevalence of poor user technique adherence, particularly amongst pMDI users. The pMDI is commonly used to deliver quick relief rescue medication. It has been reported that 33% of COPD patients and 26% of asthma patients use their rescue inhaler three or more times a day (Melani *et al.*, 2011). Therefore, it is imperative that patients know how to use the pMDI correctly. The literature suggested that many patients do not use pMDIs with correct user technique. However, many of these studies reported in the literature relied on subjective checklists to assess patient user technique. Using the audio-based algorithm described in Section 7.2 of Chapter 7, 62 asthma and COPD patients were assessed before and after receiving tuition on their inhaler user technique from an expert clinical reviewer. The study assessed patients on two of the most common pMDI critical user technique errors; poor actuation coordination and inhaling too fast (PIFR>90 L/min). It was observed that 82% of patients had poor actuation coordination and 84% of patients inhaled too fast even after tuition. According to the audio-based algorithm, 89% (55/62 patients) of patients still made at least one critical error after tuition. This shows that there is an urgent clinical need for objective measures of pMDI user technique in the treatment of chronic respiratory diseases. If patients cannot receive objective feedback on their inhaler technique, this will lead to persistently poor adherence and potentially severe clinical outcomes.

Audio-based methods provide a more clinically accurate assessment of patient inhaler user technique compared to subjective checklists (research questions 26-27)

The audio-based algorithm employed to assess patient pMDI user technique described in Section 7.2 of Chapter 7 was statistically compared to a checklist based on aural/visual assessment from an expert clinical reviewer. The Cohen's kappa analysis reported only fair to moderate agreement between the checklist method and audio-based algorithm in assessing patients' actuation coordination and inhalation flow rate in the pMDI. This provides evidence to suggest that there needs to be a change in how patient inhaler user technique is assessed. This study highlighted how checklist method assessment can over estimate patients' user technique. This agrees with previous literature discussed in Chapter 2. It can be challenging for healthcare professionals to assess if patients performed correct user technique, particularly with the pMDI as there are a number of critical steps that may occur simultaneously during inhaler use. According to Fink and Rubin (2005), the management of chronic respiratory disease is 10% medication and 90% education (Fink and Rubin, 2005). However, if the education being given to patients is not well informed, this can have detrimental clinical consequences. Opinions on patient user technique are subjective and may vary across different healthcare professionals, hence, there is a need for a new standard objective method, such as the audio-based method described in Section 7.2 of Chapter 7, to assess patient user technique.

Audible feedback and tuition from healthcare professionals may improve patient inhaler inhalation technique (research questions 26-27)

Another advantage of using the Flo-Tone device in the study described in Section 7.2 of Chapter 7 was that it could give patients an audible signal once they reached the clinically optimum PIFR (40-60 L/min). However, the device does not indicate when the patient inhales too fast as it only becomes louder with increasing flow rate. Although 84% of the 62 patients recruited inhaled too fast with a PIFR of over 90 L/min after receiving tuition, it was observed that there was a statistically significant decrease in PIFR (according to the audio-based algorithm) after patients received tuition on their user technique ($p=0.001$). This may be due to the tuition from the clinical reviewer or the audible feedback from the Flo-Tone device. It is likely that it is a mixture of both. Additionally, the clinical reviewer was trained on the sound generated from the Flo-Tone at clinically optimal flow rates, hence, the device may have improved both the patients'

and clinical reviewer's knowledge of inhalation flow rate in the pMDI. Real time feedback from sensor-based technologies such as audio-based systems on user technique may be of significant clinical benefit to both patients and healthcare professionals as a result. However, real time feedback should be implemented into audio-based inhaler monitoring systems with an element of caution as patients may attempt to take multiple doses of medication if they consistently receive negative feedback regarding their inhaler user technique. Further research is required to investigate whether real time feedback from audio-based inhaler monitoring systems improves user technique and patient clinical outcomes longitudinally.

8.3 Limitations of Research

Exhalation sound event detection remains challenging

Exhalations can vary both in spectral and temporal domains across and within patients. Additionally, patients are instructed to always exhale away from the inhaler device. As a result, the patient usually exhales at a distance away from the inhaler and also in a direction away from the inhaler, making it challenging to interpret exhalation sounds. It was observed in the study described in Section 7.2 of Chapter 7 that many patients exhaled with a low flow rate on many occasions. Although this is clinically acceptable, exhalation sounds are commonly interpreted as background noise as a result, even to an expert reviewer of inhaler audio recordings. This makes it challenging to quantify the duration of a patient's breath hold. There are currently no other inhaler monitoring systems available, other than INCA, to assess exhalations during inhaler use. Future research will aim to improve audio-based exhalation detection during inhaler use.

Healthy participant cohorts were recruited for certain studies

The studies described in Chapter 4, Chapter 6 and a subsection of the study described in Section 7.2 of Chapter 7 recruited cohorts of healthy participants. This was necessary for each of these studies to investigate the acoustic properties of inhalation sounds and the relationship between audio-based features and flow rate. This is because a number of inhalation recordings were required from each participant. This may not have been possible with patients suffering from chronic respiratory diseases. Moreover, there were no other studies in the literature that analysed the specific acoustic properties of inhalation sounds that were reported in this thesis. Additionally, instructing patients to inhale at a

wide range of inspiratory flow rates through different inhaler devices is not recommended as it may confuse the patient as to how they should use their inhaler. The specific studies obtained sufficient audio data to demonstrate the applicability of employing audio-signal processing methods to assess inhalation technique in both DPIs and pMDIs.

Limitations due to the airtight container

In certain studies in this thesis, inhalers were placed inside airtight containers and connected to a spirometer. This was done to objectively measure PIFR through the inhaler device. The airtight container may have influenced some audio-based features of inhaler inhalation sounds, particularly spectral features. Although the specific values of the audio-based features may be affected due to the airtight container, this method still provided sufficient information regarding the acoustic properties of inhaler inhalation sounds. Power and amplitude based features using the airtight container setup have been previously validated using a flow sensor within inhaler devices (Seheult *et al.*, 2014b). Furthermore, some of the spectral properties reported in this thesis have been validated without the use of the airtight container. Figure 8.1 demonstrates the PSD of inhalation sounds recorded using a microphone attached to inhaler devices (Ellipta DPI and Evohaler pMDI) without the airtight container (Taylor *et al.*, 2018b). It is evident that the higher frequencies become more emphasised with increasing flow rate, indicating that there exists a relationship between PIFR and quartile frequencies (as reported in the study described in Chapter 4).

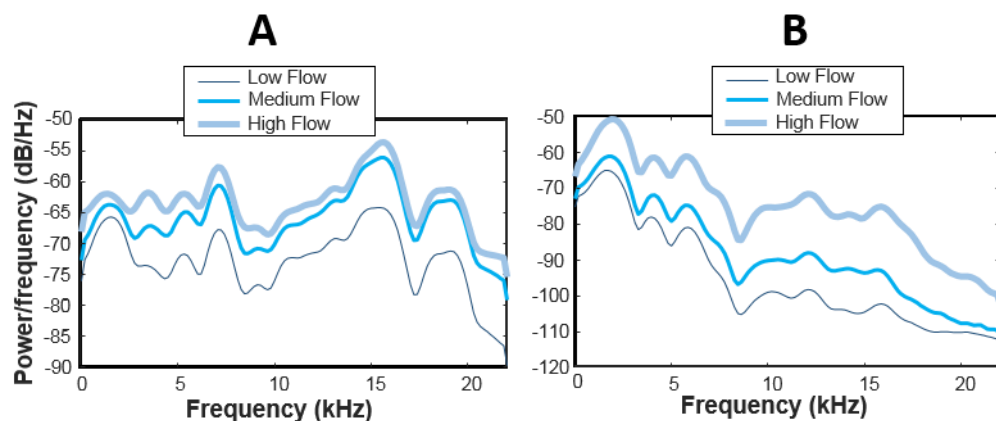


Figure 8.1. Power spectral density estimates of inhalation sounds at low, medium and high flow rates in (A) Ellipta DPI and (B) Evohaler pMDI.

The INCA device was designed specifically for the Diskus and not for pressurised metered dose inhalers or other dry powder inhalers

The studies described in Chapter 6 and Section 7.2 of Chapter 7 employed the INCA device to record inhaler audio signals from the Ellipta DPI and Evohaler pMDI. The INCA device was designed specifically for the Diskus DPI and so may not be used for recording Ellipta DPI or pMDI audio signals in future clinical applications. However, as INCA was the only inhaler-based monitoring system available at the time the studies were performed, it was decided to use the device to record inhaler audio signals. The audio signal was obtained from the INCA device and resampled to 48 kHz sampling rate with 16 bits per sample resolution for each study. Therefore, the lower quality INCA audio signals were not used and so did not influence the analysis. The acoustic response of the INCA device casing may have also influenced the audio analysis. As the INCA microphone is situated inside of the device casing, it represented possible future attachable inhaler audio device designs. Research is currently ongoing at the Trinity Centre for Bioengineering, Trinity College Dublin, to design and validate new enhanced inhaler audio recording devices which will be further discussed in Section 8.5.

Other limitations associated with audio-based inhaler monitoring systems

Patients use their inhalers in many different environments inside and outside of the clinic; therefore, inhaler audio recordings may contain some level of noise. Audio-based noise reduction methods should be considered when developing audio analysis algorithms for inhalers. It is challenging to develop a single model for all possible noise events. For this reason, a noise model was developed for each inhaler audio recording in the study described in Section 7.2 of Chapter 7. The audio data obtained in this study contained high levels of background noise but the method could still generate a high level of performance.

Accurate estimation of inhalation flow parameters (such as PIFR and IC) may be influenced by the inhaler design and the microphone location, particularly with pMDIs. DPIs with greater airflow resistance generate louder audio signals compared to pMDIs for example; therefore the location of the microphone is important. It is evident from Figure 8.2 that the attachable microphone setup increases the intensity of inhalation audio signals in pMDIs (Taylor *et al.*, 2018b). However, the pMDI inhalation signal generates less acoustic energy than the DPI inhalation. As discussed in the study described in

Section 7.2 of Chapter 7, the addition of a Flo-Tone device to the pMDI greatly enhances the inhalation audio signal.

Audio-based inhaler monitoring systems are currently being validated in on-going clinical trials, however, they need to be integrated into existing clinical management systems with sufficient reimbursement in place before this technology is implemented into current clinical work flows worldwide. Certain clinical applications may have an issue with privacy when using audio-based monitoring systems. In terms of patient privacy when using audio-based systems, the audio quality of ambient sounds, such as background conversation, is poor and difficult to interpret. Generally, audio-based analysis algorithms focus on specific inhaler events and frequency bands. This process naturally de-identifies the individual from the recorded data. Health data is private and users should be reminded on consent forms that audio data is recorded.

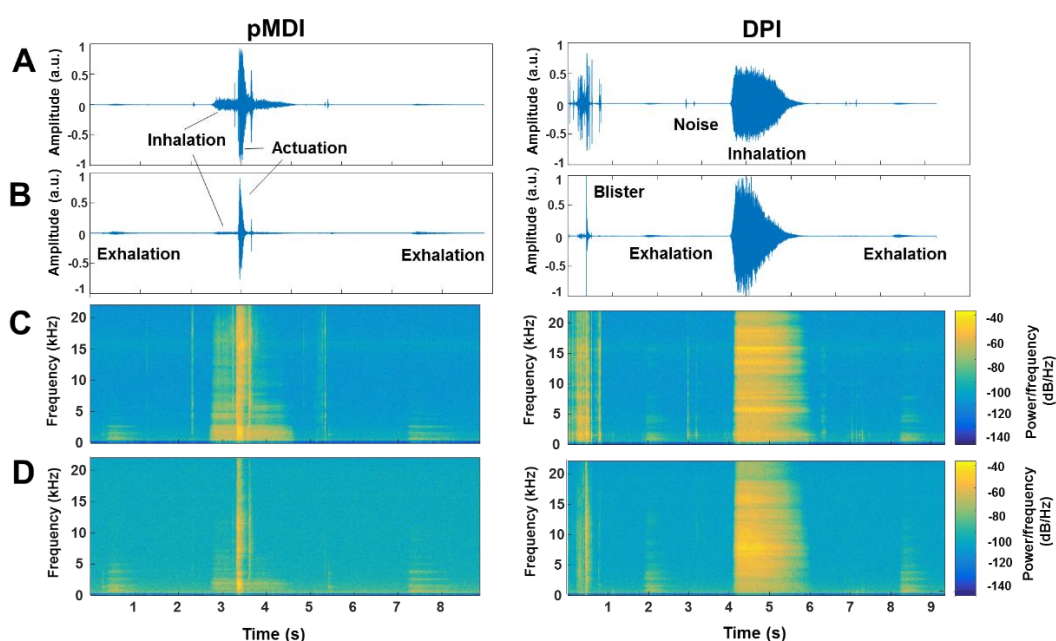


Figure 8.2. Typical examples of inhaler audio signals using attachable and non-contact microphone setups.

Left) pMDI, Right) DPI. The audio signals for each inhaler were recorded simultaneously using a digital audio recorder [ZOOM, H4n, Japan]. (A) and (C) present an audio recording time domain signal and spectrogram respectively from an attachable microphone (Knowles SPU0414HR5H-SB microelectromechanical systems). (B) and (D) present the same recording time domain signal and spectrogram respectively from a distant microphone (the internal ZOOM microphone). The sampling rate of all audio channels was 44.1 kHz (16 bits/sample, linear PCM).

8.4 Clinical Impact of Research

The audio-based signal processing methods presented in this research provide the opportunity to objectively monitor patient inhaler user technique adherence. The objective measures provided by these methods offer unbiased, clinically accurate assessment in comparison to the patient self-reports and checklists that are currently being used in clinical practice to assess inhaler user technique. The objective quantification of inhaler adherence, presented in the form of intuitive longitudinal feedback, and in conjunction with the monitoring of physiological, psychological, lifestyle, and environmental factors, could provide a comprehensive picture of patient disease control. It may assist healthcare professionals in initiating dialogue with the patient about health-related behavioural issues, co-morbidities such as cognitive impairment and in establishing new personalised strategies for behavioural changes.

Furthermore, objective inhaler adherence measures could improve the clinical assessment of chronic respiratory diseases. COPD is usually diagnosed using spirometry lung function tests, but it has been reported that such measurements may not provide sufficient information regarding the response to bronchodilator medication due to the irreversible pathophysiology of the disease (Celli, 2000). As it has been previously reported that COPD patients' inhaler PIFR changes according to respiratory function, audio-based measures of PIFR may provide additional physiological data to make a more informed clinical diagnosis of respiratory disease. Providing healthcare professionals with objective adherence measures can improve the efficacy of treatment and help personalise treatment to the patient also. Patients can be educated on user technique errors they may often make and learn how to improve their user technique accordingly. Moreover, there is an ongoing discussion in the literature regarding the clinical benefits of stepping down patients from combination medication therapies in asthma (Koskela *et al.*, 2016). This aims to remove cases of over medicating patients particularly with well controlled asthma. Recommended methods to validate inhaler medication changes are through spirometry and subjective questionnaires (Koskela *et al.*, 2016). However, audio-based inhaler adherence measures could also provide pertinent information regarding the effects of changing inhaler medication over the course of treatment for asthma patients. Reducing the medication dosage for patients who do not need combination therapies or large doses of single medications may significantly reduce medical costs also as a result.

As mentioned in Chapter 2, the patient's ability to use an inhaler device is critical in treating asthma and COPD. The audio-based methods presented in this thesis can highlight critical errors associated with inhaler use and be used to select a suitable inhaler for patients. This may improve patient's confidence towards their inhaler medication and inherently improve adherence and the treatment of chronic respiratory diseases as a result. Objective longitudinal monitoring of user inhaler technique by means of audio-based systems would finally provide the opportunity to carry out patient-interaction trials for the development of new inhaler designs and build user inhaler inhalation profiles for the development of new medication formulations. Audio-based inhaler monitoring methods represent a critical means of assessing adherence and drug delivery in other pulmonary and respiratory-related diseases as well as in diseases that may involve inhalation therapy (e.g. Parkinson's disease, Type I and II diabetes) (Luinstra *et al.*, 2015; Selam, 2003; Pittas *et al.*, 2015).

8.5 Future Research Directions

The algorithm will see you now...: Development of new audio-based inhaler monitoring systems and their implementation into clinical infrastructure

The Trinity Centre for Bioengineering, Trinity College Dublin, Ireland are currently designing, developing and validating new audio-based inhaler monitoring systems. The systems will be used in biomedical engineering and clinical research to develop new audio-based signal processing algorithms to objectively assess patient adherence using the Ellipta DPI and pMDI devices. The prototype inhaler audio acquisition devices are presented in Figure 8.3 (Taylor *et al.*, 2018b). Each device will consist of the same microphone used in the INCA device (Knowles SPU0414HR5H-SB microelectromechanical systems), however audio will be recorded onto the device at 44.1 kHz with 16 bits per sample resolution (in comparison to 8 kHz sampling rate and 8 bits per sample resolution in the INCA device). The location of the microphone for each of

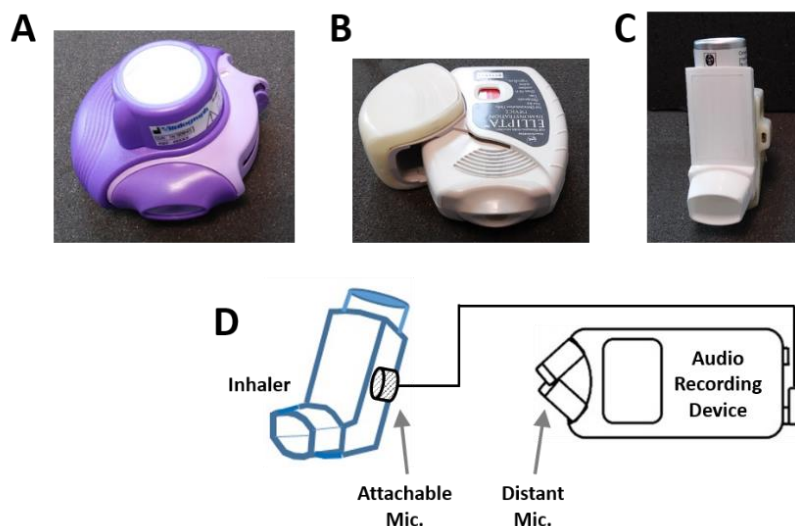


Figure 8.3. Current and future inhaler audio recording devices.

(A) Inhaler Compliance Assessment [INCA, Vitalograph LTD, Co. Clare, Ireland] device attached to a Diskus DPI. (B) An original prototype audio acquisition device [Trinity Centre for Bioengineering, Trinity College Dublin, Ireland] attached to an Ellipta DPI. (C) An original prototype audio acquisition device [Trinity Centre for Bioengineering, Trinity College Dublin, Ireland] attached to a pMDI. (D) Illustration of attachable and distant microphones recording setup to select the optimum microphone location for new inhaler audio acquisition devices.

the Ellipta and pMDI audio recording devices will be selected through a series of audio analysis tests. These audio analysis tests will involve recording the different inhaler mechanical sounds (actuation, drug preparation etc.), inhalation sounds at different flow rates and exhalation sounds into and at a distance from each inhaler and extracting pertinent features to characterise each sound. The microphone will be attached to different locations on the inhalers using the setup presented in Figure 8.3D to select the optimum microphone location (Taylor *et al.*, 2018b).

The performance of other parametric and non-parametric machine learning algorithms (linear discriminant analysis, support vector machines, random forest etc.) in automatically detecting critical inhaler events will be investigated to further enhance clinical assessment of patient inhaler use. Furthermore, employing normalised audio-based features may improve the use of spectral features to estimate inhalation flow rate. As reported in this thesis, quartile frequency features are strongly correlated with flow rate and may be used to estimate inhalation flow rate. However, the spectral features of inhalation sounds may vary across users. Therefore, their performance may decrease in generalised modelling approaches. Using spectral ratio features or perhaps normalised quartile frequency features (changes in quartile features over time) may further improve flow rate estimation with these new monitoring systems.

Future research will investigate if these automatic assessment algorithms can achieve similar performance in detecting pMDI events as the algorithm presented in Section 7.2 of Chapter 7. Furthermore, research will be carried out to objectively quantify drug delivery from the pMDI and Ellipta inhalers using the newly developed audio-based systems. Combining these new inhaler audio recording devices with other types of sensors may provide additional information such as patient respiratory rate, inhaler orientation and patient location during inhaler use which may assist in understanding pathological and environmental triggers associated with chronic respiratory disease (Su *et al.*, 2017; Braido *et al.*, 2016b; Estrada *et al.*, 2015).

Implementing these new algorithms into clinical frameworks will require sophisticated planning. The technology and clinical data collection/interpretation algorithms are in place for audio-based systems to be in use at a national level within 2-3 years. The interpretation of the data from such systems and the integration into hospital electronic patient records databases may require a longer time scale. It is an interesting time to be involved in the development of smart technologies for health monitoring. As these sensor-based technologies, whether it be audio or other sensors, continue to enhance algorithmic clinical assessment, it will be interesting to see how these automated methods coincide with human clinical diagnosis and assessment. Will automatic assessment algorithms eventually remove human input from clinical diagnosis? An example of a newly developed personalised adherence report for patients using previous INCA research data is presented in Figure 8.4 (Taylor *et al.*, 2018b). These type of intuitive reports can highlight poor adherence and assist in improving respiratory disease treatment.

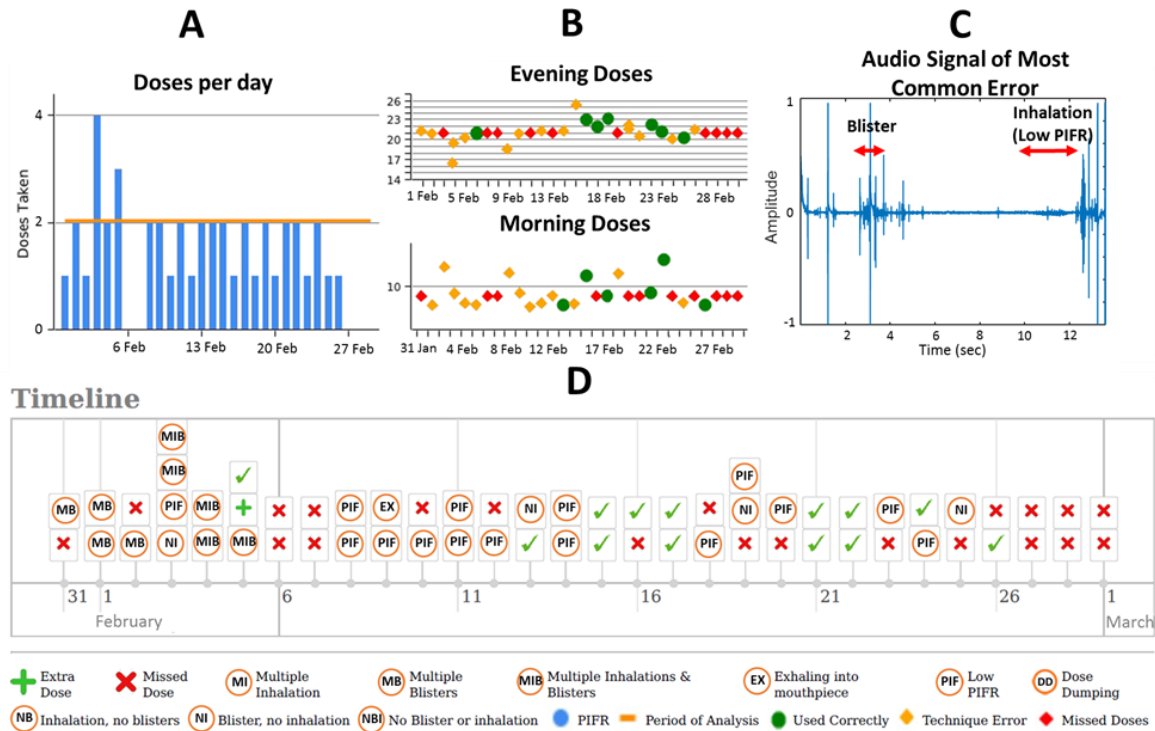


Figure 8.4. Monthly INCA patient adherence summary reports that have been used in clinical practice.

(A) Number of doses taken by the patient over the previous month. The orange horizontal line represents the target number of doses per day according to the prescribed medication. (B) Summary of temporal adherence with each data point representing a dose. A green data point represents correct user technique, orange represents a technique error and red represents a missed dose. (C) Example of an audio recording of the patient inhaling at an insufficient PIFR (<35 L/min). Panel (C) is not usually part of the monthly patient adherence summary reports but was added here to demonstrate the audio signal of the most common technique error over the course of the previous month. (D) Summary timeline with specific information regarding technique errors, missed doses and extra doses over the course of the previous month. As can be seen, this patient had poor temporal and user technique adherence. The audio analysis algorithms detected that the patient persistently could not generate a sufficient PIFR while using the Diskus DPI. According to this report, insufficient PIFR was recorded in 35% of this patient's inhaler audio recordings over the month. Patient data were obtained in an observational study that was approved by the Beaumont Hospital Research Ethics Committee in Ireland (09/58).

Get it off your chest: Estimating pertinent inhalation flow parameters using other forms of physiological signals such as respiratory inductance plethysmography

The limitations to using the airtight container setup to objectively measure the PIFR of inhaler inhalations have been previously discussed. Another possible method of estimating inhalation flow parameters could be through the use of chest and abdominal RIP analysis methods. It was previously discussed in Section 2.9 of Chapter 2 that RIP may provide useful physiological information regarding thoracoabdominal movement; however, they require specific calibration methods. It has yet to be reported, however, if

there exists a significant correlation between PIFR of inhaler inhalations and features of RIP chest and abdominal respiratory signals. If inhaler PIFR could be estimated using RIP methods this could remove the need for an airtight container or any flow sensors embedded into the inhaler device. It would also allow for inhaler audio recording without any possible influence from the airtight container or internal flow sensors on the inhaler audio signals. Thus, extracting specific features from the RIP signal could possibly be employed to calibrate audio-based flow estimation models for inhalers. Figure D1 (Appendix D) shows an example of a chest RIP signal from a healthy participant along with the corresponding flow and audio signals of inhalations through an Ellipta DPI. RIP and flow signals were recorded using a BioRadio physiological data acquisition device [Great Lakes NeuroTechnologies, Ohio, USA]. It can be observed that the negative slope of the RIP chest signal may be related to the PIFR of inhaler inhalations. However, further investigation is required to quantify the relationship between audio-based features, PIFR and RIP features, particularly with patients suffering from asthma and COPD.

Eye know you can do better than that!: Developing new objective measures of patient inspiratory effort during dry powder inhaler use

It was thoroughly discussed throughout this thesis that many patients cannot generate the sufficient inspiratory effort to reach the optimum PIFR when using a DPI. Although audio-based methods can objectively measure inhaler PIFR, they cannot measure how much physical effort patients put in to their inhalation. This makes it challenging to determine whether any observed changes in PIFR over time are related to impaired lung function or due to a lack of inspiratory effort from the patient. There are limited methods to measure inspiratory effort in patients with chronic respiratory disease. A study by Z  non *et al.* (2014) reported that increases in physical effort (as measured using a hand dynamometer) elicits an increase in pupil size (Z  non *et al.*, 2014). It may be of interest to investigate changes in pupil size during an inhaler inhalation. A pilot study will be performed to analyse pupillometry signals during inhalation from a cohort of healthy participants (n=20). The hypothesis is that there is a significant change in pupillometry-based features (e.g. pupil size and rate of change of pupil size) when the participant inhales with maximum effort as opposed to moderate effort. Each participant will perform inhalations at moderate and maximum inspiratory effort through two simulated inhaler resistances; low and medium. As the PIFR of inhalation will change according to inhaler airflow resistance, this approach aims to determine whether changes in pupillometry

features are associated with inspiratory flow rate or effort. Electrocardiography and RIP data will also be recorded from participants during the experiment. Figure D2 (Appendix D) presents preliminary data consisting of pupillometry signals (recorded from The Eye Tribe eye tracking device [The Eye Tribe, Denmark]) during moderate and maximal inspiratory effort inhalations through a medium resistance channel (Ellipta DPI). It can be observed that the average pupil size of the maximal effort signals is greater than the average of the moderate effort pupil size signals. However, more data is required to determine this relationship more quantitatively. This method may translate to a wearable headset with eye tracking technology embedded to be used in clinical consultations to objectively determine patient inspiratory effort. Combining this type of physiological data with audio-based assessment of inhaler user technique may provide a more comprehensive assessment of patient inhaler use.

Additionally, recent studies have reported that respiratory muscle mechanomyogram can be used to measure inspiratory effort and can give an estimate of the efficiency of the mechanical activation of inspiratory muscles (Sarlabous *et al.*, 2017). It may be of interest to investigate the applicability of employing these methods to measure inspiratory effort during inhaler use.

It's not what you say, it's how you say it: Using audio-based features of speech for the objective evaluation of interpersonal communication between patients and healthcare professionals and its role in predicting patient adherence

Communication style and patient-clinician relationships are critical for adherence and optimal delivery of intervention (Cleland *et al.*, 2007; Butler *et al.*, 2013; van Boven *et al.*, 2016). However, communication strategies may not be standardised across healthcare professionals. Communication training is therefore crucial for optimising health professionals' communication skills (Kelley *et al.*, 2014). Studies have reported the use of audio-based features of speech to objectively measure interpersonal communication levels (De Looze *et al.*, 2014). Extracting the fundamental frequency (f_0), intensity and articulation rate of speech audio signals can capture prosodic accommodation between two speakers (De Looze *et al.*, 2014). It may be of interest to investigate the correlation of these objective measures of communication between healthcare professionals and patients and patient adherence. This could assist in improving communication between healthcare professionals and patients and optimising clinical consultations to improve patient inhaler adherence. Furthermore, objective measures of interpersonal

communication levels could be employed with audio-based measures of adherence to predict patient adherence over the course of treatment.

8.6 Final Conclusion

The research questions posed in Chapter 3 have been answered during the course of several studies. The main findings of this thesis indicate that the developed audio-based signal processing methods can be employed to objectively assess patients' inhaler user technique in both pMDIs and DPIs. The audio-based methods developed in this thesis can provide objective information regarding the sequence of inhaler events and also the flow rate of inhalation. This creates the opportunity for healthcare professionals to make more informed clinical decisions regarding patient inhaler adherence and the efficacy of inhaler medication during treatment. Moreover, providing objective feedback to patients, using the presented audio-based methods, may improve their inhaler user technique. The conclusions drawn from the experimental results described in this thesis are informative with regards to topics of recent debate in the clinical literature on inhaler adherence, build on recent biomedical engineering studies in the research area of audio-based inhaler monitoring systems and have a number of clinical implications. Directions for future research are proposed which may extend on the audio-based signal processing methods described in this thesis.

References

- A.D.A.M 2007 Asthma. In: *Health Guide: The New York Times*)
- A.D.A.M 2017 How to use a metered-dose inhaler.
- Abushakra A and Faezipour M 2013 Acoustic signal classification of breathing movements to virtually aid breath regulation *IEEE journal of biomedical and health informatics* **17** 493-500
- Accordini S, Corsico A G, Braggion M, Gerbase M W, Gislason D, Gulsvik A, Heinrich J, Janson C, Jarvis D and Jögi R 2013 The cost of persistent asthma in Europe: an international population-based study in adults *International archives of allergy and immunology* **160** 93-101
- Ait-Khaled N, Enarson D and Bousquet J 2001 Chronic respiratory diseases in developing countries: the burden and strategies for prevention and management *Bulletin of the World Health Organization* **79** 971-9
- Al-Showair R A, Tarsin W Y, Assi K H, Pearson S B and Chrystyn H 2007a Can all patients with COPD use the correct inhalation flow with all inhalers and does training help? *Respiratory medicine* **101** 2395-401
- Al-Showair R A M, Pearson S B and Chrystyn H 2007b The Potential of a 2Tone Trainer To Help Patients Use Their Metered-Dose Inhalers *Chest* **131** 1776-82
- Alessio S M 2015 *Digital Signal Processing and Spectral Analysis for Scientists: Concepts and Applications*: Springer)
- Allen S C and Ragab S 2002 Ability to learn inhaler technique in relation to cognitive scores and tests of praxis in old age *Postgraduate medical journal* **78** 37-9
- Ammari W G, Al-Hyari N, Obeidat N, Khater M, Sabouba A and Sanders M 2017 Mastery of pMDI technique, asthma control and quality-of-life of children with asthma: A randomized controlled study comparing two inhaler technique training approaches *Pulmonary pharmacology & therapeutics* **43** 46-54
- Ammari W G and Chrystyn H 2013 Optimizing the inhalation flow and technique through metered dose inhalers of asthmatic adults and children attending a community pharmacy *The Journal of asthma : official journal of the Association for the Care of Asthma* **50** 505-13
- Apter A J, Tor M and Feldman H I 2001 Testing the reliability of old and new features of a new electronic monitor for metered dose inhalers *Annals of Allergy, Asthma & Immunology* **86** 421-4
- Ari A 2015 Patient Education and Adherence to Aerosol Therapy *Respiratory care* **60** 941-57
- Arora P, Kumar L, Vohra V, Sarin R, Jaiswal A, Puri M M, Rathee D and Chakraborty P 2014 Evaluating the technique of using inhalation device in COPD and Bronchial Asthma patients *Respiratory medicine* **108** 992-8
- Asthma Society of Ireland 2017 Asthma Basics.
- Austrheim O and Kraman S S 1985 The effect of low density gas breathing on vesicular lung sounds *Respiration physiology* **60** 145-55

- Azouz W, Campbell J, Stephenson J, Saralaya D and Chrystyn H 2014 Improved metered dose inhaler technique when a coordination cap is used *Journal of aerosol medicine and pulmonary drug delivery* **27** 193-9
- Azouz W and Chrystyn H 2012 Clarifying the dilemmas about inhalation techniques for dry powder inhalers: integrating science with clinical practice *Primary Care Respiratory Journal* **21** 208-13
- Backman P, Adelmann H, Petersson G and Jones C B 2014 Advances in inhaled technologies: understanding the therapeutic challenge, predicting clinical performance, and designing the optimal inhaled product *Clinical pharmacology and therapeutics* **95** 509-20
- Baird C, Lovell J, Johnson M, Shiell K and Ibrahim J E 2017 The impact of cognitive impairment on self-management in chronic obstructive pulmonary disease: A systematic review *Respiratory medicine* **129** 130-9
- Batchelor G K 2000 *An introduction to fluid dynamics*: Cambridge university press)
- Bateman E, Hurd S, Barnes P, Bousquet J, Drazen J, FitzGerald M, Gibson P, Ohta K, O'byrne P and Pedersen S 2008 Global strategy for asthma management and prevention: GINA executive summary *European Respiratory Journal* **31** 143-78
- Batterink J, Dahri K, Aulakh A and Rempel C 2012 Evaluation of the Use of Inhaled Medications by Hospital Inpatients with Chronic Obstructive Pulmonary Disease *The Canadian Journal of Hospital Pharmacy* **65** 111-8
- Beck R, Rosenhouse G, Mahagnah M, Chow R, Cugell D and Gavriely N 2005 Measurements and Theory of Normal Tracheal Breath Sounds *Annals of biomedical engineering* **33** 1344-51
- Begin P, Malo J, Cartier A, Sestier M and Martin R 1982 Time-course of the bronchoconstriction induced by histamine and methacholine *Journal of Allergy and Clinical Immunology* **69** 105
- Bender B, Milgrom H and Rand C 1997 Nonadherence in Asthmatic Patients: Is there a Solution to the Problem ? *Annals of Allergy, Asthma & Immunology* **79** 177-87
- Bishop C M 2006 *Pattern Recognition and Machine Learning*: Springer Science+Business Media)
- Blackman N J M and Koval J J 2000 Interval estimation for Cohen's kappa as a measure of agreement *Statistics in medicine* **19** 723-41
- Blaschke T F, Osterberg L, Vrijens B and Urquhart J 2012 Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories *Annual review of pharmacology and toxicology* **52** 275-301
- Bonini M and Usmani O S 2015 The importance of inhaler devices in the treatment of COPD *COPD Research and Practice* **1** 1
- Bosnic-Anticevich S, Chrystyn H, Costello R W, Dolovich M B, Fletcher M J, Lavorini F, Rodríguez-Roisin R, Ryan D, Wan Yau Ming S and Price D B 2017 The use of multiple respiratory inhalers requiring different inhalation techniques has an adverse effect on COPD outcomes *International journal of chronic obstructive pulmonary disease* **12** 59-71
- Bourbeau J and Bartlett S J 2008 Patient adherence in COPD *Thorax* **63** 831-8
- Braido F, Chrystyn H, Baiardini I, Bosnic-Anticevich S, van der Molen T, Dandurand R J, Chisholm A, Carter V and Price D 2016a "Trying, But Failing" — The Role of Inhaler Technique and Mode of Delivery in Respiratory Medication Adherence *The Journal of Allergy and Clinical Immunology: In Practice* **4** 823-32
- Braido F, Paa F, Ponti L and Canonica G 2016b A new tool for inhalers' use and adherence monitoring: the Amiko® validation trial *International Journal of Engineering Research & Science* **2** 159-66
- Brand P L P, Baraldi E, Bisgaard H, Boner A L, Castro-Rodriguez J A, Custovic A, de Blic J, de Jongste J C, Eber E, Everard M L, Frey U, Gappa M, Garcia-Marcos L, Grigg J, Lenney W, Le Souëf P, McKenzie S, Merkus P J F M, Midulla F, Paton J Y, Piacentini G, Pohunek P, Rossi G A, Seddon P, Silverman M, Sly P D, Stick S, Valiulis A, van Aalderen W M C, Wildhaber J H, Wennergren G, Wilson N, Zivkovic Z and Bush A

- 2008 Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach *European Respiratory Journal* **32** 1096
- Broeders M E A C, Molema J, Hop W C J, Vermue N A and Folgering H T M 2004 The course of inhalation profiles during an exacerbation of obstructive lung disease *Respiratory medicine* **98** 1173-9
- Broeders M E A C, Sanchis J, Levy M L, Crompton G K and Dekhuijzen P N R 2009 The ADMIT series — Issues in Inhalation Therapy. 2) Improving technique and clinical effectiveness *Primary Care Respiratory Journal* **18** 76
- Burgess S, Sly P and Devadason S 2011 Adherence with preventive medication in childhood asthma *Pulmonary medicine* **2011** 973849
- Busse W W 2007 Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007 *The Journal of allergy and clinical immunology* **120** S94-138
- Butler C C, Simpson S A, Hood K, Cohen D, Pickles T, Spanou C, McCambridge J, Moore L, Randell E, Alam M F, Kinnersley P, Edwards A, Smith C and Rollnick S 2013 Training practitioners to deliver opportunistic multiple behaviour change counselling in primary care: a cluster randomised trial *BMJ : British Medical Journal* **346**
- Capgemini Consulting 2016 Estimated Annual Pharmaceutical Revenue Loss Due to Medication Non-Adherence.
- Celli B R 2000 The importance of spirometry in copd and asthma*: Effect on approach to management *Chest* **117** 15S-9S
- Chah E, Glynn S, Atiyeh M, Costello R W and Reilly R B 2009 *4th European Conference of the International Federation for Medical and Biological Engineering: ECIFMBE 2008 23–27 November 2008 Antwerp, Belgium*, ed J Vander Sloten, *et al.* (Berlin, Heidelberg: Springer Berlin Heidelberg) pp 176-9
- Chan A H, Reddel H K, Apter A, Eakin M, Riekert K and Foster J M 2013 Adherence monitoring and e-health: how clinicians and researchers can use technology to promote inhaler adherence for asthma *The journal of allergy and clinical immunology. In practice* **1** 446-54
- Charbonneau G 2000 Basic techniques for respiratory sound analysis *European Respiratory Review* **10** 625-35
- Charles T, Quinn D, Weatherall M, Aldington S, Beasley R and Holt S 2007 An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma *Journal of Allergy and Clinical Immunology* **119** 811-6
- Chinn S, Burney P, Jarvis D and Luczynska C 1997 Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS) *European Respiratory Journal* **10** 2495
- Choo P W, Rand C S, Inui T S, Lee M-L T, Canning C and Platt R 2001 Derivation of adherence metrics from electronic dosing records *Journal of clinical epidemiology* **54** 619-26
- Chrystyn H 2003 Is inhalation rate important for a dry powder inhaler? using the In-Check Dial to identify these rates *Respiratory medicine* **97** 181-7
- Chrystyn H and Niederlaender C 2012 The Genuair® inhaler: a novel, multidose dry powder inhaler *International journal of clinical practice* **66** 309-17
- Chrystyn H and Price D 2009 Not all asthma inhalers are the same: factors to consider when prescribing an inhaler *Primary care respiratory journal : journal of the General Practice Airways Group* **18** 243-9
- Chrystyn H, Small M, Milligan G, Higgins V, Gil E G and Estruch J 2014 Impact of patients' satisfaction with their inhalers on treatment compliance and health status in COPD *Respiratory medicine* **108** 358-65
- Cilluffo G, Fasola S, Malizia V, Ferrante G, Montalbano L, Montalbano M, Viegi G and La Grutta S 2016 Measuring lung function in asthmatic children: A spirometry and forced oscillation technique (FOT) comparison *European Respiratory Journal* **48**
- Cleland J A, Hall S, Price D and Lee A J 2007 An exploratory, pragmatic, cluster randomised trial of practice nurse training in the use of asthma action plans *Primary care respiratory journal : journal of the General Practice Airways Group* **16** 311-8

- Conn K M, Halterman J S, Lynch K and Cabana M D 2007 The impact of parents' medication beliefs on asthma management *Pediatrics* **120** e521-6
- Crompton G, Barnes P, Broeders M, Corrigan C, Corbetta L, Dekhuijzen R, Dubus J, Magnan A, Massone F and Sanchis J 2006 The need to improve inhalation technique in Europe: a report from the Aerosol Drug Management Improvement Team *Respiratory medicine* **100** 1479-94
- Crompton G K 1982 Problems patients have using pressurized aerosol inhalers *European journal of respiratory diseases. Supplement* **119** 101-4
- Crompton G K 2004 How to achieve good compliance with inhaled asthma therapy *Respiratory medicine* **98 Suppl B** S35-40
- Cruz A A, Bousquet J and Khaltayev N 2007 *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach*: World Health Organization)
- Curle N 1955 The influence of solid boundaries upon aerodynamic sound *Proceedings of the Royal Society of London. Series A. Mathematical and Physical Sciences* **231** 505
- D'Arcy S, MacHale E, Seheult J, Holmes M S, Hughes C, Sulaiman I, Hyland D, O'Reilly C, Glynn S, Al-Zaabi T, McCourt J, Taylor T, Keane F, Killane I, Reilly R B and Costello R W 2014 A Method to Assess Adherence in Inhaler Use through Analysis of Acoustic Recordings of Inhaler Events *PloS one* **9** e98701
- Dafna E, Tarasiuk A and Zigel Y 2013 Automatic Detection of Whole Night Snoring Events Using Non-Contact Microphone *PloS one* **8** e84139
- Dafna E, Tarasiuk A and Zigel Y 2015 Sleep-Wake Evaluation from Whole-Night Non-Contact Audio Recordings of Breathing Sounds *PloS one* **10** e0117382
- Dalal A A, Shah M, D'Souza A O and Rane P 2011 Costs of COPD exacerbations in the emergency department and inpatient setting *Respiratory medicine* **105** 454-60
- Davis J R, Wu B, Kern D M, Tunceli O, Fox K M, Horton J, Legg R F and Trudo F 2017 Impact of Nonadherence to Inhaled Corticosteroid/LABA Therapy on COPD Exacerbation Rates and Healthcare Costs in a Commercially Insured US Population *American health & drug benefits* **10** 92-102
- de Boer A H, Hagedoorn P, Hoppentocht M, Buttini F, Grasmeijer F and Frijlink H W 2016 Dry powder inhalation: past, present and future *Expert opinion on drug delivery* 1-14
- De Looze C, Scherer S, Vaughan B and Campbell N 2014 Investigating automatic measurements of prosodic accommodation and its dynamics in social interaction *Speech Communication* **58** 11-34
- Decramer M, Janssens W and Miravittles M 2012 Chronic obstructive pulmonary disease *The Lancet* **379** 1341-51
- Ditcham W, Murdzoska J, Zhang G, Roller C, von Hollen D, Nikander K and Devadason S G 2014 Lung deposition of ^{99m}Tc-radiolabeled albuterol delivered through a pressurized metered dose inhaler and spacer with facemask or mouthpiece in children with asthma *Journal of aerosol medicine and pulmonary drug delivery* **27 Suppl 1** S63-75
- Dolovich M B, Ahrens R C, Hess D R, Anderson P, Dhand R, Rau J L, Smaldone G C and Guyatt G 2005 Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology *Chest* **127** 335-71
- Dorosz A, Pencone A and Moskal A 2016 In vitro study on the aerosol emitted from the DPI inhaler under two unsteady inhalation profiles *Journal of Aerosol Science* **101** 104-17
- Earis J and Cheetham B 2000 Current methods used for computerized respiratory sound analysis *European Respiratory Review* **10** 586-90
- Epstein R M, Alper B S and Quill T E 2004 Communicating evidence for participatory decision making *Jama* **291** 2359-66
- Estrada L, Torres A, Sarlabous L and Jané R 2015 Respiratory signal derived from the smartphone built-in accelerometer during a Respiratory Load Protocol. In: *2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp 6768-71
- European Respiratory Society 2017 *European Lung White Book*,

- Everard M L 2003 Role of inhaler competence and contrivance in “difficult asthma” *Paediatric respiratory reviews* **4** 135-42
- Fahr G 1927 The acoustics of the bronchial breath sounds: Application to phenomena of auscultation as heard in lobar pneumonia *Archives of Internal Medicine* **39** 286-302
- Fenerty S D, West C, Davis S A, Kaplan S G and Feldman S R 2012 The effect of reminder systems on patients' adherence to treatment *Patient Prefer Adherence* **6** 127-35
- Ferkol T and Schraufnagel D 2014 The Global Burden of Respiratory Disease *Annals of the American Thoracic Society* **11** 404-6
- Fink J B and Rubin B K 2005 Problems with inhaler use: a call for improved clinician and patient education *Respiratory care* **50** 1360-75
- Fiz J A, Jané R, Salvatella D, Izquierdo J, Lores L, Caminal P and Morera J 1999 Analysis of tracheal sounds during forced exhalation in asthma patients and normal subjects*: Bronchodilator response effect *Chest* **116** 633-8
- Ford E S, Murphy L B, Khavjou O, Giles W H, Holt J B and Croft J B 2014 Total and state-specific medical and absenteeism costs of chronic obstructive pulmonary disease among adults aged ≥ 18 years in the united states for 2010 and projections through 2020 *CHEST Journal*
- Forgacs P 1971 Breath sounds *Thorax* **33** 681-3
- Foster J M, Smith L, Usherwood T, Sawyer S M, Rand C S and Reddel H K 2012 The reliability and patient acceptability of the SmartTrack device: a new electronic monitor and reminder device for metered dose inhalers *The Journal of asthma : official journal of the Association for the Care of Asthma* **49** 657-62
- Gabrio B J, Stein S W and Velasquez D J 1999 A new method to evaluate plume characteristics of hydrofluoroalkane and chlorofluorocarbon metered dose inhalers *International journal of pharmaceutics* **186** 3-12
- Gavriely N and Cugell D W 1996 Airflow effects on amplitude and spectral content of normal breath sounds *Journal of applied physiology (Bethesda, Md. : 1985)* **80** 5-13
- Gavriely N, Nissan M, Rubin A H and Cugell D W 1995 Spectral characteristics of chest wall breath sounds in normal subjects *Thorax* **50** 1292-300
- Gavriely N, Palti Y and Alroy G 1981 Spectral characteristics of normal breath sounds *Journal of applied physiology: respiratory, environmental and exercise physiology* **50** 307-14
- Giraud V, Allaert F-A and Roche N 2011 Inhaler technique and asthma: Feasibility and acceptability of training by pharmacists *Respiratory medicine* **105** 1815-22
- Giraud V and Roche N 2002 Misuse of corticosteroid metered-dose inhaler is associated with decreased asthma stability *The European respiratory journal* **19** 246-51
- Gnitecki J, Moussavi Z and Pasterkamp H 2004 Classification of lung sounds during bronchial provocation using waveform fractal dimensions. In: *Engineering in Medicine and Biology Society, 2004. IEMBS'04. 26th Annual International Conference of the IEEE: IEEE* pp 3844-7
- GOLD 2017 Global strategy for the diagnosis, management and prevention of COPD. Global Initiative for Chronic Obstructive Pulmonary Disease)
- Göriş S, Taşci S and Elmali F 2013 The Effects of Training on Inhaler Technique and Quality Of Life in Patients with COPD *Journal of aerosol medicine and pulmonary drug delivery* **26** 336-44
- Grand View Research 2016 Digital Dose Inhaler Market Analysis By Product (Metered Dose Inhaler, Dry Powder Inhaler), By Type (Branded Medication, Generics Medication) And Segment Forecasts to 2024.
- Gross V, Dittmar A, Penzel T, SchÜttler F and von Wichert P 2000 The Relationship between Normal Lung Sounds, Age, and Gender *American Journal of Respiratory and Critical Care Medicine* **162** 905-9
- Güler E Ç, Sankur B, Kahya Y P and Raudys S 2005 Two-stage classification of respiratory sound patterns *Computers in biology and medicine* **35** 67-83
- Habukawa C, Nagasaka Y, Murakami K and Takemura T 2009 High-pitched breath sounds indicate airflow limitation in asymptomatic asthmatic children *Respirology (Carlton, Vic.)* **14** 399-403

- Hagman C, Janson C, Malinovschi A, Hedenström H and Emtner M 2015 Measuring breathing patterns and respiratory movements with the respiratory movement measuring instrument *Clinical physiology and functional imaging*
- Hajian B, Backer J, Vos W, Aerts J, Cluckers J and De Backer W 2016 Efficacy of inhaled medications in asthma and COPD related to disease severity *Expert opinion on drug delivery*
- Hamilton M, Leggett R, Pang C, Charles S, Gillett B and Prime D 2015 In Vitro Dosing Performance of the ELLIPTA® Dry Powder Inhaler Using Asthma and COPD Patient Inhalation Profiles Replicated with the Electronic Lung (eLung™) *Journal of aerosol medicine and pulmonary drug delivery* **28** 498-506
- Hanania N A and Sharafkhaneh A 2011 *COPD: A Guide to Diagnosis and Clinical Management*: New York : Humana Press, c2011.)
- Harper V P, Pasterkamp H, Kiyokawa H and Wodicka G R 2003 Modeling and measurement of flow effects on tracheal sounds *IEEE Transactions on Biomedical Engineering* **50** 1-10
- Hasan M R, Jamil M and Rahman M G R M S 2004 Speaker identification using mel frequency cepstral coefficients *variations* **1**
- Hatley R H, Parker J, Pritchard J N and von Hollen D 2017 Variability in Delivered Dose from Pressurized Metered-Dose Inhaler Formulations Due to a Delay Between Shake and Fire *Journal of aerosol medicine and pulmonary drug delivery* **30** 71-9
- Haughney J, Price D, Barnes N C, Virchow J C, Roche N and Chrystyn H 2010 Choosing inhaler devices for people with asthma: Current knowledge and outstanding research needs *Respiratory Medicine CME* **3** 125-31
- Health Service Executive 2017a Asthma.
- Health Service Executive 2017b COPD.
- Hidalgo H A, Wegmann M J and Waring W W 1991 Frequency spectra of normal breath sounds in childhood *Chest* **100** 999-1002
- Holmes M S, D'Arcy S, Costello R W and Reilly R B 2013a An acoustic method of automatically evaluating patient inhaler technique. In: *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, pp 1322-5
- Holmes M S, D'Arcy S, Costello R W and Reilly R B 2014a Acoustic Analysis of Inhaler Sounds From Community-Dwelling Asthmatic Patients for Automatic Assessment of Adherence *Translational Engineering in Health and Medicine, IEEE Journal of* **2** 1-10
- Holmes M S, Le Menn M, D'Arcy S, Rapcan V, MacHale E, Costello R W and Reilly R B 2012 Automatic identification and accurate temporal detection of inhalations in asthma inhaler recordings. In: *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference*, pp 2595-8
- Holmes M S, Seheult J, Geraghty C, D'Arcy S, Costello R W and Reilly R B 2013b Using acoustics to estimate inspiratory flow rate and drug removed from a dry powder inhaler *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference* **2013** 6866-9
- Holmes M S, Seheult J N, Geraghty C, D'Arcy S, O'Brien U, Crispino O'Connell G, Costello R W and Reilly R B 2013c A method of estimating inspiratory flow rate and volume from an inhaler using acoustic measurements *Physiological measurement* **34** 903-14
- Holmes M S, Seheult J N, O'Connell P, D'Arcy S, Ehrhardt C, Healy A M, Costello R W and Reilly R B 2014b An Acoustic-Based Method to Detect and Quantify the Effect of Exhalation into a Dry Powder Inhaler *Journal of aerosol medicine and pulmonary drug delivery*
- Horak F, Doberer D, Eber E, Horak E, Pohl W, Riedler J, Szépfalusi Z, Wantke F, Zacharasiewicz A and Studnicka M 2016 Diagnosis and management of asthma – Statement on the 2015 GINA Guidelines *Wiener klinische Wochenschrift* **128** 541-54

- Horváth A, Balásházy I, Tomisa G and Farkas Á 2017 Significance of breath-hold time in dry powder aerosol drug therapy of COPD patients *European Journal of Pharmaceutical Sciences* **104** 145-9
- Hossain I and Moussavi Z 2002a Relationship between airflow and normal lung sounds. In: *Canadian Conference on Electrical and Computer Engineering, 2002 IEEE.* , pp 1120-2 vol.2
- Hossain I and Moussavi Z 2002b Respiratory airflow estimation by acoustical means. In: *Engineering in Medicine and Biology Society (EMBC), 2002 24th Annual International Conference of the IEEE*, pp 1476-7 vol.2
- Hossain I and Moussavi Z 2004 Finding the Lung sound-Flow Relationship in Normal and Asthmatic Subjects. In: *Engineering in Medicine and Biology Society, 2004. IEMBS '04. 26th Annual International Conference of the IEEE*, pp 3852-5
- Houghton A M 2013 Mechanistic links between COPD and lung cancer *Nat Rev Cancer* **13** 233-45
- Howard S, Lang A, Patel M, Sharples S and Shaw D 2014 Electronic Monitoring of Adherence to Inhaled Medication in Asthma *Current Respiratory Medicine Reviews* **10** 50-63
- Howe M S 1978 A review of the theory of trailing edge noise *Journal of Sound and Vibration* **61** 437-65
- Huq S and Moussavi Z 2012 Acoustic breath-phase detection using tracheal breath sounds *Medical & biological engineering & computing* **50** 297-308
- Imran S, Elaine M, Ann C, Shona D A, Jansen N S and Richard W C 2014 A37. COST, TECHNOLOGY, AND COMPARATIVE EFFECTIVENESS: American Thoracic Society) pp A1401-A
- Jahedi L, Downie S R, Saini B, Chan H-K and Bosnic-Anticevich S 2016 Inhaler Technique in Asthma: How Does It Relate to Patients' Preferences and Attitudes Toward Their Inhalers? *Journal of aerosol medicine and pulmonary drug delivery* **30** 42-52
- Jain A and Vepa J 2008 Lung sound analysis for wheeze episode detection. In: *2008 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pp 2582-5
- Jain A K, Duin R P W and Jianchang M 2000 Statistical pattern recognition: a review *IEEE Transactions on Pattern Analysis and Machine Intelligence* **22** 4-37
- Jarvis S, Ind P W and Shiner R J 2007 Inhaled therapy in elderly COPD patients; time for re-evaluation? *Age and ageing* **36** 213-8
- Jha T, Sahai A K, Sarkar M, Kaundal P K, Bhardwaj P and Sharma I 2017 Assessment of inhalation technique and predictors of incorrect performance among patients of chronic obstructive pulmonary disease and asthma *International Journal of Basic & Clinical Pharmacology* **5** 1598-605
- Kanga J F and Kraman S S 1986 Comparison of the lung sound frequency spectra of infants and adults *Pediatric pulmonology* **2** 292-5
- Katz M J 1988 Fractals and the analysis of waveforms *Computers in biology and medicine* **18** 145-56
- Kawamatawong T, Khiawwan S and Pornsuriyasak P 2017 Peak inspiratory flow rate measurement by using In-Check DIAL for the different inhaler devices in elderly with obstructive airway diseases *Journal of Asthma and Allergy* **10** 17-21
- Kelley J M, Kraft-Todd G, Schapira L, Kossowsky J and Riess H 2014 The influence of the patient-clinician relationship on healthcare outcomes: a systematic review and meta-analysis of randomized controlled trials *PloS one* **9** e94207
- Kikidis D, Konstantinos V, Tzovaras D and Usmani O S 2016 The Digital Asthma Patient: The History and Future of Inhaler Based Health Monitoring Devices *Journal of aerosol medicine and pulmonary drug delivery*
- Kikidis D, Votis K and Tzovaras D 2015 Utilizing convolution neural networks for the acoustic detection of inhaler actuations. In: *2015 E-Health and Bioengineering Conference (EHB)*, pp 1-4
- Killane I, Sulaiman I, MacHale E, Breathnach A, Taylor T E, Holmes M S, Reilly R B and Costello R W 2016 Predicting asthma exacerbations employing remotely monitored

- adherence. In: *Healthcare Technology Letters: Institution of Engineering and Technology*) pp 51-5
- Kindig D A, Panzer A M and Nielsen-Bohlman L 2004 *Health literacy: a prescription to end confusion*: National Academies Press)
- Kondo T, Hibino M, Tanigaki T, Ohe M and Kato S 2015 Exhalation immediately before inhalation optimizes dry powder inhaler use *Journal of Asthma* **52** 935-9
- Koskela H O, Purokivi M K and Kokkarinen J 2016 Stepping down from combination asthma therapy: The predictors of outcome *Respiratory medicine* **117** 109-15
- Kraman S S, Pasterkamp H, Kompis M, Takase M and Wodicka G R 1998 Effects of breathing pathways on tracheal sound spectral features *Respiration physiology* **111** 295-300
- Kraman S S, Pressler G A, Pasterkamp H and Wodicka G R 2006 Design, construction, and evaluation of a bioacoustic transducer testing (BATT) system for respiratory sounds *IEEE transactions on biomedical engineering* **53** 1711-5
- Kraman S S, Wodicka G R, Oh Y and Pasterkamp H 1995 Measurement of respiratory acoustic signals. Effect of microphone air cavity width, shape, and venting *Chest* **108** 1004-8
- Lalos A S, Lakoumentas J, Dimas A and Moustakas K 2016 Energy Efficient Monitoring of Metered Dose Inhaler Usage *Journal of Medical Systems* **40** 285
- Laube B L, Janssens H M, de Jongh F H C, Devadason S G, Dhand R, Diot P, Everard M L, Horvath I, Navalesi P, Voshaar T and Chrystyn H 2011 What the pulmonary specialist should know about the new inhalation therapies *European Respiratory Journal* **37** 1308-417
- Lavorini F 2013 The Challenge of Delivering Therapeutic Aerosols to Asthma Patients *ISRN Allergy* **2013** 17
- Lavorini F, Fontana G A and Usmani O S 2014 New inhaler devices - the good, the bad and the ugly *Respiration; international review of thoracic diseases* **88** 3-15
- Lavorini F, Levy M L, Corrigan C and Crompton G 2010 The ADMIT series - issues in inhalation therapy. 6) Training tools for inhalation devices *Primary care respiratory journal : journal of the General Practice Airways Group* **19** 335-41
- Lee H, Boo S, Lim Y, Kim S and Kim I A 2014 Accuracy of inhaler use in patients with chronic obstructive pulmonary disease *Clinical nursing research* **23** 560-74
- Lei B, Rahman S A and Song I 2014 Content-based classification of breath sound with enhanced features *Neurocomputing* **141** 139-47
- Lessard C S and Wong W C 1986 Correlation of constant flow rate with frequency spectrum of respiratory sounds when measured at the trachea *IEEE transactions on bio-medical engineering* **33** 461-3
- Levy M L, Dekhuijzen P N, Barnes P J, Broeders M, Corrigan C J, Chawes B L, Corbetta L, Dubus J C, Hausen T, Lavorini F, Roche N, Sanchis J, Usmani O S, Viejo J, Vincken W, Voshaar T, Crompton G K and Pedersen S 2016 Inhaler technique: facts and fantasies. A view from the Aerosol Drug Management Improvement Team (ADMIT) *NPJ Prim Care Respir Med* **26** 16017
- Lewis A, Torvinen S, Dekhuijzen P N R, Chrystyn H, Watson A T, Blackney M and Plich A 2016 The economic burden of asthma and chronic obstructive pulmonary disease and the impact of poor inhalation technique with commonly prescribed dry powder inhalers in three European countries *BMC Health Services Research* **16** 1-12
- Li J T and O'Connell E J 1996 Clinical evaluation of asthma *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* **76** 1-13; quiz -5
- Liang Y, Hu H, Tian C, Lei Y, Liu C and Luo F 2016 A New Quantitative Method for Evaluating Dry Powder Inhalation Efficiency in Asthma Patients *Journal of aerosol medicine and pulmonary drug delivery* **29** 432-8
- Lighthill M J 1952 On sound generated aerodynamically I. General theory *Proceedings of the Royal Society of London. Series A. Mathematical and Physical Sciences* **211** 564-87
- Lo W L A and Huang D F 2016 Assessment of an alternative calibration technique to record breathing pattern and its variability with respiratory inductive plethysmography *Journal of Clinical Monitoring and Computing* 1-10

- Lozano-García M, Fiz J A, Martínez-Rivera C, Torrents A, Ruiz-Manzano J and Jané R 2017 Novel approach to continuous adventitious respiratory sound analysis for the assessment of bronchodilator response *PloS one* **12** e0171455
- Lozano M, Fiz J A and Jane R 2016 Automatic Differentiation of Normal and Continuous Adventitious Respiratory Sounds Using Ensemble Empirical Mode Decomposition and Instantaneous Frequency *IEEE journal of biomedical and health informatics* **20** 486-97
- Luinstra M, Rutgers A W, Dijkstra H, Grasmeijer F, Hagedoorn P, Vogelzang J M, Frijlink H W and de Boer A H 2015 Can Patients with Parkinson's Disease Use Dry Powder Inhalers during Off Periods? *PloS one* **10** e0132714
- Lurslurchachai L, Krauskopf K, Roy A, Halm E A, Leventhal H and Wisnivesky J P 2014 Metered dose inhaler technique among inner-city asthmatics and its association with asthma medication adherence *The clinical respiratory journal* **8** 397-403
- Lyons R G 2010 *Understanding digital signal processing*: Pearson Education)
- Mac Hale E, Costello R W and Cowman S 2014 A nurse-led intervention study: Promoting compliance with Diskus Inhaler use in asthma patients *Nursing Open* **1** 42-52
- Magnussen H, Watz H, Zimmermann I, Macht S, Greguletz R, Falques M, Jarreta D and Garcia Gil E 2009 Peak inspiratory flow through the Genuair® inhaler in patients with moderate or severe COPD *Respiratory medicine* **103** 1832-7
- Mahagnah M and Gavriely N 1994 Repeatability of measurements of normal lung sounds *American Journal of Respiratory and Critical Care Medicine* **149** 477-81
- Mahler D A, Waterman L A and Gifford A H 2012 Prevalence and COPD Phenotype for a Suboptimal Peak Inspiratory Flow Rate against the Simulated Resistance of the Diskus® Dry Powder Inhaler *Journal of aerosol medicine and pulmonary drug delivery* **26** 174-9
- Mahtani K R, Heneghan C J, Glasziou P P and Perera R 2011 Reminder packaging for improving adherence to self-administered long-term medications *Cochrane Database Syst Rev* Cd005025
- Mäkelä M J, Backer V, Hedegaard M and Larsson K 2013 Adherence to inhaled therapies, health outcomes and costs in patients with asthma and COPD *Respiratory medicine* **107** 1481-90
- Malmberg L, Paajanen E, Haahtela T and Katila T 1994 Changes in frequency spectra of breath sounds during histamine challenge test in adult asthmatics and healthy control subjects *CHEST Journal* **105** 122-31
- Malmberg L P, Pesu L and Sovijarvi A R 1995 Significant differences in flow standardised breath sound spectra in patients with chronic obstructive pulmonary disease, stable asthma, and healthy lungs *Thorax* **50** 1285-91
- Malmberg L P, Rytälä P, Happonen P and Haahtela T 2010 Inspiratory flows through dry powder inhaler in chronic obstructive pulmonary disease: age and gender rather than severity matters *International journal of chronic obstructive pulmonary disease* **5** 257
- Mandelbrot B B, Passoja D E and Paullay A J 1984 Fractal character of fracture surfaces of metals
- Marcon A, Cerveri I, Wjst M, Antó J, Heinrich J, Janson C, Jarvis D, Leynaert B, Probst-Hensch N, Svanes C, Toren K, Burney P and de Marco R 2014 Can an airway challenge test predict respiratory diseases? A population-based international study *Journal of Allergy and Clinical Immunology* **133** 104-10.e4
- Masoli M, Fabian D, Holt S, Beasley R and Global Initiative for Asthma P 2004 The global burden of asthma: executive summary of the GINA Dissemination Committee Report *Allergy* **59** 469-78
- McCartan T A, Taylor T E, Sulaiman I, Costello R W and Reilly R B 2016 Changes in inhaler inhalation acoustic features during induced bronchoconstriction: A pilot study. In: *Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the: IEEE* pp 3749-52
- McCormack P, McNamara P S and Southern K W 2011 A randomised controlled trial of breathing modes for adaptive aerosol delivery in children with cystic fibrosis *Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society* **10** 343-9

- McFadden Jr E R 1995 Improper patient techniques with metered dose inhalers: Clinical consequences and solutions to misuse *Journal of Allergy and Clinical Immunology* **96** 278-83
- McMenamin B W and Pessoa L 2015 Discovering networks altered by potential threat (“anxiety”) using quadratic discriminant analysis *NeuroImage* **116** 1-9
- McQuaid E L, Kopel S J, Klein R B and Fritz G K 2003 Medication adherence in pediatric asthma: reasoning, responsibility, and behavior *Journal of pediatric psychology* **28** 323-33
- Meddings J, Kerr E A, Heisler M and Hofer T P 2012 Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss *BMC Health Serv Res* **12** 270
- Melani A S 2007 Inhalatory therapy training: a priority challenge for the physician *Acta bio-medica : Atenei Parmensis* **78** 233-45
- Melani A S, Bonavia M, Cilenti V, Cinti C, Lodi M, Martucci P, Serra M, Scichilone N, Sestini P, Aliani M and Neri M 2011 Inhaler mishandling remains common in real life and is associated with reduced disease control *Respiratory medicine* **105** 930-8
- Melzer A C, Ghassemieh B J, Gillespie S E, Lindenauer P K, McBurnie M A, Mularski R A, Naureckas E T, Vollmer W M and Au D H 2017 Patient characteristics associated with poor inhaler technique among a cohort of patients with COPD *Respiratory medicine* **123** 124-30
- Micallef J, Micallef L A and Gouder C 2014 Comparison of asthma and COPD patients' perception of appropriate metered-dose inhaler technique with a questionnaire and supervision based reference standard *European Respiratory Journal* **44**
- Miller M K, Lee J H, Miller D P, Wenzel S E and Group T S 2007 Recent asthma exacerbations: a key predictor of future exacerbations *Respiratory medicine* **101** 481-9
- Miller M R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten C P, Gustafsson P, Jensen R, Johnson D C, MacIntyre N, McKay R, Navajas D, Pedersen O F, Pellegrino R, Viegi G and Wanger J 2005 Standardisation of spirometry *European Respiratory Journal* **26** 319-38
- Miravittles M, Vogelmeier C, Roche N, Halpin D, Cardoso J, Chuchalin A G, Kankaanranta H, Sandström T, Śliwiński P, Zatloukal J and Blasi F 2016 A review of national guidelines for management of COPD in Europe *European Respiratory Journal* **47** 625
- Mokoka M C, Lombard L, MacHale E M, Walsh J, Cushen B, Sulaiman I, Carthy D M, Boland F, Doyle F, Hunt E, Murphy D M, Faul J, Butler M, Hetherington K, Mark FitzGerald J, Boven J F M v, Heaney L G, Reilly R B and Costello R W 2017 In patients with severe uncontrolled asthma, does knowledge of adherence and inhaler technique using electronic monitoring improve clinical decision making? A protocol for a randomised controlled trial *BMJ Open* **7**
- Molimard M 2005 How to achieve good compliance and adherence with inhalation therapy *Curr Med Res Opin* **21** S33-S7
- Molimard M, Raherison C, Lignot S, Balestra A, Lamarque S, Chartier A, Droz-Perroteau C, Lassalle R, Moore N and Girodet P-O 2016 Chronic obstructive pulmonary disease exacerbation and inhaler device handling: real-life assessment of 2935 patients *European Respiratory Journal*
- Moran C, Doyle F, Sulaiman I, Bennett K, Greene G, J Molloy G, Reilly R B, Costello R W and Mellon L 2017 The INCA™ (Inhaler Compliance Assessment™): A comparison with established measures of adherence *Psychology & Health* **28** 1-21
- Motamedi-Fakhr S, Wilson R C and Iles R 2017 Tidal breathing patterns derived from structured light plethysmography in COPD patients compared with healthy subjects *Medical Devices (Auckland, N.Z.)* **10** 1-9
- Moussavi Z 2006 Fundamentals of Respiratory Sounds and Analysis *Synthesis Lectures on Biomedical Engineering* **1** 1-68
- Moussavi Z K, Leopando M T, Pasterkamp H and Rempel G 2000 Computerised acoustical respiratory phase detection without airflow measurement *Med. Biol. Eng. Comput.* **38** 198-203

- MPR 2017 Breath-Actuated vs. Metered-Dose Inhaler for Beclomethasone Dipropionate Compared. MPR)
- Muchão F P and Silva Filho L V R F 2010 Advances in inhalation therapy in pediatrics *Jornal de pediatria* **86** 367-76
- Murphy A 2016 How to help patients optimise their inhaler technique *The Pharmaceutical Journal* **297**
- Murphy R L 2008 In defense of the stethoscope *Respiratory care* **53** 355-69
- Nguyen T L and Won Y 2015 Sleep snoring detection using multi-layer neural networks *Bio-medical materials and engineering* **26 Suppl 1** S1749-55
- Nides M A, Tashkin D P, Simmons M S, Wise R A, Li V C and Rand C S 1993 Improving inhaler adherence in a clinical trial through the use of the nebulizer chronolog *Chest* **104** 501-7
- Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keenanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa R A, Jedraszewski D, Cotoi C and Haynes R B 2014 Interventions for enhancing medication adherence *Cochrane Database Syst Rev* Cd000011
- Nikander K, Turpeinen M, Pelkonen A S, Bengtsson T, Selroos O and Haahtela T 2011 True adherence with the Turbuhaler in young children with asthma *Arch Dis Child* **96** 168-73
- Normansell R and Kew K M 2016 Interventions to improve inhaler technique for people with asthma *Cochrane Database of Systematic Reviews*
- Nousias S, Lakoumentas J, Lalos A, Kikidis D, Moustakas K, Votis K and Tzovaras D 2016 Monitoring asthma medication adherence through content based audio classification. In: *2016 IEEE Symposium Series on Computational Intelligence (SSCI)*, pp 1-5
- O'Connor R, Wolf M S, Smith S G, Martynenko M, Vicencio D P, Sano M, Wisnivesky J P and Federman A D 2015 Health literacy, cognitive function, proper use, and adherence to inhaled asthma controller medications among older adults with asthma *Chest* **147** 1307-15
- O'Dwyer S M, MacHale E, Sulaiman I, Holmes M, Hughes C, D'Arcy S, Rapcan V, Taylor T, Boland F and Bosnic-Anticevich S 2016 The effect of providing feedback on inhaler technique and adherence from an electronic audio recording device, INCA®, in a community pharmacy setting: study protocol for a randomised controlled trial *Trials* **17** 1
- Onyirimba F, Apter A, Reisine S, Litt M, McCusker C, Connors M and ZuWallack R 2003 Direct clinician-to-patient feedback discussion of inhaled steroid use: its effect on adherence *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* **90** 411-5
- Osterberg L and Blaschke T 2005 Adherence to medication *New England Journal of Medicine* **353** 487-97
- Ozturk A B, Ozyigit Pur L, Kostek O and Keskin H 2015 Association between asthma self-management knowledge and asthma control in the elderly *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* **114** 480-4
- Paajanen E 1996 Averaged and Time-Gated Spectral Analysis of Respiratory Sounds *Chest* **109** 1283-90
- Palaniappan R, Sundaraj K, Sundaraj S, Hularaj N and Revadi S S 2016 A novel approach to detect respiratory phases from pulmonary acoustic signals using normalised power spectral density and fuzzy inference system *Clin Respir J* **10** 486-94
- Pasterkamp H, Kraman S S, DeFrain P D and Wodicka G R 1993 Measurement of respiratory acoustical signals. comparison of sensors *Chest* **104** 1518-25
- Pasterkamp H, Kraman S S and Wodicka G R 1997 Respiratory sounds. Advances beyond the stethoscope *American journal of respiratory and critical care medicine* **156** 974-87
- Pasterkamp H, Powell R E and Sanchez I 1996 Lung sound spectra at standardized air flow in normal infants, children, and adults *American journal of respiratory and critical care medicine* **154** 424-30
- Pasterkamp H and Sanchez I 1992 Tracheal sounds in upper airway obstruction *Chest* **102** 963-5

- Pasterkamp H and Sanchez I 1996 Effect of gas density on respiratory sounds *American journal of respiratory and critical care medicine* **153** 1087-92
- Patel M, Pilcher J, Chan A, Perrin K, Black P and Beasley R 2012 Six-month in vitro validation of a metered-dose inhaler electronic monitoring device: implications for asthma clinical trial use *The Journal of allergy and clinical immunology* **130** 1420-2
- Pauwels R A and Rabe K F 2004 Burden and clinical features of chronic obstructive pulmonary disease (COPD) *Lancet (London, England)* **364** 613-20
- Pirozynski M and Sosnowski T R 2016 Inhalation devices: from basic science to practical use, innovative vs generic products *Expert opinion on drug delivery* **13** 1559-71
- Pittas A G, Westcott G P and Balk E M 2015 Efficacy, safety, and patient acceptability of Technosphere inhaled insulin for people with diabetes: a systematic review and meta-analysis *The Lancet Diabetes & Endocrinology* **3** 886-94
- Plaza Moral V and Giner Donaire J 2016 Inhaled therapy in asthma *Medicina clinica* **146** 316-23
- Price D, Bosnic-Anticevich S, Briggs A, Chrystyn H, Rand C, Scheuch G and Bousquet J 2013 Inhaler competence in asthma: common errors, barriers to use and recommended solutions *Respiratory medicine* **107** 37-46
- Price D, Freeman D, Cleland J, Kaplan A and Cerasoli F 2011 Earlier diagnosis and earlier treatment of COPD in primary care *Primary care respiratory journal : journal of the General Practice Airways Group* **20** 15-22
- Price D B, Roman-Rodriguez M, McQueen R B, Bosnic-Anticevich S, Carter V, Gruffydd-Jones K, Haughney J, Henrichsen S, Hutton C, Infantino A, Lavorini F, Law L M, Lisspers K, Papi A, Ryan D, Stallberg B, van der Molen T and Chrystyn H 2017 Inhaler Errors in the CRITIKAL Study: Type, Frequency, and Association with Asthma Outcomes *The journal of allergy and clinical immunology. In practice*
- Prime D, de Backer W, Hamilton M, Cahn A, Preece A, Kelleher D, Baines A, Moore A, Brealey N and Moynihan J 2015 Effect of Disease Severity in Asthma and Chronic Obstructive Pulmonary Disease on Inhaler-Specific Inhalation Profiles Through the ELLIPTA® Dry Powder Inhaler *Journal of aerosol medicine and pulmonary drug delivery* **28** 486-97
- Pritchard J N and Nicholls C 2015 Emerging technologies for electronic monitoring of adherence, inhaler competence, and true adherence *Journal of aerosol medicine and pulmonary drug delivery* **28** 69-81
- Proakis J G, Manolakis, Dimitris G. 1992 *Digital Signal Processing Principles, Algorithms, and Applications*: Macmillan)
- Que C L, Kolmaga C, Durand L G, Kelly S M and Macklem P T 2002 Phonosprometry for noninvasive measurement of ventilation: methodology and preliminary results *Journal of applied physiology (Bethesda, Md. : 1985)* **93** 1515-26
- Raman S and Druzgalski C 2015 *World Congress on Medical Physics and Biomedical Engineering, June 7-12, 2015, Toronto, Canada*, ed D A Jaffray (Cham: Springer International Publishing) pp 974-7
- Rau J L 2006 Practical problems with aerosol therapy in COPD *Respiratory care* **51** 158-72
- Redmond S J and Heneghan C 2006 Cardiorespiratory-based sleep staging in subjects with obstructive sleep apnea *IEEE Transactions on Biomedical Engineering* **53** 485-96
- Reljin N, Reyes B and Chon K 2015 Tidal Volume Estimation Using the Blanket Fractal Dimension of the Tracheal Sounds Acquired by Smartphone *Sensors* **15** 9773
- Restrepo R D, Alvarez M T, Wittnebel L D, Sorenson H, Wettstein R, Vines D L, Sikkema-Ortiz J, Gardner D D and Wilkins R L 2008 Medication adherence issues in patients treated for COPD *International journal of chronic obstructive pulmonary disease* **3** 371-84
- Reyes B A, Reljin N and Chon K H 2014 Tracheal Sounds Acquisition Using Smartphones *Sensors* **14** 13830-50
- Roche N and Dekhuijzen P N R 2016 The Evolution of Pressurized Metered-Dose Inhalers from Early to Modern Devices *Journal of aerosol medicine and pulmonary drug delivery* **29** 311-27
- Rodriguez-Martinez C E, Sossa-Briceno M P and Nino G 2016 A systematic review of instruments aimed at evaluating metered-dose inhaler administration technique in

- children *The Journal of asthma : official journal of the Association for the Care of Asthma* **0**
- Rossi M, Sovijarvi A, Piirila P, Vannuccini L, Dalmaso F and Vanderschoot J 2000 Environmental and subject conditions and breathing manoeuvres for respiratory sound recordings *European Respiratory Review* **10** 611-5
- Rottier B L and Rubin B K 2013 Asthma medication delivery: mists and myths *Paediatric respiratory reviews* **14** 112-8; quiz 8, 37-8
- Ruinskiy D and Lavner Y 2007 An Effective Algorithm for Automatic Detection and Exact Demarcation of Breath Sounds in Speech and Song Signals *IEEE Transactions on Audio, Speech, and Language Processing* **15** 838-50
- Sabaté E 2003 *Adherence to long-term therapies: evidence for action*: World Health Organization)
- Sanchez I and Pasterkamp H 1993 Tracheal sound spectra depend on body height *The American review of respiratory disease* **148** 1083-7
- Sanchez I and Vizcaya C 2003 Tracheal and lung sounds repeatability in normal adults *Respiratory medicine* **97** 1257-60
- Sánchez Morillo D, Astorga Moreno S, Fernández Granero M Á and León Jiménez A 2013 Computerized analysis of respiratory sounds during COPD exacerbations *Computers in biology and medicine* **43** 914-21
- Sanchis J, Gich I and Pedersen S 2016 Systematic Review of Errors in Inhaler Use: Has Patient Technique Improved Over Time? *Chest* **150** 394-406
- Sander N, Fusco-Walker S J, Harder J M and Chipps B E 2006 Dose counting and the use of pressurized metered-dose inhalers: running on empty *Annals of Allergy, Asthma & Immunology* **97** 34-8
- Sanduzzi A, Balbo P, Candoli P, Catapano G A, Contini P, Mattei A, Puglisi G, Santoiemma L and Stanziola A A 2014 COPD: adherence to therapy *Multidisciplinary respiratory medicine* **9** 60
- Sarlabous L, Torres A, Fiz J A, Martínez-Llorens J M, Gea J and Jané R 2017 Inspiratory muscle activation increases with COPD severity as confirmed by non-invasive mechanomyographic analysis *PloS one* **12** e0177730
- Schappert S M and Rechtsteiner E A 2008 Ambulatory medical care utilization estimates for 2006 *National health statistics reports* **1-29**
- Schreur H J, Vanderschoot J, Zwinderman A H, Dijkman J H and Sterk P J 1995 The effect of methacholine-induced acute airway narrowing on lung sounds in normal and asthmatic subjects *The European respiratory journal* **8** 257-65
- Seheult J N, Costello S, Tee K C, Bholah T, Al Bannai H, Sulaiman I and Costello R W 2014a Investigating the relationship between peak inspiratory flow rate and volume of inhalation from a Diskus™ Inhaler and baseline spirometric parameters: a cross-sectional study *SpringerPlus* **3** 496
- Seheult J N, O'Connell P, Tee K C, Bholah T, Al Bannai H, Sulaiman I, MacHale E, D'Arcy S, Holmes M S, Bergin D, Reeves E, Reilly R B, Crispino-O'Connell G, Ehrhardt C, Healy A M and Costello R W 2014b The Acoustic Features of Inhalation can be Used to Quantify Aerosol Delivery from a Diskus Dry Powder Inhaler *Pharmaceutical research*
- Selam J L 2003 Inhaled insulin for the treatment of diabetes: projects and devices *Expert opinion on pharmacotherapy* **4** 1373-7
- Sello S, Strambi S-k, De Michele G and Ambrosino N 2008 Respiratory sound analysis in healthy and pathological subjects: A wavelet approach *Biomedical Signal Processing and Control* **3** 181-91
- Semmlow J L and Griffel B 2014 *Biosignal and medical image processing*: CRC press)
- Sengupta N, Sahidullah M and Saha G 2016 Lung sound classification using cepstral-based statistical features *Computers in biology and medicine* **75** 118-29
- Shokrollahi M, Saha S, Hadi P, Rudzicz F and Yadollahi A 2016 Snoring sound classification from respiratory signal *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference* **2016** 3215-8

- Silverman B W 1981 Using kernel density estimates to investigate multimodality *Journal of the Royal Statistical Society. Series B (Methodological)* **97**-9
- Small M, Anderson P, Vickers A, Kay S and Fermer S 2011 Importance of inhaler-device satisfaction in asthma treatment: Real-world observations of physician-observed compliance and clinical/patient-reported outcomes *Advances in Therapy* **28** 202-12
- Sola-Soler J, Fiz J A, Morera J and Jané R 2011 Bayes classification of snoring subjects with and without Sleep Apnea Hypopnea Syndrome, using a Kernel method *Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference* **2011** 6071-4
- Soufflet G, Charbonneau G, Polit M, Attal P, Denjean A, Escourrou P and Gaultier C 1990 Interaction between tracheal sound and flow rate: a comparison of some different flow evaluations from lung sounds *IEEE transactions on bio-medical engineering* **37** 384-91
- Sovijarvi A, Malmberg L, Charbonneau G, Vanderschoot J, Dalmasso F, Sacco C, Rossi M and Earis J 2000 Characteristics of breath sounds and adventitious respiratory sounds *European Respiratory Review* **10** 591-6
- Spaulding S A, Devine K A, Duncan C L, Wilson N W and Hogan M B 2012 Electronic monitoring and feedback to improve adherence in pediatric asthma *J Pediatr Psychol* **37** 64-74
- Spencer T, Daniels T, Pollard K, Agent P, Morgan G, Madge S, Bilton D and Peckham D 2012 85 I-neb Insight Online—a telemedicine option in the treatment of cystic fibrosis *Journal of Cystic Fibrosis* **11** S78
- Su J G, Barrett M A, Henderson K, Humblet O, Smith T, Sublett J W, Nesbitt L, Hogg C, Van Sickle D and Sublett J L 2017 Feasibility of Deploying Inhaler Sensors to Identify the Impacts of Environmental Triggers and Built Environment Factors on Asthma Short-Acting Bronchodilator Use *Environmental Health Perspectives* **125** 254-61
- Sulaiman I, Cushen B, Greene G, Seheult J, Seow D, Rawat F, MacHale E, Mokoka M, Moran C N, Sartini Bhreathnach A, MacHale P, Tappuni S, Deering B, Jackson M, McCarthy H, Mellon L, Doyle F, Boland F, Reilly R B and Costello R W 2016a Objective Assessment of Adherence to Inhalers by COPD Patients *American Journal of Respiratory and Critical Care Medicine*
- Sulaiman I, Greene G, MacHale E, Seheult J, Mokoka M, D'Arcy S, Taylor T, Murphy D M, Hunt E, Lane S J, Diette G B, Fitzgerald M J, Boland F, Sartini Bhreathnach A, Cushen B, Reilly R B, Doyle F and Costello R W 2018 A randomised clinical trial of feedback on inhaler adherence and technique in patients with severe uncontrolled asthma *European Respiratory Journal* **51**
- Sulaiman I, Mac Hale E, Holmes M, Hughes C, D'Arcy S, Taylor T, Rapcan V, Doyle F, Breathnach A and Seheult J 2016b A protocol for a randomised clinical trial of the effect of providing feedback on inhaler technique and adherence from an electronic device in patients with poorly controlled severe asthma *BMJ open* **6** e009350
- Sulaiman I, MacHale E, Seheult J, D'Arcy S, Rapcan V, Mokoka M, Cushen B, Killane I, Franciosi A, Sahadevan A, Keane M, Keane J M, Lane S, Murphy D, Reilly R and Costello R 2016c A50. ASTHMA: OBSERVATIONAL STUDIES: American Thoracic Society) pp A1714-A
- Sulaiman I, Seheult J, Killane I, MacHale E, Reilly R and Costello R 2015 A new clinically relevant method of calculating adherence *European Respiratory Journal* **46**
- Sulaiman I, Seheult J, MacHale E, Boland F, O'Dwyer S M, Rapcan V, D'Arcy S, Cushen B, Mokoka M, Killane I, Ryder S A, Reilly R B and Costello R W 2016d A Method to Calculate Adherence to Inhaled Therapy That Reflects the Changes in Clinical Features of Asthma *Annals of the American Thoracic Society*
- Sulaiman I, Seheult J, MacHale E, D'Arcy S, Boland F, McCrory K, Casey J, Bury G, Al-Alawi M, O'Dwyer S, Ryder S A, Reilly R B and Costello R W 2016e Irregular and Ineffective: A Quantitative Observational Study of the Time and Technique of Inhaler Use *The journal of allergy and clinical immunology. In practice* **4** 900-9.e2

- Sulaiman I, Seheult J, Sadasivuni N, MacHale E, Killane I, Giannoutsos S, Cushen B, Mokoka M C, Sartini Bhreathnach A, Boland F, Reilly R B and Costello R W 2017 The Impact of Common Inhaler Errors on Drug Delivery: Investigating Critical Errors with a Dry Powder Inhaler *Journal of aerosol medicine and pulmonary drug delivery*
- Szeffler S J, Zeiger R S, Haselkorn T, Mink D R, Kamath T V, Fish J E and Chipps B E 2011 Economic burden of impairment in children with severe or difficult-to-treat asthma *Annals of Allergy, Asthma & Immunology* **107** 110-9.e1
- Tabata H, Hirayama M, Enseki M, Nukaga M, Hirai K, Furuya H and Mochizuki H 2016 A novel method for detecting airway narrowing using breath sound spectrum analysis in children *Respiratory Investigation* **54** 20-8
- Takahiro E, Masato K, Udantha R A, Ikuji K, Osamu J, Masatake A, Shinsuke K and Yohsuke k 2014 Signal shape feature for automatic snore and breathing sounds classification *Physiological measurement* **35** 2489
- Takaku Y, Kurashima K, Ohta C, Ishiguro T, Kagiya N, Yanagisawa T and Takayanagi N 2017 How many instructions are required to correct inhalation errors in patients with asthma and chronic obstructive pulmonary disease? *Respiratory medicine* **123** 110-5
- Tamura G and Ohta K 2007 Adherence to treatment by patients with asthma or COPD: comparison between inhaled drugs and transdermal patch *Respiratory medicine* **101** 1895-902
- Taplidou S A and Hadjileontiadis L J 2007 Wheeze detection based on time-frequency analysis of breath sounds *Computers in biology and medicine* **37** 1073-83
- Taylor T, E., De Looze C, MacHale P, Holmes M, S., Sulaiman I, Costello R, W. and Reilly R, B. 2016a Characterization of patient inhaler inhalation sounds using non-contact and tracheal microphones *Biomedical Physics & Engineering Express* **2** 055021
- Taylor T E, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2015 Influences of gender and anthropometric features on inspiratory inhaler acoustics and peak inspiratory flow rate. In: *Engineering in Medicine and Biology Society (EMBC), 2015 37th Annual International Conference of the IEEE*, pp 2227-30
- Taylor T E, Holmes M S, Sulaiman I, Costello R W and Reilly R B 2016b Monitoring Inhaler Inhalations Using an Acoustic Sensor Proximal to Inhaler Devices *Journal of aerosol medicine and pulmonary drug delivery* **29** 439-46
- Taylor T E, Holmes M S, Sulaiman I, D'Arcy S, Costello R W and Reilly R B 2014 An acoustic method to automatically detect pressurized metered dose inhaler actuations. In: *Engineering in Medicine and Biology Society (EMBC), 2014 36th Annual International Conference of the IEEE: IEEE* pp 4611-4
- Taylor T E, Lacalle Muls H, Costello R W and Reilly R B 2018a Estimation of inhalation flow profile using audio-based methods to assess inhaler medication adherence *PloS one* **13** e0191330
- Taylor T E, Zigel Y, De Looze C, Sulaiman I, Costello R W and Reilly R B 2018b Advances in Audio-Based Systems to Monitor Patient Adherence and Inhaler Drug Delivery *Chest* **153** 710-22
- Taylor T E, Zigel Y, Egan C, Hughes F, Costello R W and Reilly R B 2018c Objective Assessment of Patient Inhaler User Technique Using an Audio-Based Classification Approach *Scientific reports* **8** 2164
- Teulier M, Fiamma M-N, Straus C and Similowski T 2013 Acute bronchodilation increases ventilatory complexity during resting breathing in stable COPD: Toward mathematical biomarkers of ventilatory function? *Respiratory physiology & neurobiology* **185** 477-80
- Teva Respiratory 2014 Anatomy of the Respiratory System.
- Toy E L, Beaulieu N U, McHale J M, Welland T R, Plauschinat C A, Swensen A and Duh M S 2011 Treatment of COPD: Relationships between daily dosing frequency, adherence, resource use, and costs *Respiratory medicine* **105** 435-41
- van Boven J F M, Lavorini F, Dekhuijzen P N R, Blasi F, Price D B and Viegi G 2017 Urging Europe to put non-adherence to inhaled respiratory medication higher on the policy agenda: a report from the First European Congress on Adherence to Therapy *The European respiratory journal* **49**

- van Boven J F M, Ryan D, Eakin M N, Canonica G W, Barot A and Foster J M 2016 Enhancing Respiratory Medication Adherence: The Role of Health Care Professionals and Cost-Effectiveness Considerations *The Journal of Allergy and Clinical Immunology: In Practice* **4** 835-46
- Vandenbussche N L, Overeem S, van Dijk J P, Simons P J and Pevernagie D A 2015 Assessment of respiratory effort during sleep: Esophageal pressure versus noninvasive monitoring techniques *Sleep Medicine Reviews* **24** 28-36
- Vannuccini L, Earis J, Helisto P, Cheetham B, Rossi M, Sovijarvi A and Vanderschoot J 2000 Capturing and preprocessing of respiratory sounds *European Respiratory Review* **10** 616-20
- Vestbo J, Anderson J A, Calverley P M A, Celli B, Ferguson G T, Jenkins C, Knobil K, Willits L R, Yates J C and Jones P W 2009 Adherence to inhaled therapy, mortality and hospital admission in COPD *Thorax* **64** 939
- Virchow J C, Crompton G K, Dal Negro R, Pedersen S, Magnan A, Seidenberg J and Barnes P J 2008 Importance of inhaler devices in the management of airway disease *Respiratory medicine* **102** 10-9
- Vitolins M Z, Rand C S, Rapp S R, Ribisl P M and Sevic M A 2000 Measuring Adherence to Behavioral and Medical Interventions *Controlled Clinical Trials* **21** S188-S94
- Vrijens B, Dima A L, Van Ganse E, van Boven J F M, Eakin M N, Foster J M, de Bruin M, Chisholm A and Price D 2016 What We Mean When We Talk About Adherence in Respiratory Medicine *The Journal of Allergy and Clinical Immunology: In Practice* **4** 802-12
- Vyshedskiy A and Murphy R 2016 Acoustic biomarkers of Chronic Obstructive Lung Disease *Research Ideas and Outcomes* **2** e9173
- Wei W 2007 Extracting signal frequency information in time/frequency domain by means of continuous wavelet transform. In: *Control, Automation and Systems, 2007. ICCAS '07. International Conference on*, pp 540-3
- WHO 2003 Adherence to Long-Term Therapies - Evidence for Action.
- WHO 2015 Chronic obstructive pulmonary disease (COPD). World Health Organization)
- Yadollahi A, Montazeri A, Azarbarzin A and Moussavi Z 2013 Respiratory Flow-Sound Relationship During Both Wakefulness and Sleep and Its Variation in Relation to Sleep Apnea *Annals of biomedical engineering* **41** 537-46
- Yadollahi A and Moussavi Z 2008 Comparison of flow-sound relationship for different features of tracheal sound. In: *Engineering in Medicine and Biology Society (EMBC), 2008 30th Annual International Conference of the IEEE*, pp 805-8
- Yadollahi A and Moussavi Z M 2006a A robust method for estimating respiratory flow using tracheal sounds entropy *IEEE Transactions on Biomedical Engineering* **53** 662-8
- Yadollahi A and Moussavi Z M 2006b A robust method for heart sounds localization using lung sounds entropy *IEEE transactions on bio-medical engineering* **53** 497-502
- Yadollahi A and Moussavi Z M 2007 Acoustical respiratory flow. A review of reliable methods for measuring air flow *IEEE engineering in medicine and biology magazine : the quarterly magazine of the Engineering in Medicine & Biology Society* **26** 56-61
- Yadollahi A and Moussavi Z M K 2011 The Effect of Anthropometric Variations on Acoustical Flow Estimation: Proposing a Novel Approach for Flow Estimation Without the Need for Individual Calibration *IEEE Transactions on Biomedical Engineering* **58** 1663-70
- Yee Leng Y and Moussavi Z 2002 Acoustic airflow estimation from tracheal sound power. In: *Electrical and Computer Engineering, 2002. IEEE CCECE 2002. Canadian Conference on*, pp 1073-6
- Yu L, Ting C-K, Hill B E, Orr J A, Brewer L M, Johnson K B, Egan T D and Westenskow D R 2013 Using the entropy of tracheal sounds to detect apnea during sedation in healthy nonobese volunteers *Anesthesiology* **118** 1341-9
- Zaugg V, Savoldelli V, Durieux P and Sabatier B 2016 Providing physicians with feedback on medication adherence. Effect on processes of care and patient outcomes *Cochrane Database of Systematic Reviews*

- Zeki A A 2014 Statins and asthma: where we stand, and the next critical steps in research *Curr Med Res Opin* **30** 1051-4
- Zénon A, Sidibé M and Olivier E 2014 Pupil size variations correlate with physical effort perception *Frontiers in Behavioral Neuroscience* **8** 286
- Zheng F, Zhang G and Song Z 2001 Comparison of different implementations of MFCC *Journal of Computer Science and Technology* **16** 582-9
- Zolnierek K B and Dimatteo M R 2009 Physician communication and patient adherence to treatment: a meta-analysis *Medical care* **47** 826-34

Appendices

Appendix A: Chapter 4 Supplementary Material

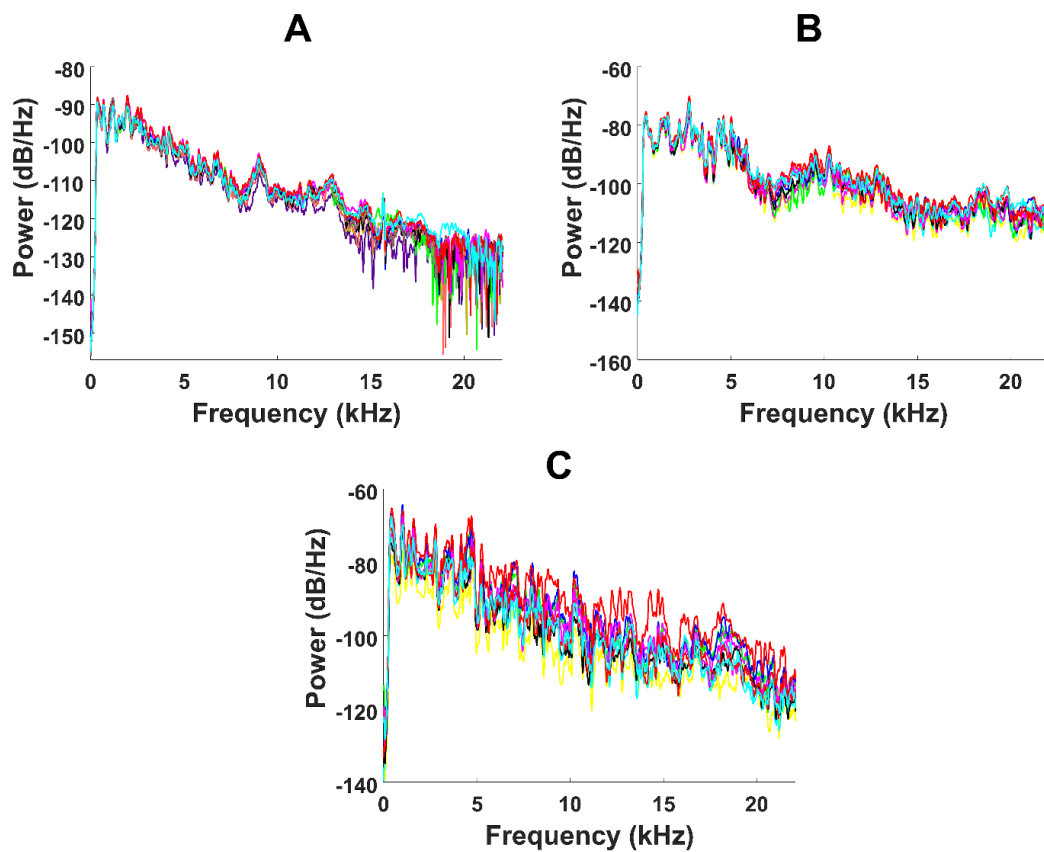


Figure A1. Power spectral density estimates of inhaler inhalations through different inhaler devices.

The PSD estimates present 10 inhaler inhalations from one participant at 40-50 L/min for (A) Diskus DPI, (B) Turbuhaler DPI and at 150-200 L/min for (C) Evohaler pMDI demonstrating high repeatability.

Appendix B: Chapter 6 Supplementary Material

Table B1. Average peak inspiratory flow rate values from inhalation flow profiles for each participant.

Participant No.	PIFR – High (L/min)	PIFR – Medium (L/min)	PIFR – Low (L/min)
1	79	64	42
2	107	66	42
3	132	54	44
4	134	60	33
5	102	66	43
6	97	58	34
7	134	53	35
8	100	62	43
9	70	55	42
10	123	52	32
11	113	58	37
12	115	61	40
13	142	61	38
14	129	64	42
15	126	65	41
16	83	63	38
17	87	54	41
18	88	60	42
19	112	62	35
20	N/A	57	41

Table B2. Average inspiratory capacity values from inhalation flow profiles for each participant.

Participant No.	IC – High (L)	IC – Medium (L)	IC – Low (L)
1	1.90	1.28	0.94
2	2.33	1.19	0.96
3	2.86	1.98	2.07
4	3.09	1.31	0.84
5	2.61	1.73	1.40
6	2.64	1.61	1.01
7	2.53	1.57	1.11
8	2.16	1.88	1.48
9	2.68	1.98	1.45
10	3.95	2.98	2.48
11	2.36	1.20	0.92
12	3.73	2.07	1.45
13	4.02	1.18	0.71
14	3.27	2.03	1.28
15	4.09	2.84	2.28
16	1.82	1.25	0.95
17	2.47	1.75	1.80
18	2.36	1.81	0.87
19	2.57	1.88	1.20
20	N/A	1.84	1.45

Table B3. Average ramp time values from inhalation flow profiles for each participant.

Participant No.	Tr – High (ms)	Tr – Medium (ms)	Tr – Low (ms)
1	304	306	390
2	223	155	146
3	134	251	240
4	188	175	245
5	409	344	336
6	563	770	464
7	168	244	317
8	329	314	214
9	485	239	241
10	335	470	390
11	270	195	171
12	232	373	280
13	164	176	341
14	254	299	243
15	315	376	562
16	577	347	436
17	193	258	302
18	597	361	400
19	286	407	448
20	N/A	281	285

Appendix C: Chapter 7 Supplementary Material

	Rec1	Rec2	Rec3	Rec4
Checklist	Y/N	Y/N	Y/N	Y/N
Does the patient hold the inhaler upright, with their thumb on the base and their index/middle finger on the top of the canister, and the inhaler facing towards them?				
Does the patient exhale sufficiently (breathe out as far as comfortable) prior to inhalation?				
Does the patient place their teeth around the Flo-Tone, without biting the mouthpiece, and close their lips around it correctly?				
Does the patient inhale through their mouth?				
Does the patient inhale at an appropriate flow rate suitable for metered dose inhalers? (Is the whistle too loud or not heard at all?)				
When hearing the Flo-Tone, does the patient press down on the canister to release the aerosol?				
Does the patient continue to inhale steadily, slowly and deeply after they actuate the inhaler? (Does the Flo-Tone still generate a sound after the canister is pressed?)				
After a full inhalation, does the patient hold their breath? (up to 10 seconds)				
Does the patient exhale after holding their breath?				

Figure C1. Inhaler user technique checklist used for patient pMDI recordings.

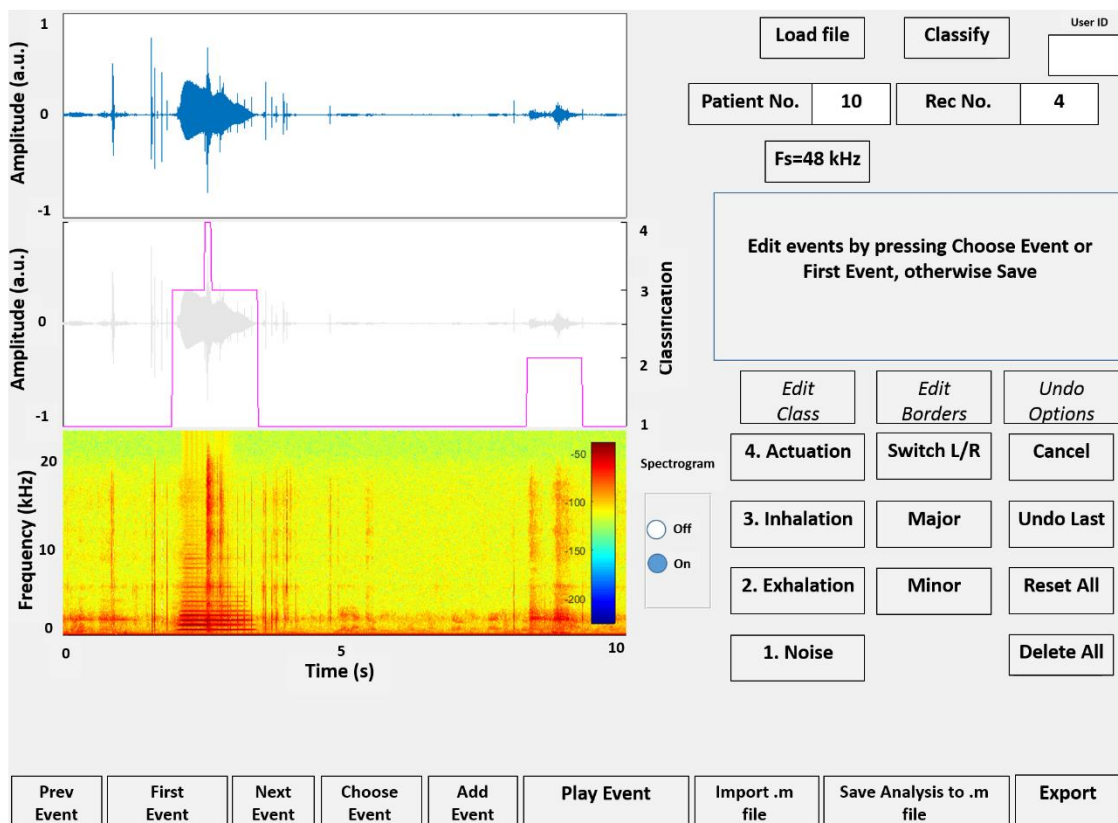


Figure C2. Graphical user interface for labelling inhaler audio frames.

The graphical user interface (GUI) allows each inhaler audio signal to be manually labelled for the training process and for the evaluation of the inhaler sound event classification algorithm in the testing phase. Once an audio signal is loaded into the GUI, the audio time domain signal as well as the spectrogram of the audio signal are displayed. From here, each sound event can be manually labelled. Additionally, each labelled sound event can be played to assist the labelling process. The labelled signal (pink) is also shown. Once the labelling process is complete, the user can save a segmentation text file which contains the labelling information of sound events for the corresponding audio signal.

Table C1. Audio-based feature set employed for inhaler sound event classification.

#	Feature name	No. of features	Feature symbol	Selected Features
1	Energy	1	E	-
2	Pitch	1	f_0	-
3	Zero crossing rate	1	Z	-
4	Harmonic	1	ρ	*
5	Shannon entropy	1	H	*
6	Linear predictive coding coef.	10	a_1 - a_{10}	* a_1, a_2
7	Skewness	1	Sk	*
8	Kurtosis	1	K	*
9	Wavelet power	1	ψ	-
10	Mel-frequency cepstral coef.	12	C_1 - C_{12}	* $C_1, C_3, C_6, C_{11}, C_{12}$

* Selected

- Not Selected

Comparison between quadratic discriminant analysis with artificial neural network:

A feed forward artificial neural network (ANN) with three hidden layers was compared to the quadratic discriminant analysis (QDA) method described in this study. The ANN performance measures generated using 11 selected features from the QDA feature selection process are presented in comparison to the QDA results in Table C2 and Table C3. In order to assess whether the selected features were biased only to the QDA, a sequential forward feature selection process was also performed with the ANN. It was observed that the ANN feature selection selected eight optimum features which included: E , Z , f_0 , c_9 , c_{22} , c_{30} , a_1 , and a_3 . The performance measure results generated from the training and testing datasets using the eight ANN selected features with QDA and ANN classification methods are presented in Table C4 and Table C5.

Table C2. Performance measures of quadratic discriminant analysis and artificial neural network classification methods on training dataset using 11 selected features from quadratic discriminant analysis feature selection.

Performance Measure	Symbol	QDA Result (%)	ANN Result (%)
Weighted performance measure	J	80.38	65.28
Accuracy (frame-by-frame)	Acc	90.88	52.74
Sensitivity of inhalation detection	S^I	82.93	82.93
Positive predictive value of inhalation detection	P^I	92.73	79.69
Sensitivity of actuation detection	S^A	98.25	95.61
Positive predictive value of actuation detection	P^A	90.32	36.95
Sensitivity of exhalation detection	S^E	48.62	52.29
Positive predictive value of exhalation detection	P^E	26.77	10.16

Table C3. Performance measures of quadratic discriminant analysis and artificial neural network classification methods on testing dataset using 11 selected features from quadratic discriminant analysis feature selection.

Performance Measure	Symbol	QDA Result (%)	ANN Result (%)
Weighted performance measure	J	80.22	64.51
Accuracy (frame-by-frame)	Acc	88.20	52.98
Sensitivity of inhalation detection	S^I	90	83.08
Positive predictive value of inhalation detection	P^I	92.13	66.26
Sensitivity of actuation detection	S^A	92.11	91.23
Positive predictive value of actuation detection	P^A	94.59	48.6
Sensitivity of exhalation detection	S^E	40.77	54.62
Positive predictive value of exhalation detection	P^E	23.77	12.18

Table C4. Performance measures of quadratic discriminant analysis and artificial neural network classification methods on training dataset using eight selected features from artificial neural network feature selection.

Performance Measure	Symbol	QDA Result (%)	ANN Result (%)
Weighted performance measure	J	67.07	74.17
Accuracy (frame-by-frame)	Acc	90.81	65.50
Sensitivity of inhalation detection	S^I	87.81	86.18
Positive predictive value of inhalation detection	P^I	54.27	92.17
Sensitivity of actuation detection	S^A	99.12	93.86
Positive predictive value of actuation detection	P^A	82.48	49.30
Sensitivity of exhalation detection	S^E	10.09	87.16
Positive predictive value of exhalation detection	P^E	13.25	11.54

Table C5. Performance measures of quadratic discriminant analysis and artificial neural network classification methods on testing dataset using eight selected features from artificial neural network feature selection.

Performance Measure	Symbol	QDA Result (%)	ANN Result (%)
Weighted performance measure	J	71.02	73.70
Accuracy (frame-by-frame)	Acc	88.64	65.56
Sensitivity of inhalation detection	S^I	90.77	85.38
Positive predictive value of inhalation detection	P^I	58.42	84.09
Sensitivity of actuation detection	S^A	98.25	91.23
Positive predictive value of actuation detection	P^A	91.06	59.09
Sensitivity of exhalation detection	S^E	13.85	84.62
Positive predictive value of exhalation detection	P^E	19.36	12.82

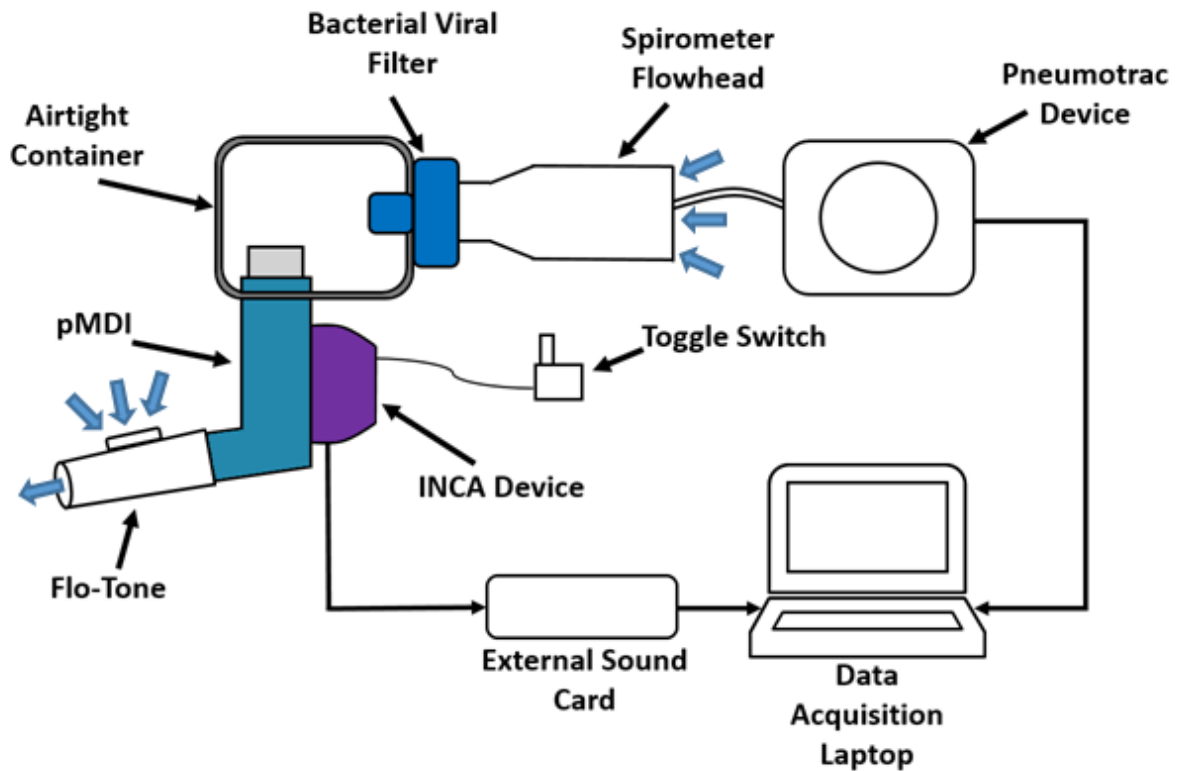


Figure C3. pMDI audio-based flow estimation experimental setup.

Blue arrows indicate the airflow during the inhalation recordings. Airflow passes through the spirometer to measure peak inspiratory flow rate (PIFR) and volume during inhalation. Airflow also passes through the reed on the Flo-Tone which was accounted for in the *in-vitro* experiment described in the next section of Appendix C.

Comparing the peak inspiratory flow rate measurements at the spirometer and the Flo-Tone mouthpiece:

Methods:

In order to ensure that the flow measurements obtained from the spirometer represented the true flow measurements of the participant's inhalation (and not influenced by the additional airflow at the Flo-Tone reed aperture), an *in-vitro* experiment was performed relating the PIFR recorded from the spirometer to the PIFR recorded from the mouthpiece of the Flo-Tone. This was performed by connecting the Flo-Tone mouthpiece to a high capacity vacuum pump [HCP4, Copley Scientific] and Critical Flow Controller (air valve) [TPK 2000, Copley Scientific]. The flow pump simulated inhalations through the device at 10 flow rates between 20-100 L/min, which covers the clinically relevant inspiratory flow rates for pMDIs (the flow pump setup was calibrated up to 100 L/min also so it was not recommended to exceed 100 L/min). The setup for this *in-vitro* experiment is shown in Figure C4. The PIFR recorded from the spirometer was compared to that of the reading on the vacuum pump.

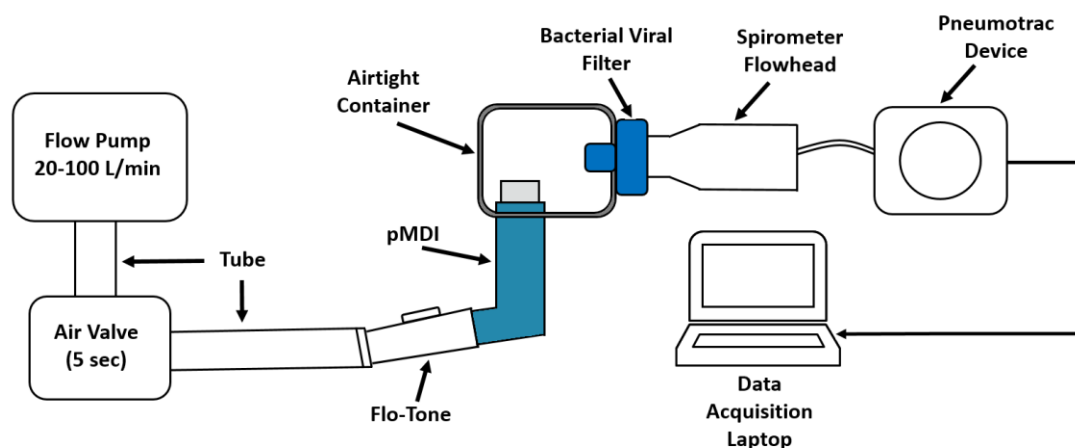


Figure C4. Inhaler flow measurement setup comparing difference in measured PIFR between the spirometer and inhaler mouthpiece.

Result:

It was observed that the difference between the PIFR measurements obtained from the spirometer and the vacuum pump was almost negligible ($4.65 \pm 2.54\%$ error (mean $\pm$ SD)). There was a highly statistically significant linear relationship between the PIFR measured at the spirometer and at the mouthpiece (vacuum pump) ($R^2=0.99$, $p<0.0001$). This linear relationship is presented in Figure C5. Therefore, this indicated that the flow measurements obtained from the pneumotachograph spirometer were reliable measurements of flow through the Flo-Tone mouthpiece.

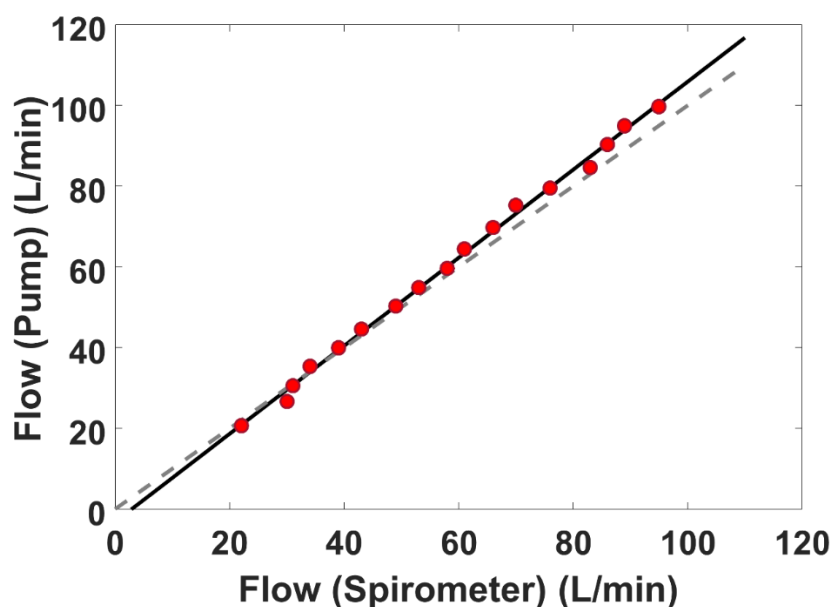


Figure C5. Linear relationship between flow rate measured at the inhaler mouthpiece (pump) and the spirometer ($R^2=0.99$, $p<0.0001$). Equal line is also plotted (grey).

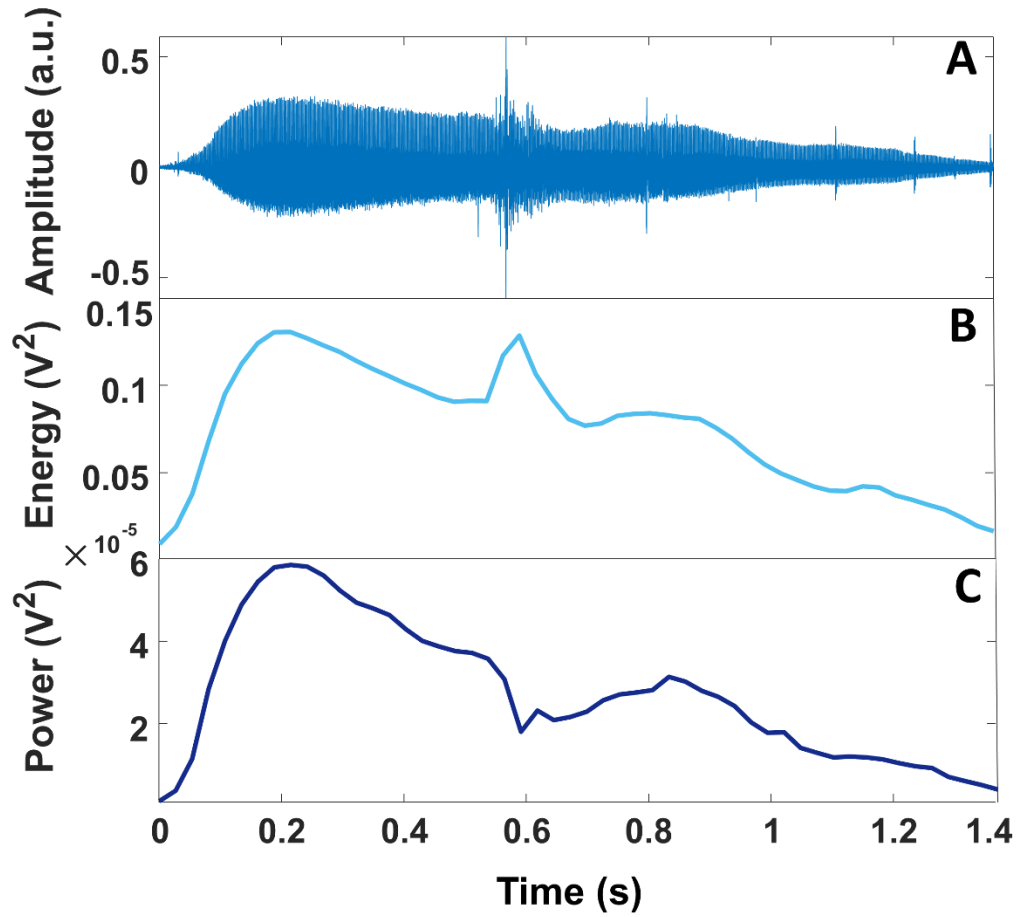


Figure C6. Example of a patient pMDI inhalation audio signal.

An example of a patient actuating the inhaler to release medication during inhalation at approximately 0.6 s into an inhalation (placebo inhalers were used in this study so no active medication was administered). (A) Audio time domain signal of pMDI inhalation audio signal. (B) Energy of each frame. (C) Power of the fundamental frequency for each frame. It is evident that selecting the frame of maximum energy may be influenced by the actuation occurring at 0.6 s in the audio signal.

Table C6. R^2 values describing the relationship between Flo-Tone inhalation audio-based features and PIFR in the pressurised metered dose inhaler. All R^2 values were highly statistically significant ($p < 0.0001$).

Flow Estimation Model	E	P_{f0}	P_{f0f1}
<i>Linear Model</i>	0.87	0.88	0.62
<i>Power Law Model</i>	0.87	0.87	0.90

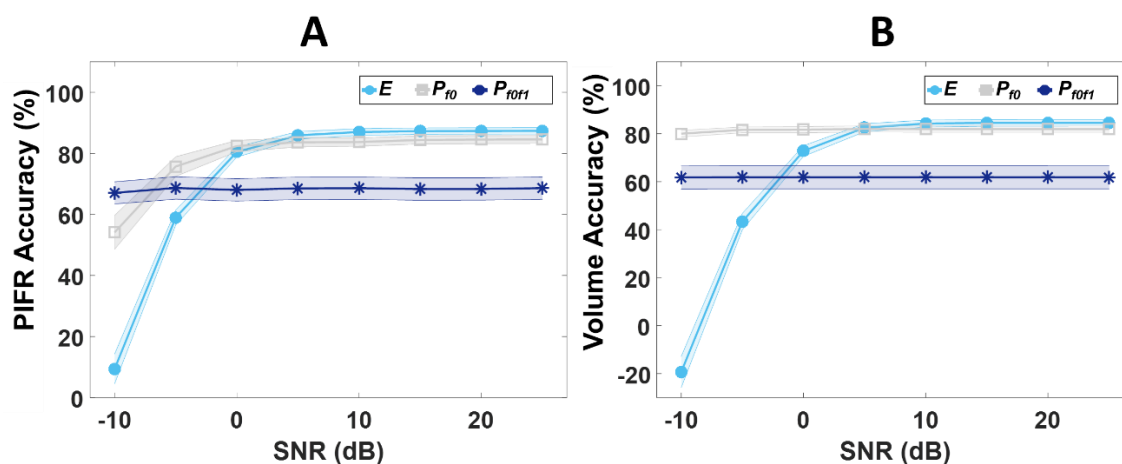


Figure C7. Audio-based pMDI inhalation flow estimation performance within different SNR levels using linear models.

Average $\pm$ standard error (shaded region) of (A) PIFR and (B) IC estimation accuracy for three audio-based features (E , P_{f0} and P_{f0f1}) using power law regression models across different SNR levels.

Wilcoxon signed rank test analysis comparing inhaler PIFR and volume before and after tuition:

If a patient did not inhale before tuition or did not inhale after tuition they were discarded from this statistical analysis as at least one inhalation was needed to compare before and after tuition. This was the case for 16 patients where they did not inhale either before or after tuition. A further four patients were removed from this analysis across labelled and detected audio data due to the presence of outliers in the PIFR and IC values according to Grubbs' outlier test ($p < 0.05$).

Table C7. Wilcoxon signed rank test results comparing median difference in PIFR between before and after tuition.

Audio Dataset	No. patients	Median	Wilcoxon Statistic	p-value
<i>Labelled</i>	41	36.69	669	0.002
<i>Detected</i>	42	39.53	709	0.001

Table C8. Wilcoxon signed rank test results comparing median difference in inhalation volume between before and after tuition.

Audio Dataset	No. patients	Median	Wilcoxon Statistic	p-value
<i>Labelled</i>	41	0.22	594.5	0.034
<i>Detected</i>	42	0.39	696.5	0.002

Table C9. Percentage (%) of patients who made critical user technique errors (poor actuation coordination and inhaling too fast) before and after tuition.

		Critical User Technique Error			
		<i>Poor Actuation Coordination (before tuition)</i>	<i>Poor Actuation Coordination (after tuition)</i>	<i>Inhaling Too Fast (before tuition)</i>	<i>Inhaling Too Fast (after tuition)</i>
Method of Assessment	<i>Checklist (Clinical reviewer)</i>	90	84	79	56
	<i>Labelled Audio (GUI)</i>	82	79	87	81
	<i>Detected Audio (Algorithm)</i>	85	82	89	84

Appendix D: Chapter 8 Supplementary Material

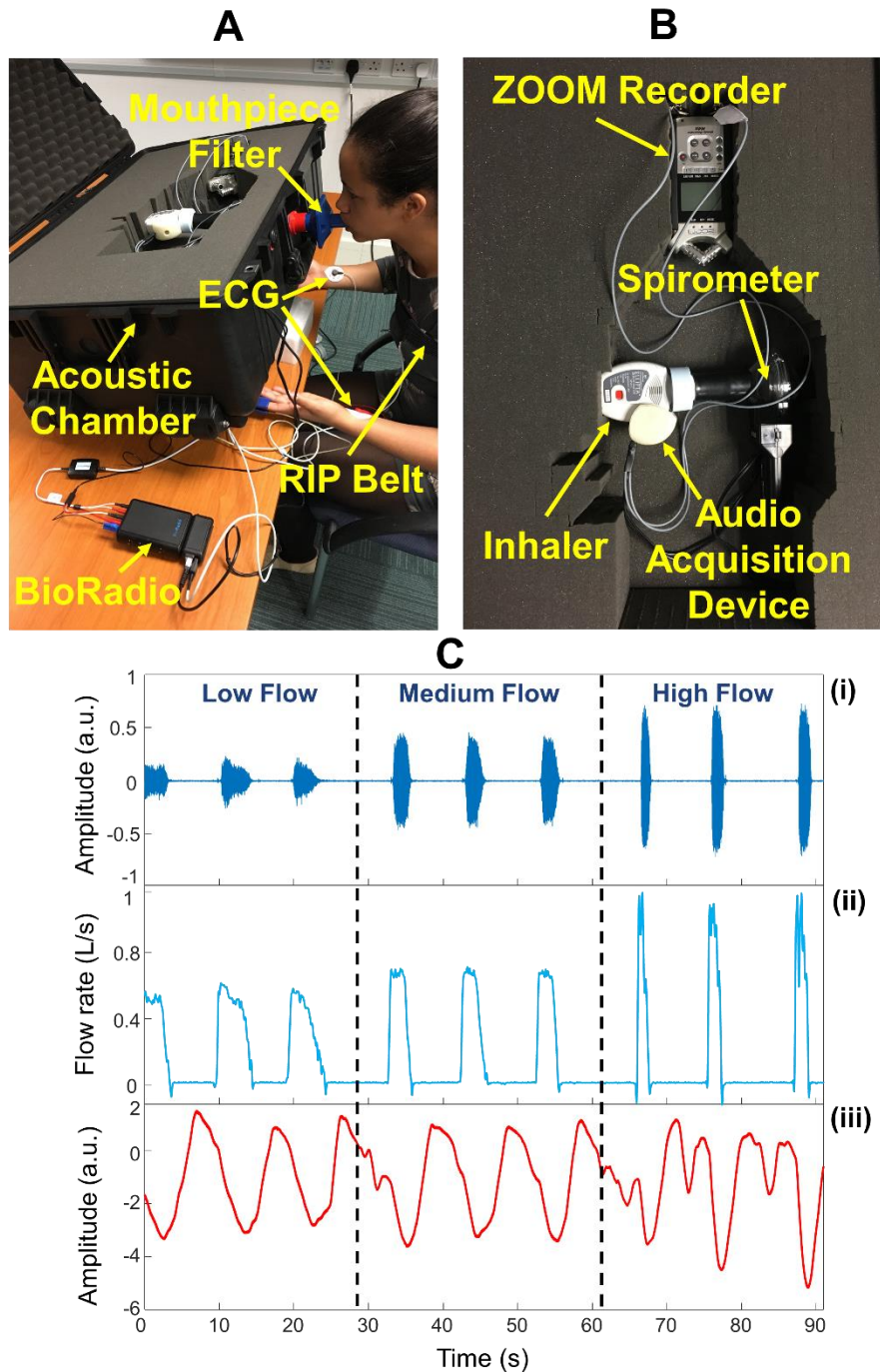


Figure D1. Physiological signals obtained during Ellipta DPI inhalations with increasing flow rate.

(A) Audio signals of inhaler inhalations. Inhalation audio signals were sampled at 44.1 kHz at 16 bits per sample resolution using a ZOOM recorder [ZOOM, H4n, Japan]. (B) Inhalation flow signal of inhaler inhalations recorded using a spirometer connected to a BioRadio acquisition system [Great Lakes NeuroTechnologies, Ohio, USA]. (C) Respiratory inductance plethysmography (RIP) signal obtained from the chest of a healthy participant during inhaler inhalations using an RIP belt connected to a BioRadio acquisition system. In order to simultaneously record the signals, the Ellipta DPI was placed inside a closed custom built acoustic chamber which was fitted with sound proof material to reduce background

noise (opened in the picture just for illustrative purposes). The spirometer was connected to the inhaler mouthpiece to measure the inhalation flow signal. A mouthpiece was fitted to an aperture in the acoustic chamber to allow the participant to perform inhalations as they wore the RIP belt around the chest. Flow and RIP signals were sampled at 250 Hz. It can be observed that the negative slope of the RIP signal corresponds to the peak flow rate of each inhalation. Hence, this could be a feature employed to estimate PIFR from chest RIP signals in future studies.

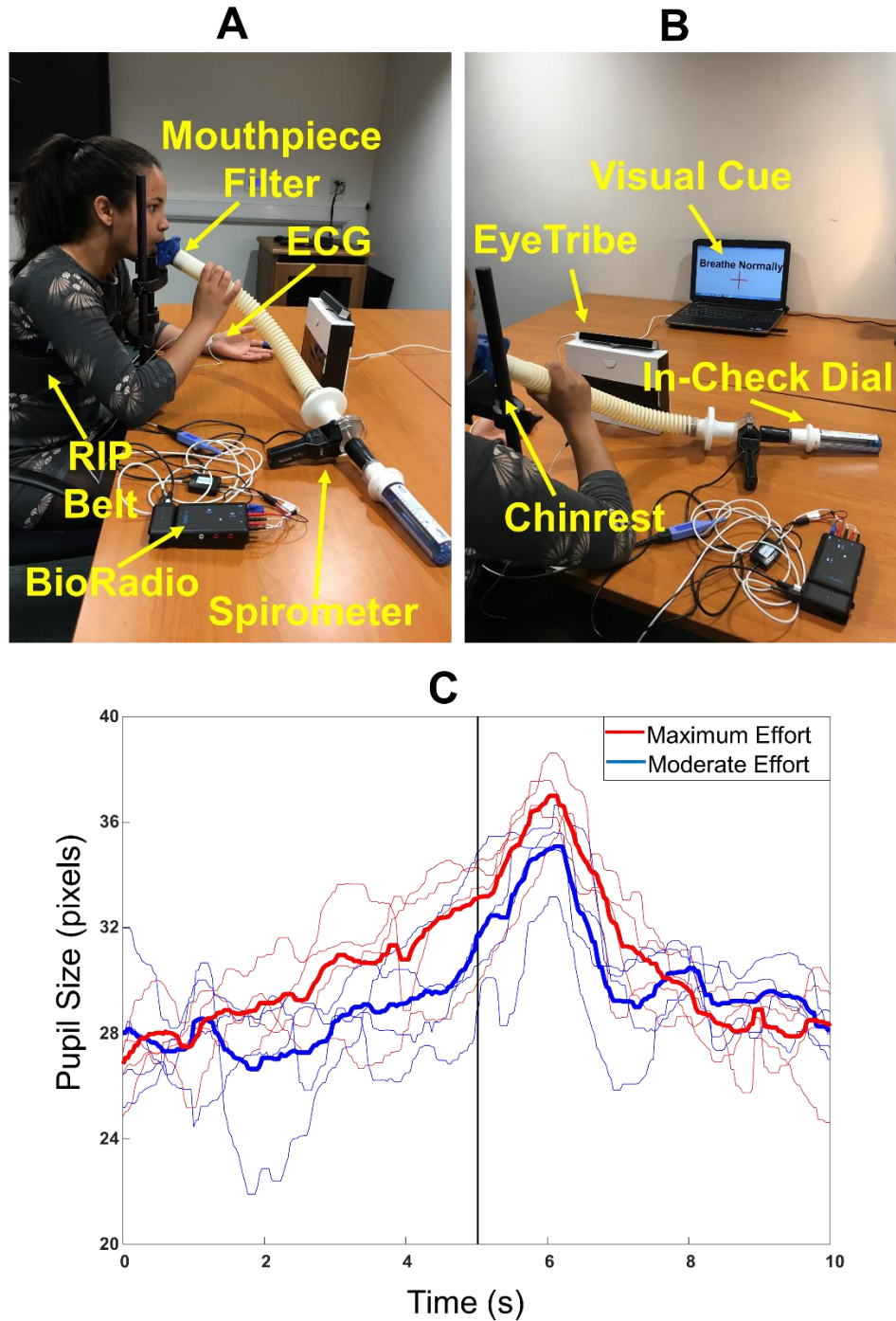


Figure D2. Using pupillometry methods to develop new objective measures of inspiratory effort during dry powder inhaler use.

(A) and (B) present the recording setup for the pupillometry pilot study. Pupil size, electrocardiography (ECG), RIP and flow rate signals are recorded during inhalation using the BioRadio device. Participants are instructed to focus, with minimal blinking, on a visual cue presented on a screen. Participants are then given a visual cue to inhale at a specific inspiratory effort (moderate or maximal). (C) Four pupillometry signals for each of moderate (blue) and maximal (red) inspiratory effort from one participant inhaling through a medium resistance channel using the In-Check Dial. The In-Check Dial device simulates the medium resistance of an Ellipta DPI. The average of the four moderate (thick blue) and maximal (thick red) inspiratory effort pupillometry signals are also presented. The black marker is the time at which the visual cue was presented to the participant instructing them to inhale. A median filter of order 7 was used to remove eye blinks.