# CALCULATING CARDIOVASCULAR LUMPED-PARAMETER MODEL VALUES BY INJECTING SMALL VOLUME PERTURBATIONS IN AN ISOVOLUMIC HEART

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**Title**

Calculating Cardiovascular Lumped-Parameter Model Values by Injecting Small Volume Perturbations

**By**

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

**MASTER OF SCIENCE**

## ABSTRACT

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Diagnosing cardiac patient problems contains many uncertainties, and to fully diagnose the patient's condition usually requires a lengthy drug regimen to see what works and what does not. Compounding this problem is that even after the correct drug regimen has been discovered, the underlying cause for the problem may remain a mystery. Thus, the uncertainty and the length of time required to provide an accurate and adequate solution makes it very difficult to provide quality care to the patient.

Templeton and others have shown that lumped cardiac muscle parameters can be extracted from an isolated heart by injecting small volumes at high frequencies relative to the heart rate and measuring the pressure response to this volume change. Using the Hill muscle model of two springs and a dashpot to portray the different elements of the cardiac muscle, the pressure and volume relationship makes it possible to calculate these muscle parameters using frequency response analysis techniques.

The hypothesis to be tested is "Is it possible to develop a method to test cardiac muscle for stiffness, resistance, and contractile force from measuring ventricular pressure and injected flow?"

To test this hypothesis, an isovolumic heart model is developed and allowed to develop pressure, along with a small volume injected to create a pressure response. Analysis of the pressure and flow waveforms produces a measured value of the cardiac model parameter values to compare to the model values.

Results from injecting small volume changes into a mathematical heart model show that it is possible to extract the muscle model parameters of non-linear resistance, inertia of the fluid and muscle, and stiffness of the muscle while filling and contracting. The injected frequency and volume were varied to find usable conditions, both with regard to the calculations and the practical limits. Analyzing the error between the measured and model values for a large number of different combinations of model parameters shows an average error of less than 1%.

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# INTRODUCTION

Due to the interaction between many components in the cardiac muscle, and also the interdependence of the cardiac muscle with the rest of the cardiovascular system, it can be very difficult to diagnose the true cause of cardiac problems quickly. A new way of performing faster cardiac parameter measurements would be beneficial in diagnosing cardiac dysfunction. Is it possible to calculate cardiac lumped parameter model values by injecting small volumes into an isovolumic heart and measuring the resulting pressure and flow relationships?

In the early days of muscle research, Hill proposed a simple muscle model [1,2] consisting of a series elastic spring and a contractile spring connected one after the other in a series system, as shown in Figure 1.

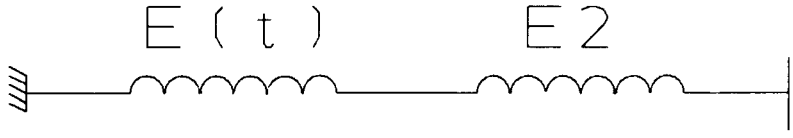


*Figure 1. Hill Muscle Model Consisting of Two Springs. The contractile spring (E(t)) and the restorative spring (E2) connected in series.*

This model was used to explained the contractile force and also the relaxation decay force curves. The model was later fitted with a dashpot in parallel with the contractile spring to provide resistance to contraction and account for force losses during a muscle contraction such as friction. An additional spring, E1, was later added to the model, also in

parallel with the contractile spring, to account for the stiffness of the muscle while not contracting, as in Figure 2.

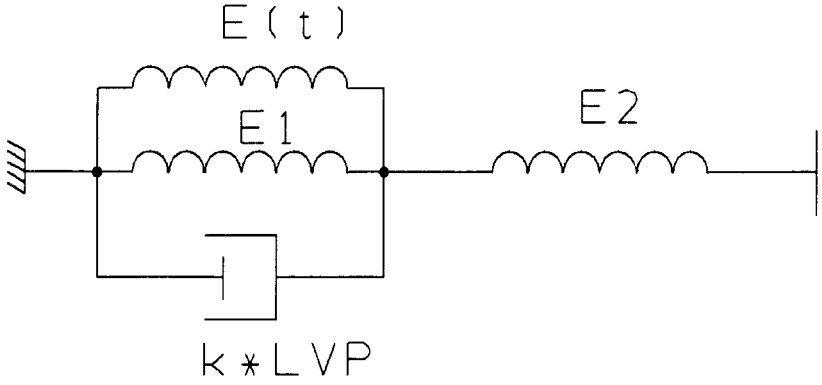


*Figure 2. Cardiac Model Used for Simulation and Analysis.*
*E(t) is the contractile force, E1 is the spring constant of the muscle mass, and k*LVP is the resistance to motion of the heart. E2 is assumed to be large enough to ignore in the model.*

This lumped parameter system models the connections between the actin and myosin chains, the Z bands and the titin filaments that hold the myosin centered in the sarcomeres for the heart muscle [3].

The Hill muscle model has been used for many years, and provides a useful lumped parameter model of cardiac muscle. A lumped-parameter model takes the elements of the individual cells and creates a single lumped value for the whole which resembles the sum of the individual components, much like the Thevenin equivalent of an electrical circuit. The Thevenin equivalent allows for simple analysis of a "black box" system by measuring the input voltage and current relationship. A lumped-parameter cardiac model also

provides for simpler analysis, in contrast to finite element analysis on a distributed model.

In the lumped-parameter model, the stiffness of the heart is represented by two springs in parallel – one which produces a constant stiffness, E1, and the second produces a time-varying stiffness which provides the contractile force as the heart beats, E(t).

The dashpot element in the model designates the resistance of the cardiac muscle while contracting, similar to friction. This dashpot also exhibits a non-linear property where the resistance is proportional to the pressure developed by the heart at that point. Thus, the resistance produces a non-linear effect, where R = k*LVP, and as the generated pressure increases, the resistance force of the contraction also increases.

A fourth element in the muscle model is another elastance element, E2, which is placed in series with the three other elements. The E2 element represents the stiffness of the Z-bands of the cardiac muscle, and in many approaches is considered much larger than the other spring constants, and ignored. For this thesis, E2 is assumed to be much larger than E(t) and E1 and ignored in the analysis of the lumped-parameter model of Figure 2 above.

Besides the cardiac muscle elements of the model, a series inductive element is added in the flow path to account for the inertia of the fluid volume in the heart and also the mass of the heart muscle. This element is an inductor and represents amount of force it takes to move the heart wall and the enclosed volume during a volume change. The inductor represents an inertial component, and for inertial components, the higher the injected volume change, the larger the inertial response will be and requires greater pressure changes.

The updated model with the inductance explains the results obtained by Templeton in 1974 [4] when he accounted for the phase shift experienced with small volume perturbations in cardiac muscle. Using an isolated canine heart, Templeton calculated the cardiac parameters of elastic and viscous stiffness of the Hill muscle model by injecting small volumes at 22 Hz through a balloon catheter, and measuring the pressure response [4,5]. He then calculated values for both stiffness values and also the inertial effects with the phase component [4].

In 1997, Campbell also tested a cardiac muscle model by injecting small volumes into an isolated rabbit heart at different volumes and frequencies [6]. Campbell used volume perturbations up to 100 Hz and also used a fluid filled balloon catheter to create the volume changes. Campbell's results support the hypothesis that cardiac model parameters can be calculated using pressure and volume measurements.

The majority of the muscle models contain a time-varying elastance element to produce the contractile force. A mechanical model of this element is a spring with a time varying spring force constant K(t), designated as E(t) in Figure 2. As the value of K(t) increases during the contractile period, the force due to the corresponding length change also increases.

The electrical equivalent to the mechanical spring is a variable capacitance, C(t), which changes voltage as the capacitance decreases. The value of E(t) shown in Figure 2 is the reciprocal of C(t). An electrical model, consisting of time-varying capacitors, inductors, resistors and diodes can be used to model the entire cardiovascular system, including both sides of the heart, and the arterial and venous systems for analysis [7]. To

create isovolumic contractions, any elements of the cardiovascular system model outside of the ventricle are ignored.

There is some concern about whether the Hill muscle model is correct [8], and though the point that trying to create a simple lumped parameter model out of a vast number of smaller elements does introduce errors, these errors – for the purpose of understanding the potential to measure cardiac performance – may be assumed to be not important or minimal.

Much work has been put into different techniques to measure cardiac parameters in an attempt to quantify the cardiac mechanics and provide diagnostic abilities. Some techniques are non-invasive, such as with external pressure measurements and ultrasound [9], while others, like Templeton and Campbell, use an isovolumic isolated heart. The invasive measurements, especially to create an isovolumic contraction, provide much better model parameter results, but also limit the ability to do diagnostic work quickly and easily in a clinical setting.

It is this background, however, that allows for the possibility to calculate the cardiac model parameters using small volume changes. By injecting small volume changes into an isovolumic heart and measuring the pressure and flow relationships, the cardiac lumped-parameter model values of elastance E(t), resistance k, and inductance L can be calculated.

## METHOD

The method used to provide for parameter estimation relies on first creating an isovolumic heart model. The isovolumic heart, which requires invasive surgery, allows for a better test of the theory due to the fewer number of assumptions and volume paths.

The assumptions for an isovolumic beat model parameter estimation require that the only flow into and out of the system are from the intended volume changes, and this provides a calculable pressure and flow relationship. The other assumptions of the model are that R = k*LVP, with k being a constant, and that the elastance consists of two elements, with one – C1 – dominating during relaxation, and the other contractile force – C(t) – dominating during the contraction. The Z-band elastance, E2, is assumed to be large, and ignored.

The values of C1, k, and L are also assumed to be constant for an isovolumic heart during both relaxation and contraction. The volume injected by the external source is also assumed to be injected directly into the heart ventricle by some process without any lag or unaccounted losses external to the heart. This is equivalent to a previously characterized system in which the input and system response are known to produce a sinusoidal output wave at the point of insertion into the heart.

The electrical equivalent model is shown below in Figure 3. A typical electrical series RLC circuit is comprised of a resistor, inductor and capacitor one after another connected end to end to be in a series configuration, and provides a total impedance consisting of the resistance value as the real component, and the sum of the capacitive and inductive reactances as the imaginary component.

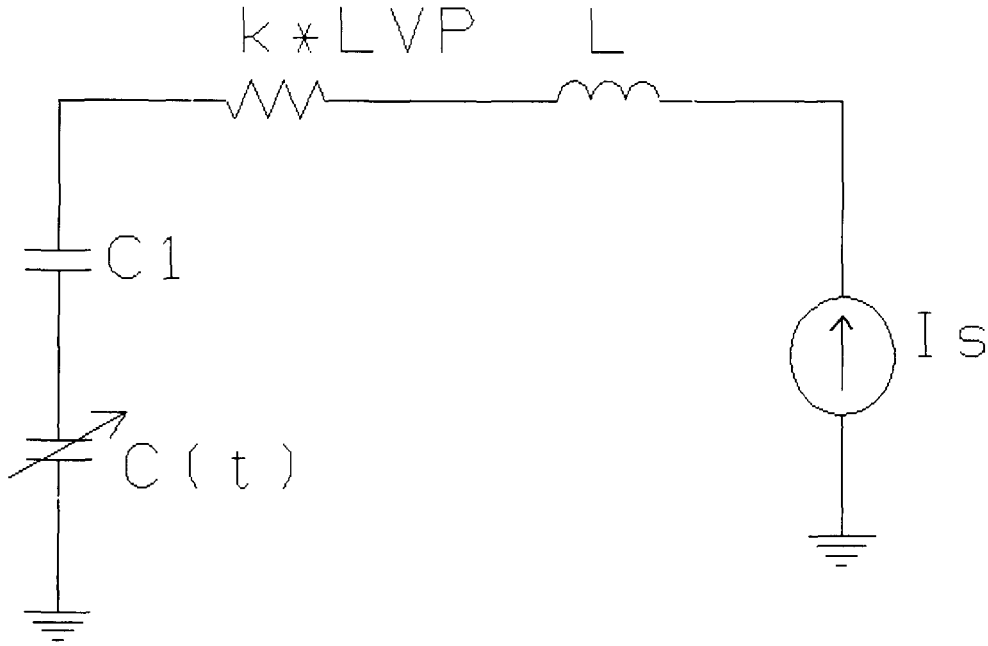


*Figure 3. Electrical Circuit Equivalent of the Hill Muscle Model used for Cardiac Modeling.*

In the model of Figure 3, L is the inductance to account for the inertia of the cardiac muscle mass and the fluid volume in the heart, R is k*LVP and accounts for the friction in the heart muscle during any wall motion. C1 and C(t) are the elements which produce the stiffness of the heart. C1 is the constant value of stiffness for the cardiac muscle at all times, and C(t) is the stiffness that creates the contractile force. Together the two capacitances produce an effective capacitance of Ceff.

During filling C1 >> C(t) and during the contractile period, C(t) >> C1. These two elements are combined together to form an effective stiffness, Ceff, but the capacitance conversion contains fractions. C1 and C(t) can be converted into elastances E1 and E(t) respectively by using the reciprocals, 1/C1 and 1/C(t). The two elastances directly add

together to produce an effective elastance, Eeff, whch is equal E1+E(t), whereas the compliances would add to $\frac{1}{\frac{1}{C1}+\frac{1}{C(t)}}$ for the capacitive equivalent.

LVP is the pressure measured in the left ventricle, or at the aortic valve, and to produce an isovolumic system, the aortic valve is continually closed. This shows the pressure response to the injected volume signal from the external source at the particular frequency. The current source produces a volume change independent of the pressure of the heart, and thus produces a pressure response proportional to both the injected volume and the applied frequency.

In an isovolumic system, a larger volume change produces a larger pressure response at any given frequency, and an injected volume change at a higher frequency also produces a larger pressure response for the same volume change.

Pe is the pressure developed in the heart muscle by the sarcomeres. During filling, Pe is very low – approximately 5 mmHg. The measured LVP signal then has a lower pressure due to less stiffness of the cardiac muscle to work against as the volume is injected. This produces a lower pressure response during filling for the entire system. As the cardiac muscle stiffens, the generated pressure in the heart, Pe, increases, which also increases the pressure response of the volume changes.

The inductance, L, of the model also plays a role in how much pressure is generated at LVP by the injected volume signal. The inductance represents the inertia of the system and the inertial component increases for large or rapid volume changes since the flow is the derivative of the volume, and is therefore larger. The pressure response generated at LVP

from the volume changes is delayed by the inductance of the system, causing a lag between LVP and Pe. This lag can be measured to calculate the inductance of the system.

At high frequencies, the inertial component is large, and thus LVP signal perturbations are larger than Pe signal perturbations. For the same injected volumes, high frequencies produce a larger LVP signal perturbation due to the inductive component compared to low frequencies. This conforms to the findings of Campbell that at the higher frequency of 100 Hz, the measured LVP signals were much higher than at all of the lower frequencies.

The model is constructed by starting with a time varying elastance, or time varying capacitance. Typically, the time varying current into a capacitor is written electrically as

$$I = C \cdot \frac{dV}{dt}. \tag{1}$$

The unstated assumption in this equation is that the capacitance remains constant over all time. The physics equation for a capacitor is

$$Q = C \cdot V, \tag{2}$$

where Q is the charge on the capacitor, C is capacitance and V is voltage.

When both voltage and capacitance vary, taking the derivative of this equation with respect to time produces the equation:

$$I = \frac{dQ}{dt} = \frac{dC}{dt} \cdot V + C \cdot \frac{dV}{dt}. \tag{3}$$

With a constant capacitance, $\frac{dC}{dt} = 0$, but with a time varying capacitor, this will not cancel, and both terms for C and V are required, along with the derivative terms.

In the circuit model Figure 3, for the time varying capacitance element, Pe is the voltage (V), C is the effective capacitance, which is the combination of the time varying capacitance C(t) and C1, and the current into the capacitor, Is, is from the injected volume change.

Rewriting the differential equation for the hemodynamic model, and solving for Pe:

$$\frac{dPe}{dt} = \frac{1}{C(t)} \cdot \left( Is - Pe \cdot \frac{dC}{dt} \right). \tag{4}$$

Using terms of elastance instead of capacitance, where E(t) = 1/C(t), and using the chain rule, the differential equations become:

$$\frac{dC(t)}{dt} = \frac{-1}{E(t)^2} \cdot \frac{dE}{dt} \tag{5}$$

$$\frac{dPe}{dt} = E(t) \cdot \left( Is + Pe \cdot \frac{1}{E(t)^2} \cdot \frac{dE}{dt} \right). \tag{6}$$

Elastance was chosen over capacitance because it did not require the use of a fraction when calculating the values for the model and because elastance is the common vernacular in the cardiac model parameters. Using elastance also allowed directly working with literature values of previous research.

As can be seen in the equation above, the variables required to solve the differential equation (6) are Pe and E(t), and their respective derivatives. Pe and dPe are the solution variables for the model, which then requires E(t) and its derivative to be calculated values. The values of E(t) can represent any condition, but to remain true to the purpose of the simulation, values for E(t) appropriate for common canine cardiac situations were used.

A single heartbeat consists of a period of relaxation for filling, followed by a period

of contraction. Using nominal canine values, the elastance during filling is around 0.1 mmHg/cc, and the elastance during contraction has an ESPVR of around 4 mmHg/cc. Using an effective volume of 50 cc, this produces a pressure during relaxation of 5 mmHg in the heart, and a maximum isovolumic pressure of around 200 mmHg during contraction.

To produce this waveform of E(t), and also keeping the time component somewhat balanced with a 50% filling period, and a 50% contractile period, an equation was developed using the standard normal distribution equation [10]:

$$E(t) = \frac{1}{\sqrt{2 \cdot \pi}} e^{\frac{-1}{2} x^2} . \tag{7}$$

The standard normal distribution has a maximum value at x = 0, and then decays to zero as x $\rightarrow$ infinity in both positive and negative directions. The standard normal distribution doesn't look like a contraction waveform, however, because it is distributed over the positive and negative values of x, or time in the simulation. The time values used to solve the differential equations vary between 0 and 1. Thus time would end up always positive. To make the time value represent both sides of the normal distribution, time was shifted 0.5 seconds positive, and then multiplied by 2 to produce a new normal distribution with a maximum at t=0.5 and decaying to zero at positive and negative infinity.

To make the waveform fit in the t=0 to t=1 seconds window, the width of the normal distribution was compressed by using 7t instead of t in the exponent of e. This produced a distribution that reached a maximum value at t = 0.5, and had a duration of contraction from approximately 0.25 seconds to 0.75 seconds and zero otherwise. To match the normal distribution amplitude values to the elastance values needed for the

model, a scaling factor of 10 was multiplied to the equation, along with an added offset of 0.1.

The final form of the elastance waveform using the modified normal distribution waveform is:

$$E = \frac{10}{\sqrt{2\pi}} \cdot e^{\frac{-1}{2} \cdot 49tt^2} + 0.1, \tag{8}$$

where tt = 2(t-0.5).

This produced an elastance waveform with a minimum of 0.1 mmHg/CC and reaching a peak of 4 mmHg/CC when t = 0.5, which looked very similar to a typical contraction waveform, as shown in Figure 4 below.

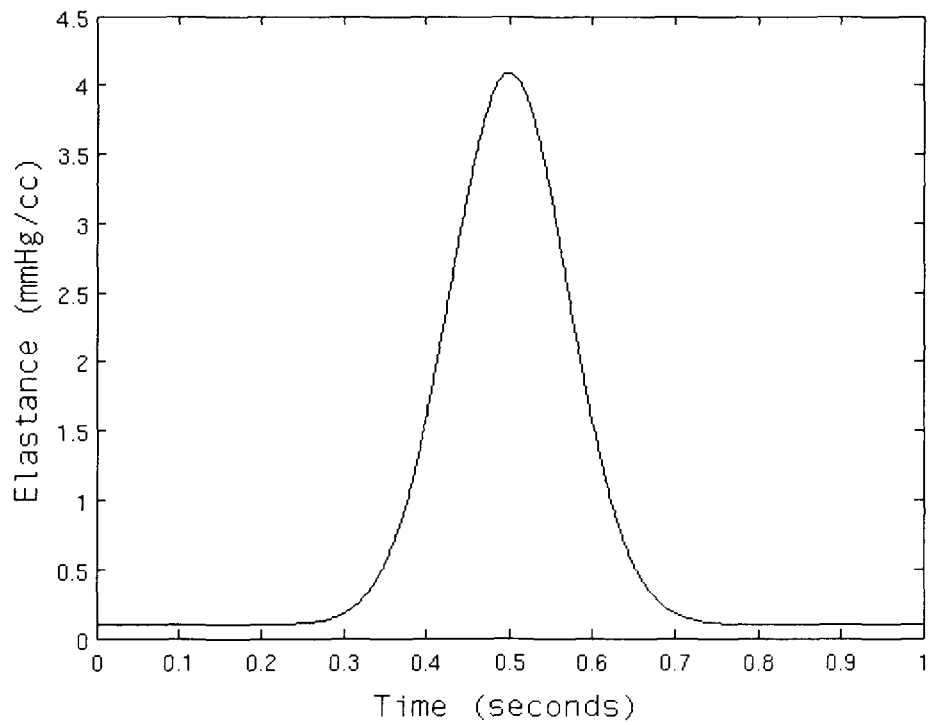


*Figure 4. Elastance Waveform Generated using a Modified Normal Distribution Equation.*

The benefit of using this equation is that since the derivative of E(t) is also needed, this equation is continuously defined in time and also differentiable. Other attempts at creating an elastance waveform produced very good cardiac waveform outputs for E(t), but were conditionally defined piece-wise functions, and thus the derivatives were very difficult to work with at the non-differentiable points. The derivative of the modified normal distribution equation for E(t) is:

$$\frac{dE}{dt} = \frac{10}{\sqrt{2\pi}} * \frac{-1}{2} 2 \cdot 49tte^{\frac{-1}{2}49tt^2} = \frac{-10}{\sqrt{2\pi}} \cdot 49tte^{\frac{-1}{2}49tt^2} \cdot 2, \qquad (9)$$

where the multiplier of 2 at the end is from the chain rule when defining tt = 2(t-.5).

The derivative of E(t) must be with respect to time, and that requires the derivative of tt with respect to time from the chain rule, for which the derivative turns out to be the multiplier 2.

Now, given any point in time needed for the differential equation solution, the values of E(t) and dE(t) can be calculated algebraically to put into the differential equation and solve for Pe, without any problems due to having piecewise functions or other constraints. This produced a better behavior over the entire simulation.

The current, Is, is also a known input value, which is the derivative of the volume injected into the system at the given frequency. Using a simple sine wave as the volume change for any particular amplitude and frequency, the actual volume change and the derivative can be calculated algebraically, eliminating any possible non-differentiable situations.

For the cardiac model series circuit in Figure 3, the current into the system, Is,

cannot go anywhere but through the three components – L, R, and C. Using Is as the current from the injected volume signal and Pe as the voltage across the effective compliance, the solution for LVP becomes:

$$LVP - Pe = L\frac{dIs}{dt} + k \cdot LVP \cdot Is \rightarrow LVP = \frac{L\frac{dIs}{dt} + Pe}{1 - k \cdot Is} \quad (10)$$

Once the differential equation for Pe (Equation 6) is solved, the LVP equation can then algebraically calculate LVP at any time using the known values of Pe, Is(t), dIs(t)/dt and the constants L and k.

## MODEL VERIFICATION

Before calculating any values for an injected volume signal, the model performance was verified to ensure the model calculations are valid and produce a proper simulation of a contracting isovolumic heartbeat.

The first verification method was to determine the isovolumic response of the model and compare that to a typical isovolumic pressure for a canine heart. Using the data from Enderle and Suga [11,12], the isovolumic pressures of a canine heart, with 50 ml of effective volume are 200 mmHg. The model isovolumic pressures reproduce these values as shown in Figure 5.

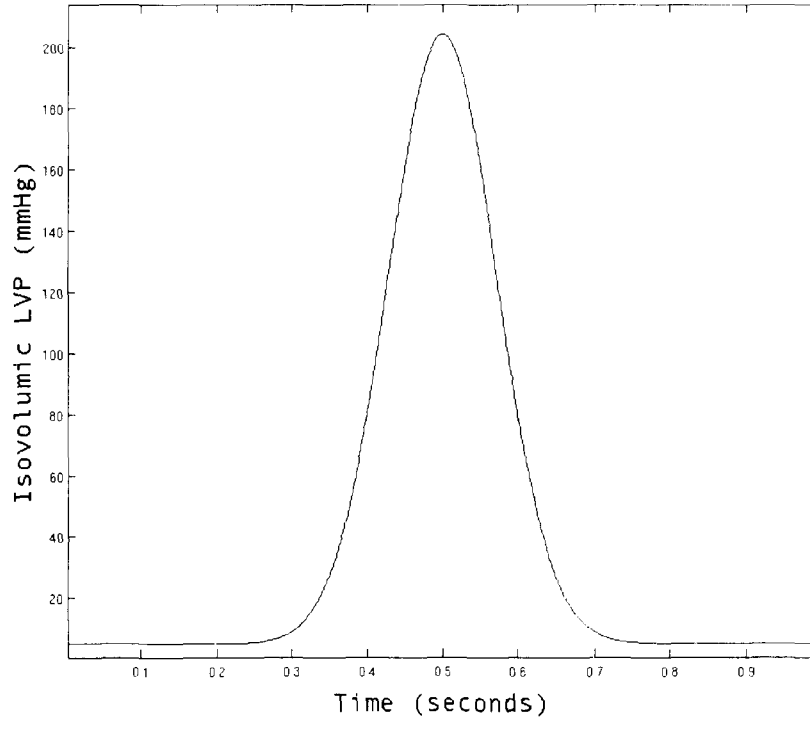


*Figure 5. Left Ventricular Pressure (LVP) Calculated during Isovolumic Contraction in Canine Heart Model.*

After verifying the isovolumic pressures for a contraction using figure 5, another step to verify the model was to compare the response to abrupt volume changes. Hunter produced LVP waveform distortions as a small volume was withdrawn from the left ventricle during contraction [13], and compared the results to a true isovolumic contraction.

The volumes Hunter extracted were 2 ml from an effective volume of 31 ml, at flow rates of 100 ml/s, and timed for early, middle and late periods of extraction during the contraction. Early volume extraction occurred at the beginning of the contraction phase, almost immediately after contraction begins, middle period extraction occurred around the inflection point of the rising pressures of systole very close to the middle of the contraction phase, and late period extraction occurred very close to the peak pressure point of LVP for the contraction, which occurs when the cardiac muscle is almost at the fully contracted state.

Using the same middle and late time sequencing as Hunter, the generated LVP waveforms of the model exhibited the same behavioral shapes as Hunter measured during the volume extraction. The volume extractions Hunter performed created a sudden halt to pressure increases, or potentially even a slight dip in measured left ventricular pressure during the extraction, and also produced the extended behaviors of a shorter overall time course and a lower pressure at each corresponding time after the extraction, returning to the true isovolumic pressure values almost asymptotically at the end of the cardiac muscle relaxation period and the beginning of what would be filling for a normal cardiac cycle.

The volume extraction performed on the model also reduces the generated left ventricular pressure compared to the true isovolumic waveform at each point in time after

the extraction, and also causes a slight deviation in the time of each corresponding pressure. These results are shown in Figure 6 and Figure 7.

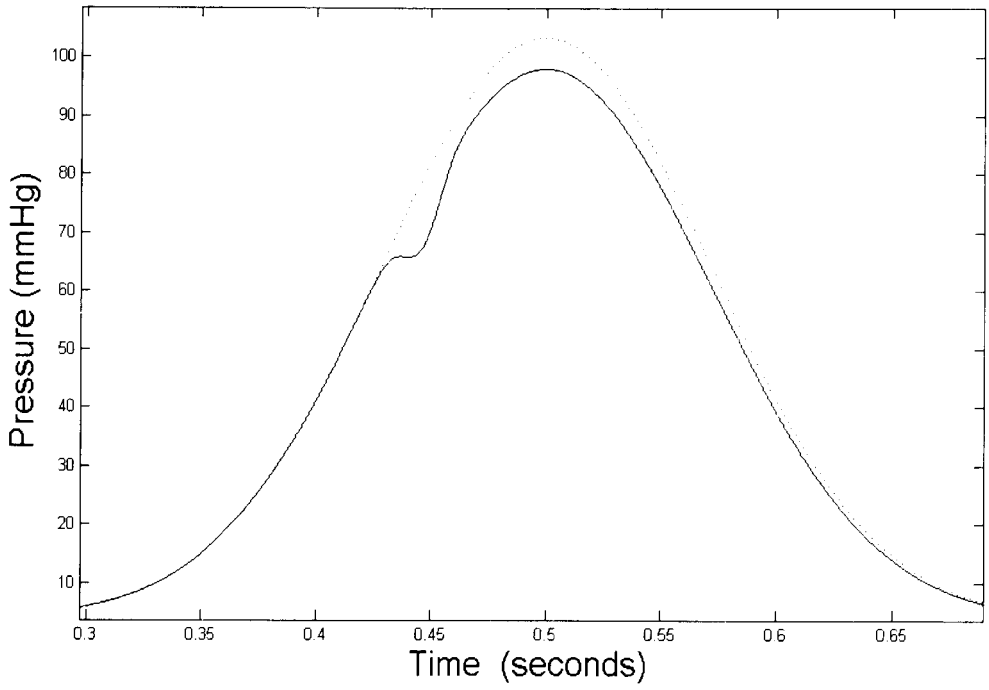


*Figure 6. Left Ventricular Pressure Response for Middle Period Volume Extraction.*

*The LVP response to extracting 2ml of volume from the ventricle during the contraction phase of the cardiac cycle compared to the true isovolumic beat.*

The model parameters of k and L, as well as E(t) were adjusted to produce the same value range as Hunter, to allow a more direct comparison to Hunter's results [13]. Hunter controlled the experiment by inflating a compliant balloon into the left ventricle of the canine heart and using a piston to extract the volume at the proper time and flow rate. The electrical circuit model used in the simulation also adjusted the values to look for behavior characteristics that matched the experimental characteristics from Hunter's work.

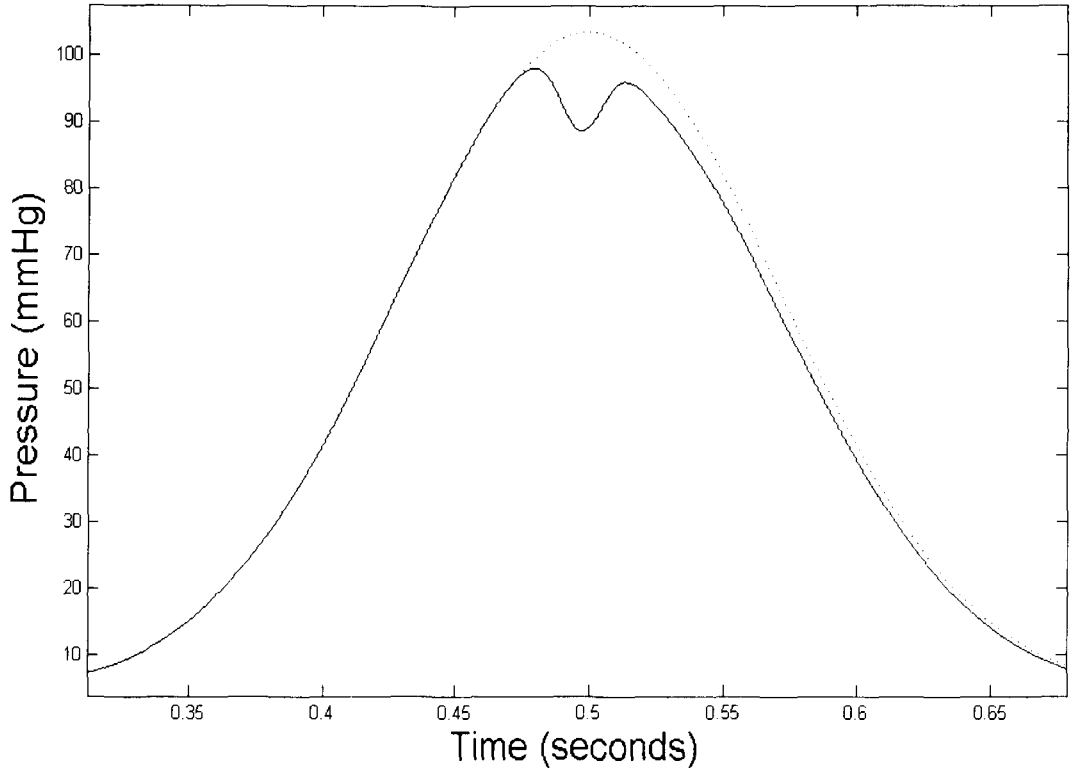


*Figure 7. Left Ventricular Pressure Response for Late Period Volume Extraction.*

*The LVP response to extracting 2ml of volume from the ventricle during the peak contraction of the cardiac cycle compared to the true isovolumic beat.*

## SIMULATION

Using the differential equation solver in Matlab, the solution to Pe is found, and with the known values of volume and flow from the equations, the derivative of Is(t) can also be calculated, either with the continuous equation, or with a numeric five point derivative method for known waveforms [14].

Using the model simulation to solve for LVP creates a waveform of the form shown in Figure 8 below for an injected volume of 0.1 ml at 20 Hz, with a k value of 0.001 and an inductance L = 0.0005.:

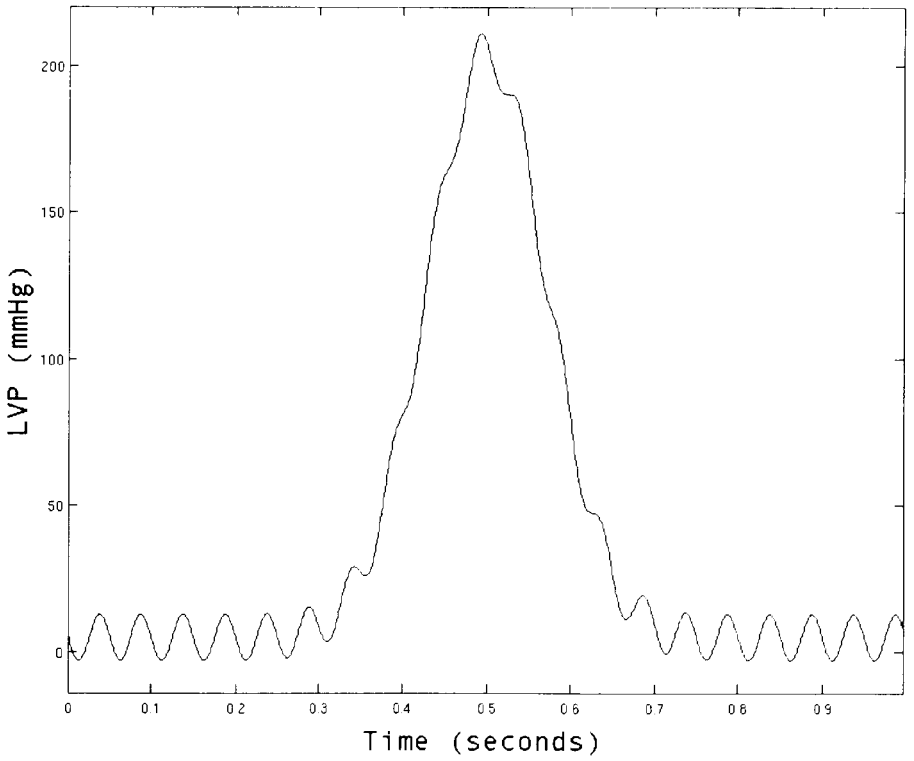


*Figure 8. Calculated LVP Waveform with 0.1 ml of Injected Volume at 20 Hz. Using an injected volume of 0.1 ml for k=0.001 and L=0.0005 for the electrical circuit cardiac model.*

Templeton studied isolated canine hearts to determine the cardiac parameters in 1970 and 1974. To conduct his studies, Templeton used a balloon to fill the hearts and control the internal pressures of the heart to between 20 and 120 mmHg. Templeton then injected volume signals with an amplitude of 0.5 ml at a frequency of 22 Hz into the partially pressurized isolated hearts and measured the pressure responses generated from the volume changes.

Using the simulation model to generate a pressure response at the same frequency as Templeton, for pressures and volumes typical for the model cardiac parameters, rather than Templeton's lower pressures and volumes, produces a waveform very similar to Templeton's, but with higher total pressures, as shown in Figure 9 below.

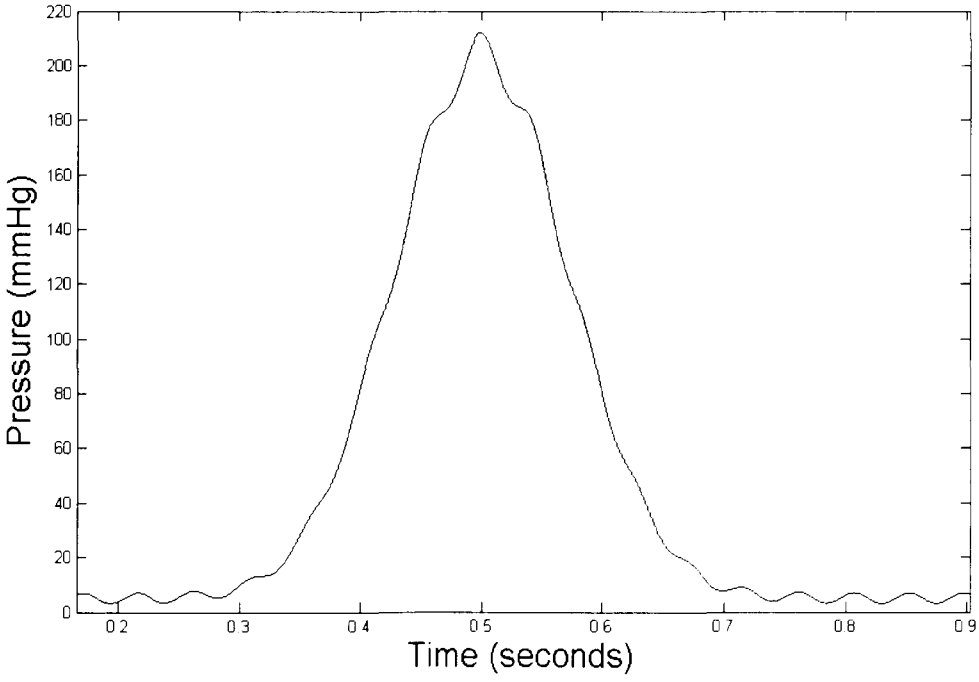


*Figure 9. Calculated LVP Waveform at 22Hz Matching the Characteristics of Templeton's Work.*

The model simulation produces results similar in shape to Templeton, in that the peak pressure change at the peak contraction LVP is larger than the filling pressure variations during diastole. The generated pressure waveform using the model simulation parameters, only differs from Templeton's work in the magnitude of these pressure changes being larger and the measured pressure values also being larger.

The generated waveform compared very well to Templeton's experimental data [4,5].

## PARAMETER EXTRACTION

Once the differential equation solution for Pe has been found, and LVP has been calculated based on the given values of Pe, Is, k and L, the new model resulting waveforms can be used to extract the values of k and L and C(t) that produced the LVP waveform.

Using electrical circuit analysis techniques, it can be seen that inductance becomes the dominant reactive component at high frequencies. In the heart model created for the simulation, the filling capacitance is 10 cc/mmHg, and the inductance of a typical system is around 0.0005 mmHg*sec^2/cc. The resonant frequency equation for an LC circuit is:

$$f = \frac{1}{2\pi \cdot \sqrt{LC}}. \tag{11}$$

Using C = 10 cc/mmHg, and L = 0.0005 mmHg*sec^2/cc, the resonant frequency is 2.25 Hz, and at frequencies significantly above this frequency, the circuit response becomes heavily inductive.

This can further be shown by building a series RLC circuit with typical electrically equivalent hemodynamic values, such as in Figure 10, and plotting the impedance vs the applied frequency of the circuit, shown in Figure 11. The reactive impedance increases linearly after a certain frequency, when the contribution to the impedance by the capacitance becomes negligible as the frequency increases, resulting in the inductive reactance as the imaginary component.

Making the assumption that the total reactive impedance comes from the inductive element, and dividing the total reactive impedance by $2\pi$ produces the equivalent L value. It can be seen that the calculated L value based on the assumption of all inductive starts to approach the true value of L very early in the frequency range when typical hemodynamic

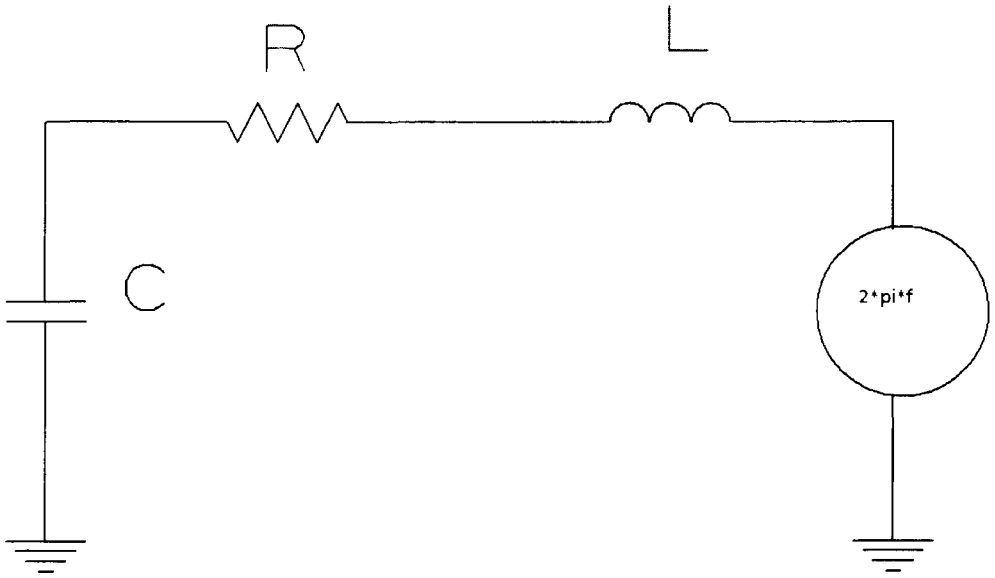


*Figure 10. Series RLC Circuit for Simple Analysis Techniques.*

values are used, and continues to asymptotically approach the true value of L as frequency continues to increase, as shown in Figure 12.

The biggest challenge to extracting the cardiac model parameters from the pressure and volume signals lies with having two reactive elements to calculate, and both of these reactive element values combine into the single unknown imaginary term. Solving for the resistive element of the total impedance can be done with a single frequency, since the resistance is the only real impedance element in the cardiac model. However, there are two reactive elements, and solving for both requires two distinct equations to solve simultaneously for the two variables. The two equations are produced by analyzing the pressure and volume waveforms for two different frequencies.

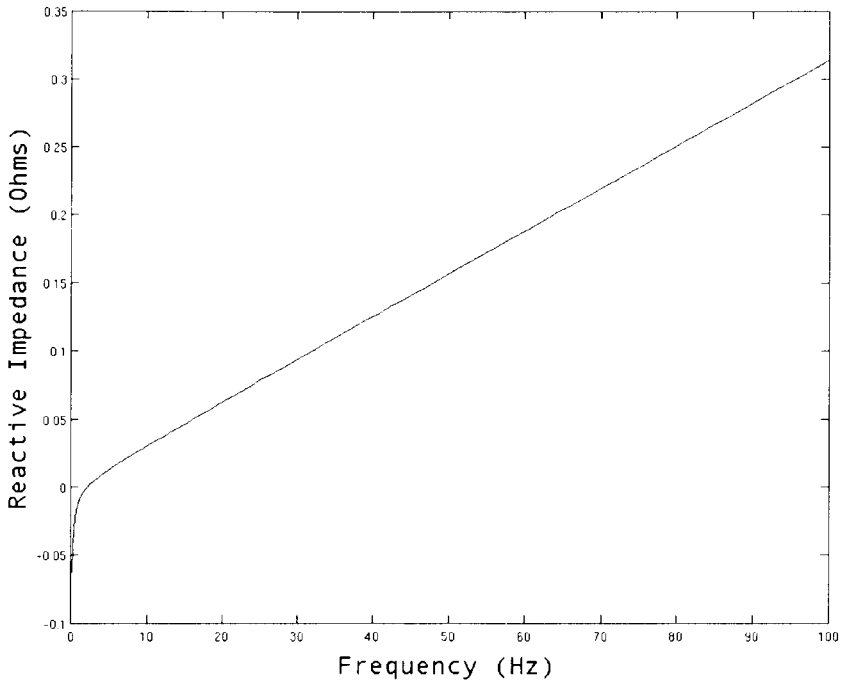


*Figure 11. Reactive Impedance vs Frequency for Typical Hemodynamic Model Electrical Component Values.*

Taking a single frequency measurements cannot solve for both L and C without making some assumptions. In a practical sense, having to take measurements at two or more different frequencies wouldn't be difficult to do, considering the hardest part would be the instrumentation setup and preparation for measurements anyway.

Taking measurements at two different frequencies produces at least two options for calculating the inductance value. Since inductance becomes asymptotic at higher frequencies, using a frequency on the high end, such as 100 Hz or higher, can be used to calculate L by assuming C is essentially negligible at these frequencies. Once L is found, then a lower frequency can be used to calculate the true C value based on the previously calculated L value.

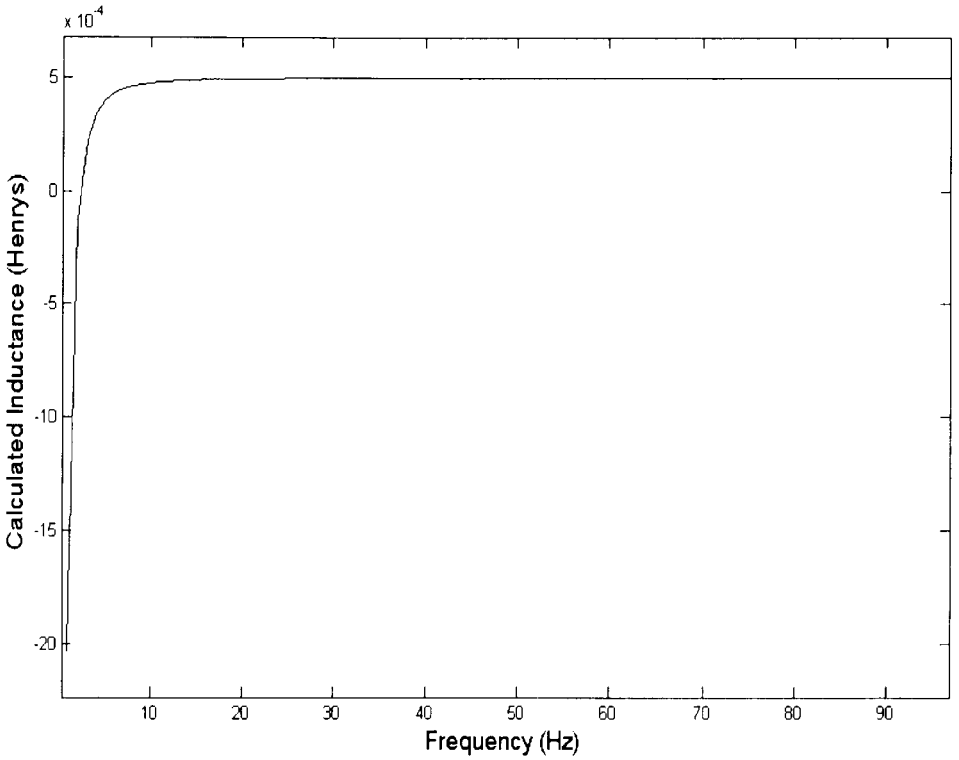


*Figure 12. Calculated Inductance vs Frequency for a Series RLC Circuit. Note that the calculated inductance value becomes asymptotic at a relatively low frequency.*

Another option useful for calculating the reactive component values of L and C would be use two different, but closer, frequencies and solve the system of two equations with two unknowns. The benefit of using closer frequencies in this method is that the physical equipment would not need to produce the higher frequencies, such as 100 Hz or higher, required when making the assumption that the imaginary impedance is all inductive. Using these two closer, but different, frequencies would only require solving two equations for two unknowns, a common mathematical practice.

To solve the problem of how to extract the individual cardiac model parameters L

and C(t) from the total imaginary impedance, a different set of equations was used for each of the solution methods. The first method, using a high frequency and assuming the imaginary impedance is all inductive, requires a different solution process than solving for two different frequencies simultaneously.

Both solutions start by using the frequency domain circuit analysis equations for electrical engineering. Knowing the frequency of the stimulus, and that there is no other input or output voltages or currents other than the stimulus, the values of real and imaginary impedance can be calculated.

Calculating the impedance is done by taking the fast Fourier transforms of the pressure and flow waveforms for that frequency. To do the FFT of the contraction cycle, each individual flow waveform is isolated in time and these waveforms are then individually stored for analysis, marking the start and stop times for each wave. The flow wave is used as the control because it is much more stable in amplitude than the pressure response, since it is the driving signal.

The stored times for the flow waveform are also used to separate the pressure response into single waves and these waves are also individually stored. Creating the pressure and flow waves using the same time values allows computing the phase response as well as the amplitude response for each wave.

The total impedance for the circuit model at any point in time can be found by taking the FFT of the pressure waveform divided by the FFT of the flow waveform at each time. In an electrical circuit the impedance would be the FFT of the voltage divided by the FFT of the current. In the cardiovascular model, the pressure is analogous to the voltage

and the flow is analogous to the current, so the total impedance is the FFT of the pressure divided by the FFT of the flow.

The assumption underlying an FFT is that the waveforms analyzed are periodic and repeatable to positive and negative infinity. In a practical sense, if the starting and stopping amplitude values of the waveforms are equal or very close, then the wave appears periodic. The periodic assumption holds true during the filling state of the cardiac cycle, since during filling the injected volume creates a steady sinusoidal flow into and out of the system, producing a steady and approximately sinusoidal pressure response which acts stable and periodic.

During the contraction phase, however, the injected volume still produces a steady sinusoidal flow waveform, but the changes in the time varying elastance create problematic pressure amplitudes when using the FFT. The changing elastance causes the measured pressure amplitude at the start of the injected flow waveform to be lower than at the end. This causes the measured pressure amplitudes to be offset lower to higher during contraction and higher to lower during relaxation.

This means the individual pressure response waveforms during the contraction and relaxation periods do not start and end at the same pressures for a single period, which fails to meet the conditions necessary for doing the FFT analysis. The starting and stopping pressure amplitudes for individual injection periods are not equal during most of the contraction phase of the cardiac cycle, and therefore fail to meet the assumptions required to do an FFT analysis.

There are two ways to manipulate the waveforms to meet the periodic waveform

assumption for using an FFT. The first is to use a filter to pass the higher frequency pressure waveform components, created by the injected volume signal, and block the lower frequency contraction waveform signal. The frequency of the contraction cycle, or heart rate, is usually significantly lower than the injected volume frequency, so using a high pass filter to remove the lower contraction waveform is possible. The disadvantage to this approach is that the filter has the potential to reduce the amplitude of the filtered signal and produce possible phase shifts between the pressure and flow signals.

The second way to generate pressure waveforms which appear repeatable, or sinusoidal, for the FFT assumption, is to create an LVP waveform without any injected volume signals riding on top of it and subtract this from the pressure waves with injected volume signals. The LVP waveform without the injected flow signal essentially creates a pure isovolumic beat from the cardiac model. The pure isovolumic beat is then subtracted from any other LVP waveform with the injected volume signal riding on top, and the resultant waveform is only the contribution to the pressure waveform from the injected volume signal, with very stable and repeatable starting and stopping values to make it look periodic.

For the analysis of this cardiac model, the best approach turned out to be the subtracted isovolumic LVP signal, which eliminated the need to create different filters and also reduce the errors due to filtering. The goal of the simulation is to determine how accurately the model can calculate the elements, and which techniques and procedures are required to to produce an accurate calculation, and the subtracted signal increased the analysis accuracy.

Once the non-perturbed LVP wave was subtracted from the LVP wave with the injected volume signal, the FFT assumptions were met for both pressure and flow waveforms. Since all of the waves were now repeatable, the point at which the waves started and stopped were not important as long as one period was captured for each waveform. This allowed using simpler techniques to find the consistent points to start from for each period.

The best signals to use are either the volume signal or the flow signal, which is just the derivative of the volume signal, because these signals are independent of all the others. These waveforms are always centered around zero and have a sinusoidal form. The flow signal was used because of the higher amplitude, which produced a greater consistency in selecting the maximums.

The peaks of the flow signal were used to select the start and stop points for each wave. The Matlab function 'extrema' was used, after running the flow signal through a low pass filter as part of the 'filtfilt' command to make sure the signal was clear of any odd spikes at the peak that might show up as a maximum. The 'filtfilt' command creates zero phase shift when filtering, making the time values for the maximums the same as before filtering, which is vital to getting the proper impedance calculations. The low pass filter was used to remove multiple relative maximums due to calculation or other errors.

Once every maximum for the flow signal was identified, a new matrix was created with each of the individual pressure wave signals occurring between these maximums, and each of the individual ( and un-filtered) flow waveforms between each maximum. Additionally, a separate LVP signal, with the true contraction pressures still intact, was

used to calculate the mean LVP for each individual pressure waveform, which is required to extract k from the total resistance value. A sample LVP and flow waveform can be seen in Figure 13.

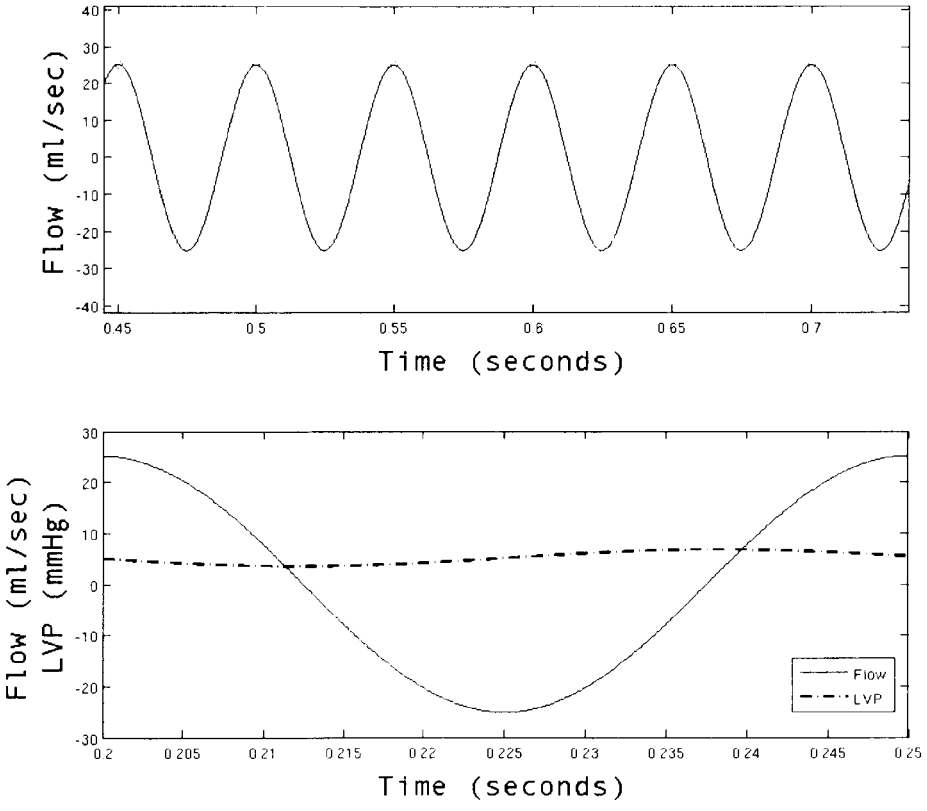


*Figure 13. Locations of Beginning and Ending Times for Injected Flow Waveforms. The top graph shows the locations of the maximum flow times. The bottom plot shows one period of flow and LVP which will be used for an FFT analysis.*

Taking the FFT of the pressure signal divided by the FFT of the flow signal produced an individual equivalent impedance for the two signals for those particular waveforms. This equivalent impedance consists of both a real and imaginary component of the total impedance. The real component is the resistance element of the cardiac model.

and is equal to k* LVP. The imaginary component of the impedance is the reactive impedance and is a combination of the inductance and the time varying elastance of the cardiac model.

In order to separate the inductance element from the time varying or effective elastance, at least two frequencies were required, as stated previously.

In the frequency domain, the imaginary impedance of an inductor is:

$$X_L = 2\pi fL. \tag{12}$$

The imaginary impedance of a capacitor is:

$$X_C = \frac{-1}{2\pi fC}. \tag{13}$$

As can be seen from the equations, when frequency is low, the inductive impedance is also low, but the imaginary impedance for the capacitor becomes very large. At high frequencies, the opposite conditions occur, the imaginary impedance of the inductor becomes large and the capacitive impedance becomes small.

Thus, with a single measurement frequency, it is impossible to extract both the inductance term and the capacitance term without making an assumption for one or the other. It is, however, possible to determine whether the overall imaginary impedance of the system is inductive or capacitive, based on the sign of the total reactive impedance. If the reactive impedance is positive, then the system at that frequency has a large inductive behavior and the flow (current) will lag the pressure (voltage) in time.

If the imaginary impedance has an overall negative value, then the system has a larger capacitive behavior, and the flow (current) will lead the pressure (voltage) in time.

These general characteristics are helpful when looking at the overall system

response, but do not provide for separating the two imaginary impedances with that single frequency.

However, since the only real impedance term at any frequency is the resistive component, a single frequency is all that is required to calculate the resistance, R. Since R is a non-linear element, which depends on the pressure, finding the mean value of pressure for each waveform can then produce the value for k. The k value is each total resistance divided by the mean LVP value during that wave.

Any frequency can be used to determine the k constant, but the lower the frequency, the larger the time period for each analyzed wave, and the larger the discrepancy may be in the mean value of LVP, since LVP is rising as the heart is contracting. A higher frequency produces more waves during the contractile portion of the cardiac cycle and enhances the resolution of the mean LVP for each wave period. This allows for better calculations of k, though for most frequencies, the duration of a single waveform is not long enough o reduce the overall accuracy of the calculation.

To determine the individual inductance and capacitance values, the single inductance process was to start with the inductance at a high frequency. Since the imaginary impedance for an inductor grows very large at high frequencies, the process was to pick a high frequency and then assume the entire imaginary impedance became only due to the inductor. Though not completely accurate, this has been shown previously to be a valid solution to the problem, as long as the high frequency is practical to generate.

A similar approach could have been used at a low frequency to calculate the capacitor impedance, since the inductor reactive impedance is very low at low frequencies.

However, this creates the problem of very few data points to work with, since the low frequencies produce very few waveforms to analyze, which also tends toward less resolution in the results.

A frequency around 100 Hz was chosen in the simulation because of the upper limit of practical implications of creating such a high frequency in a physical situation, and also because the inductive impedance proved to be dominant at this frequency. Higher frequencies would likely be impractical to create in a clinical setting, and therefore not useful to simulate.

Calculating the inductance value at this point consisted of finding the imaginary component of the FFT calculation, and dividing through by $2^* \pi$ times the frequency. This produced a value for L.

It should be noted that at even high frequencies the imaginary impedance varied during the contractile portion, producing times when C and L cannot be solved for. The way to minimize the potential inaccuracies is to identify the contractile portions of the waveform, and not perform any calculations during this time. During the filling portion, the values of L and C remain constant and the calculations can be done.

The waveform in Figure 14 below shows the first 14 terms of the FFT of an LVP signal with the injected volume of 60 Hz. Notice that the highest amplitude component is at the base frequency of 60 Hz, but that the higher harmonics, up to the $10^{th}$ harmonic, are still slightly above zero.

To solve for the real and imaginary values of the impedance of the cardiac model, and start the process of calculating L and C, the FFT of the pressure signal is divided by the

FFT of the flow signal, which produces a complex number solution. From the complex number solution, the magnitude and phase of each harmonic are then calculated.

At this point, a magnitude vector for all of the harmonic frequencies, as well as the phase vector of all the harmonic frequencies, has been created. To calculate the individual real and imaginary impedances from the model only the fundamental frequency values need to be used. When the amplitudes of the harmonic frequencies start to get very close to zero, the error effects due to dividing by small numbers becomes very large, and produces wildly varying values.

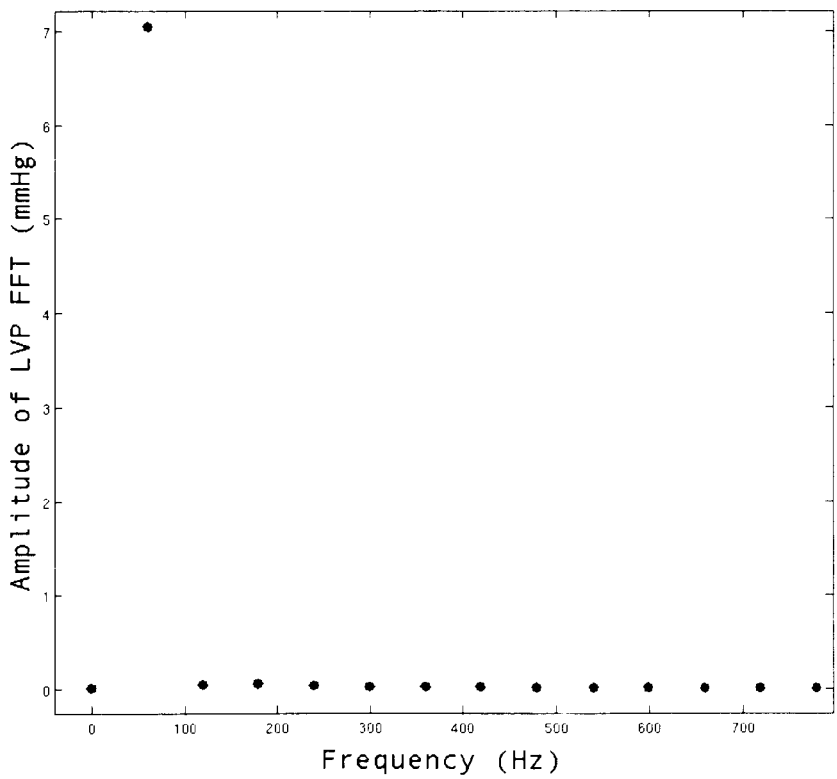


*Figure 14. First 14 FFT Terms of an Analyzed LVP wave at 60 Hz.*

To calculate the real and imaginary impedances for any harmonic, the real

impedance, $Z_R$, is calculated by:

$$Z_R = |Z| \cdot \cos(\varphi), \tag{13}$$

and the imaginary impedance, $Z_I$, is calculated by:

$$Z_I = |Z| \cdot \sin(\varphi), \tag{14}$$

where Z is the amplitude of the FFT of that harmonic and Φ is the phase angle of that harmonic.

When solving using the single high frequency method, based on the high frequency and the assumption that the imaginary impedance is purely inductive at this point, the value for L can be found by dividing the imaginary impedance by 2* π times the frequency.

Figure 15 below shows the resulting inductance calculation for several cardiac cycles. Notice that the time varying capacitance shows up even at the high frequency.

Since the high frequency pressure and flow waveform was used to calculate the inductance component, with the assumption that the imaginary impedance was only inductive, this frequency cannot be used again to calculate the imaginary capacitive impedance. To get the capacitance impedance, it is necessary to use a second frequency.

The total imaginary impedance of the second frequency is not just capacitive, however, and before calculating the capacitive component value, the calculated inductive impedance must be subtracted.

Using the second frequency total imaginary impedance and the high frequency calculated value of L produces the imaginary capacitive impedance:

$$C(t) = \frac{-1}{2\pi f\left(Z_I - 2\pi f L\right)}. \tag{15}$$

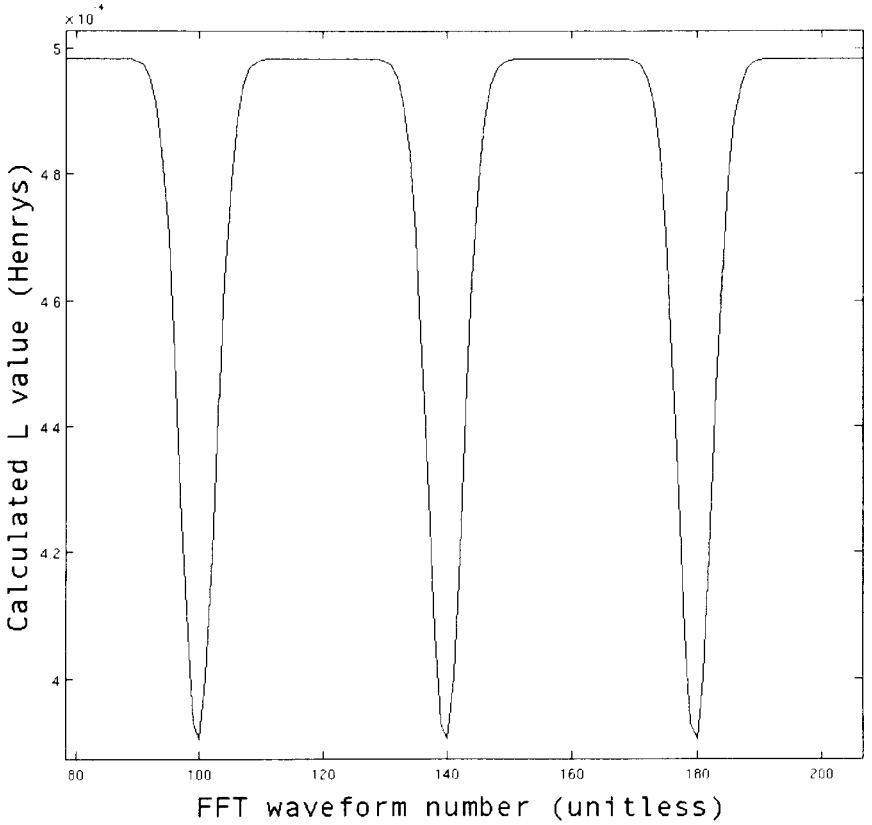


*Figure 15. Calculated Inductance Value from FFT Analysis at 40 Hz Injected Waveform.*

*Each plotted point is the resulting value calculated by a single period of the LVP and flow waveforms. Notice the contraction is evident in the calculated results as the apparent L value drops due to C(t) changing. The L value assigned was 0.0005 mmHg*sec^2/cc.*

This calculates the total time varying capacitance waveform, which can be then used to determine the accuracy of the model. The maximum values show the compliance during the filling portion of the cardiac cycle, and the minimum values are produced during the contractile portion, at peak elastance.

One potential problem with this approach, is that the calculated value of inductance

appears in the denominator of Equation 15, and any error in L becomes compounded in the division, especially since L is a very small value. Even errors of less than 1% produce significant errors in the calculated waveforms of C(t).

Figure 15 shows that the calculated inductance is approximately 0.000495 mmHg*sec^2/cc, which is an error of 1% at 40 Hz. Figure 14 also shows that 40 Hz is well into the asymptotic approach to the true value of L, but even the error of 1% would produce a large error of over 10% in the calculated values of C(t).

Plotting the calculated values of C(t) over several cardiac cycles at 40 Hz with the correct value of L produces the waveform:

When the known value of L is used, the imaginary impedances at each stage are always negative and never zero. When the values of C(t) are calculated, the reciprocal and the negative of the impedances create a positive waveform that varies from approximately 10 cc/mmHg to 0.25 cc/mmHg, corresponding to the elastances of 0.1 mmHg/cc to 4 mmHg/cc respectively.

When the calculated value of L is used in the same equation to solve for C(t), the errors in L create both positive and negative values and several zero crossings. This creates problems when taking the reciprocal of the impedances to calculate C(t) , due to dividing by numbers very close to zero, which produces erroneous peaks, as shown in Figure 16 below.

The error can be minimized by using much higher frequencies, but the practical limits of creating volume oscillations at these high frequencies soon become difficult to overcome. If implemented in practice, generating high frequency volume changes requires

a very high speed mechanical device, which may produce large forces on the mechanical elements, and increase the risk of a failure. When using high speed mechanical devices internally, the risk of failure may become unacceptable. The risk and benefit of the high frequencies in practice must be weighed against each other.

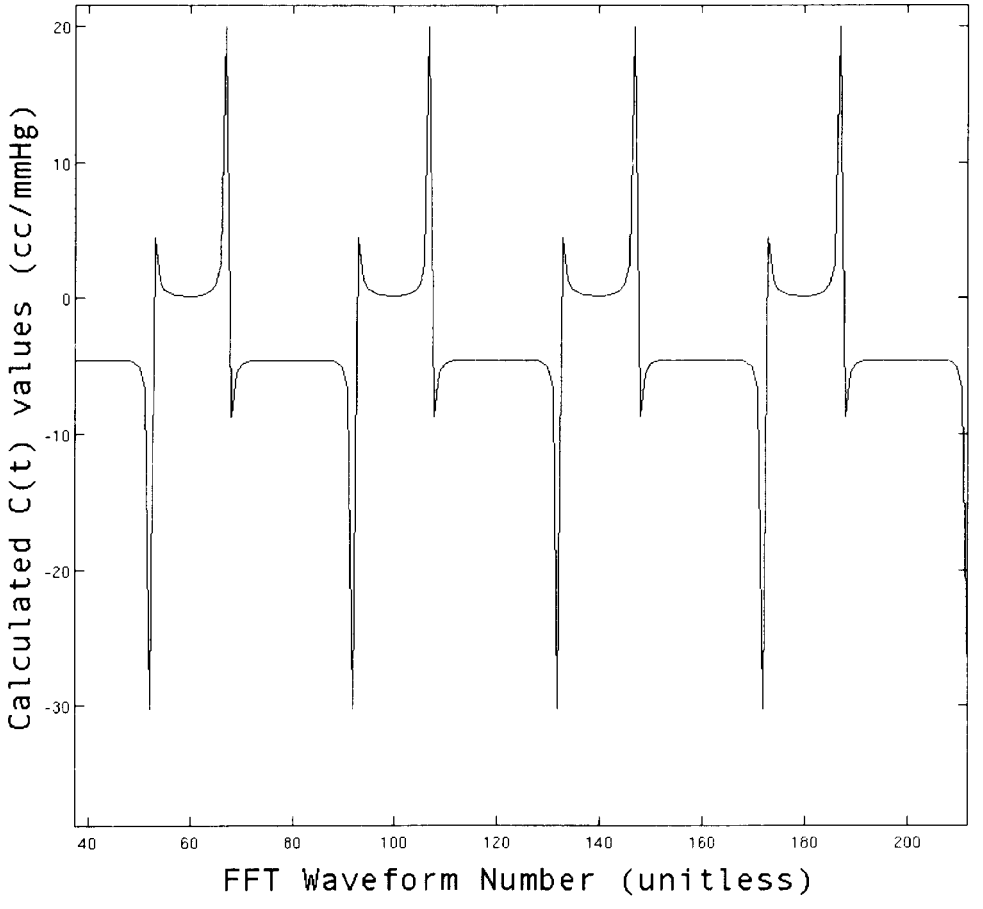


*Figure 16. Calculated C(t) Values when using the Calculated Maximum L Value. Due to the use of L in the denominator, the error in L produces large errors in the calculated value of C(t) as L approaches and passes through zero.*

The second approach to solving for the imaginary impedance element parameter values is to solve two equations with two unknowns. This approach removes the need to

make an assumption about one value, such as L, and removes the errors that might be carried with those assumptions, as well as needing a high frequency to find L.

The two equations used are:

$$Z_I 1 = 2\pi f_1 L - \frac{1}{2\pi f_1 C} \tag{16}$$

$$Z_I 2 = 2\pi f_2 L - \frac{1}{2\pi f_2 C} \tag{17}$$

Solving the first equation for L and substituting into the second equation allows solving for C;

$$C(t) = \frac{\frac{f_2}{f_1} - \frac{f_1}{f_2}}{2\pi f_1 Z_I 2 - 2\pi f_2 Z_I 1} \tag{18}$$

After solving for C, then the equation for L can be solved for:

$$L = \frac{Z_I 1 + \frac{1}{2\pi f_1 C}}{2\pi f_1} \tag{19}$$

Using these two equations together produces a mathematical solution for both L and C(t). The first issue arising when using this method result from having to pick particular values of the imaginary impedances at the two frequencies, when these impedances consist of values throughout the entire cardiac cycle. Picking values of impedance during the filling cycle allows calculating Cmax, or C1, with enough accuracy to then calculate L.

The second issue stems from the impedances appearing in the denominator in Equation 18, much like the calculated value of inductance previously. Any error in the calculations from using the values of the impedances will be compounded when subtracted

and then divided, producing the possibility of large errors in the calculated results. This problem can be minimized by using frequencies which are further apart, producing a larger value in the denominator. For example, using 20 Hz and 40 Hz as the injected volume frequencies will produce better calculated results than using 35 Hz and 40 Hz due to the denominators being larger values.

The accuracy of the calculations of the individual cardiac model elements is determined by running a large sample set of varying element values. The errors in each of the calculated values is then analyzed to determine how well the approach produced the true results, and which conditions were best for finding each element value.

## RESULTS

The model and methods above describe a possible way to calculate the cardiac lumped-parameter model values during an isovolumic beat by injecting small volume changes into the heart.

The results show that it is possible to calculate the lumped-parameter cardiac model values to within a small percentage error using relatively low frequencies and low injected volumes.

Analysis of the data shows that the model parameters start to emerge clearly at around 10 Hz, and are calculable up to 100 Hz at least. The model predicts that as frequency increases the generated pressure response will also increase, demonstrating the effects noticed by Campbell's work.

The model also shows that small volumes produce large pressure responses and allow calculating the lumped-parameter model values with volumes ranging from 0.1 to 0.5 ml, with 0.2 ml being usable at frequencies up to 60 Hz without the pressure response becoming unmanageably large. At frequencies above 60 Hz, to reduce the generated pressure response amplitude, a volume below 0.2 ml is desired.

From a practical standpoint, the frequency and volume values needed to produce measurable cardiac system responses are quite desirable. Frequencies up to 60 Hz, and volumes around 0.2 ml can be used clinically without having to develop special equipment.. Creating frequencies higher than 60 Hz can be very difficult in a clinical setting without specialized equipment, and producing large volume changes in situ has many problems. Finding a range of volumes and frequencies that produce calculable

values of the resistance, inductance and time varying elastance shows that the theory has validity.

With a working cardiac model for pressure response given an injected volume signal, the values of volume and frequency can be varied to find the optimal conditions needed in a clinical setting to allow for proper testing to calculate the hemodynamic parameters. This could dramatically improve the diagnostic capabilities for cardiac problems from both a time and causal standpoint.

Because the model mathematically constructed all of the waveform values using the given values for k and L, the solutions would seem to be very close to the exact values. However, because of the assumptions when working with the fast Fourier transforms and the sampled data points, there were some initial discrepancies. Overall though, when analyzing the data, the calculated results using just the measured flow and LVP values did show extremely accurate values, as shown in Figure 17 below.

To determine the effect of the different parameter values for k and L, a Monte Carlo approach was used. The values for k ranged from 0.0001 sec/cc, to 0.0021 sec/cc, and the values for L varied from 0.0003 mmHg*sec^2/cc to 0.0007 mmHg*sec^2/cc. A matrix was created where each value of k was tested with every value of L, ensuring a full analysis of possible parameter conditions.

The matrix of k and L values was used to calculate LVP for both a 10 Hz injected volume signal at 0.2 ml, and also a 50 Hz injected volume signal at 0.2 ml. The two equation, two unknowns process was used to calculate k and L from the resulting pressure and flow waveforms The real impedance as calculated from the FFT analysis produced the

value for k, and the imaginary impedance was solved for to get both L and a Cmax value, which is the compliance during the filling phase of the cardiac cycle.

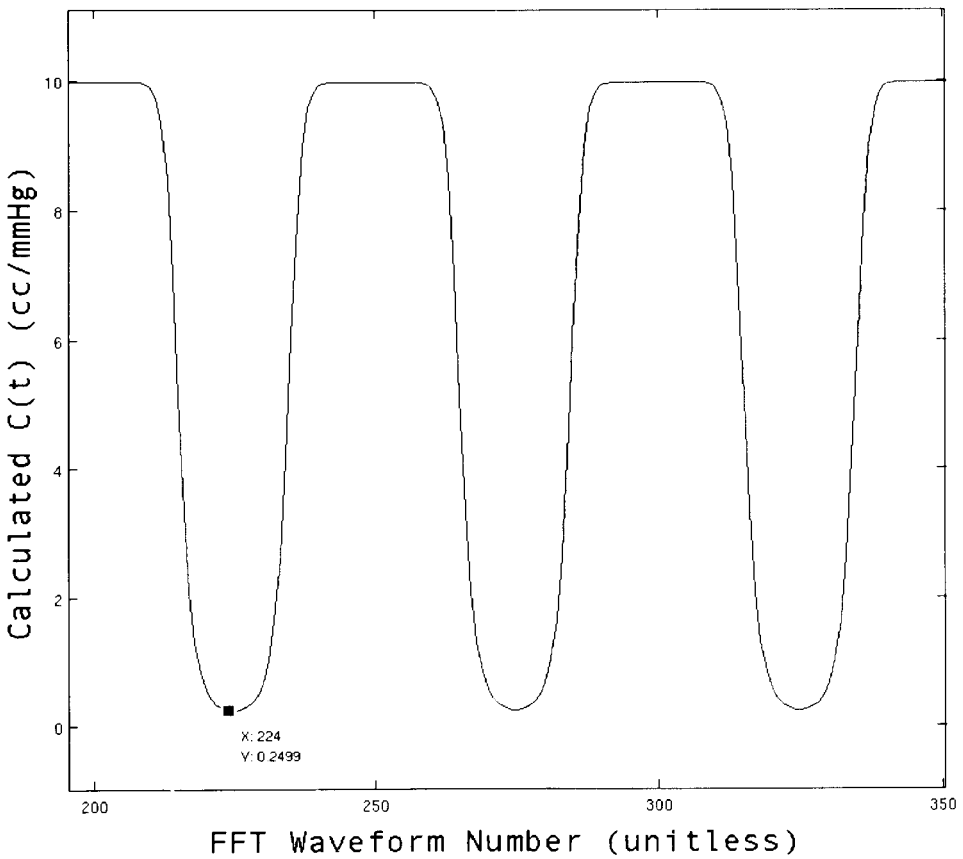


*Figure 17. Calculated C(t) Waveform using Two Equations to Solve for Two Unknowns.*

*C(t) values over several contractions as calculated using two equations and solving for the two unknowns, L and C. The two injected volume frequencies used were 10 Hz and 50 Hz. Actual C(t) values are 10 cc/mmHg during filling and 0.25 cc/mmHg during peak contraction.*

When calculating the k value, using the resistance divided by the mean LVP pressure for each period of the injected volume signal, the calculated k error for the different assigned values of k and L in the parameter matrix is shown in Figure 18 and Figure 19 below.

The absolute error in the calculated k value increases as the actual value of k increases, going from almost 0 when k = 0.0001 sec/cc, to 2e-6 when k = 0.0021 sec/cc.

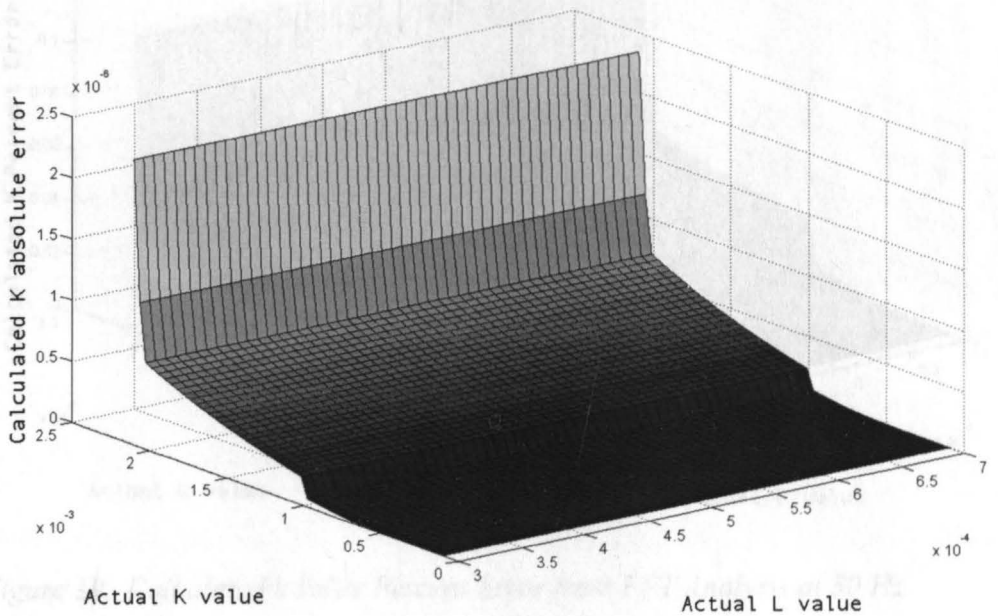


*Figure 18. Calculated k Value Absolute Error from FFT Analysis at 50 Hz.*

*The k value can be calculated with the FFT analysis at each frequency since the resistance is the only variable for the real component of the total calculated impedance. The graph shows the calculated value of k subtracted from the true value of k used in the model.*

The changing values of L seem to have a minimal effect on the calculated error in the k value, since the k value is calculated from the real impedance in the model, whereas L is changing the imaginary impedance.

The percent error of the calculated k value ranges from near 0 when the actual k = 0.0001 sec/cc, up to 0.1% error when the actual k = 0.0021 sec/cc. The percent error of 0.1% with a 2100% change in the value of k shows that the process for calculating the k

value is robust.

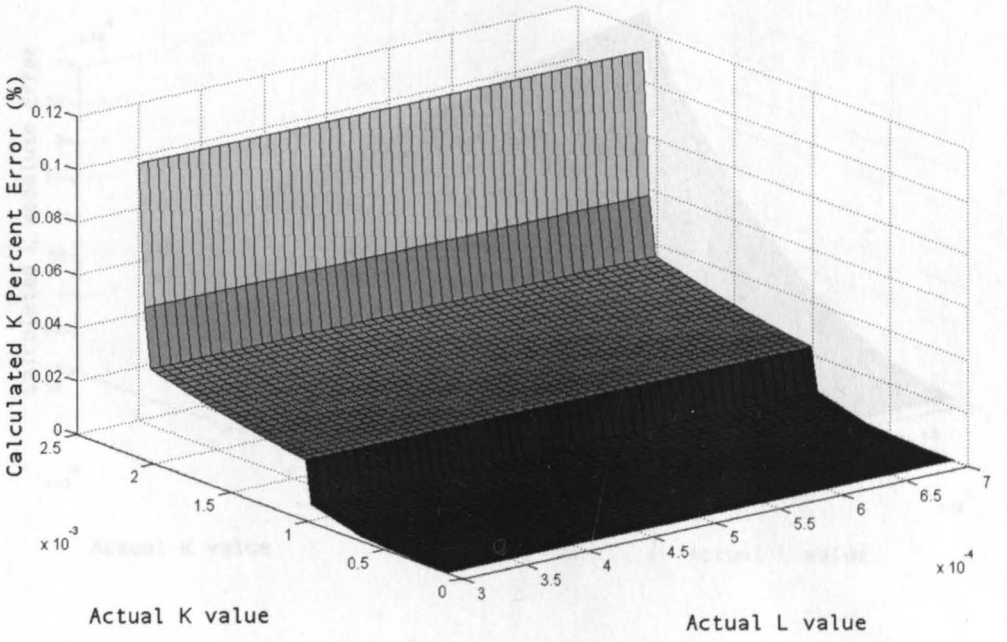


*Figure 19. Calculated k Value Percent Error from FFT Analysis at 50 Hz.*

*As the value of k increases, the amount of error starts to increase, but still remains very low. The percent error in k varies very little with changes in L values.*

The calculated error in L follows a similar process, using the two equation, two unknown method with the imaginary impedance to solve for both L and Cmax. The calculated L values for the assigned values of k and L of the parameter matrix is shown in Figure 20.

The absolute error in L increases as both k and L increase, going from an error near zero to a maximum error of approximately 4e-6 mmHg*sec^2/cc.

Figure 21 shows the percent error for each value of k and L in the parameter matrix as shown below.

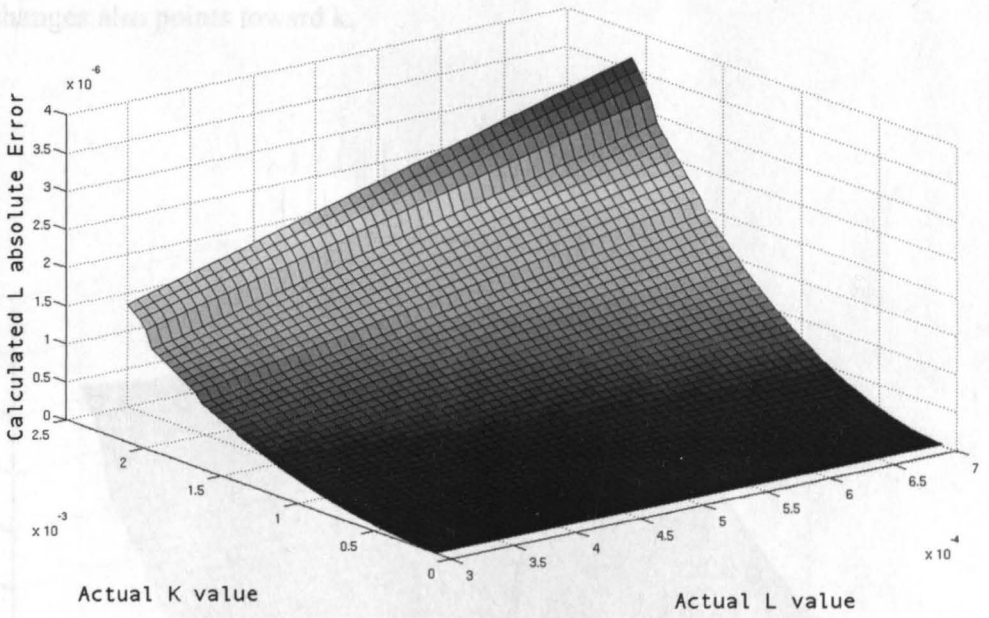


*Figure 20. Calculated Absolute Error in L Values for Different Assigned Values of k and L. The error in L is affected by both a change in k and also a change in L.*

The calculated percent error in L seems to depend more on the value of k than on the value of L, as shown in Figure 21, starting with a near zero percent error and reaching a value of approximately 0.5% error when k is 0.0021 sec/cc. The percent error does not seem to be affected by the changing L value, but rather on the value of k.

After the L value has been calculated, using both this L value and the imaginary impedance at a chosen frequency, the compliance during filling can be calculated. Figure 22 below shows the value of the total compliance during filling, which is only due to C1, over the parameter matrix values.

The plot shows that the major factor for inaccuracies in the calculated Cmax is k, and not the other imaginary impedance, L. It seems counter-intuitive at first, but after

looking at the plot of calculated error and calculated percent error in L, the major factor for those changes also points toward k.

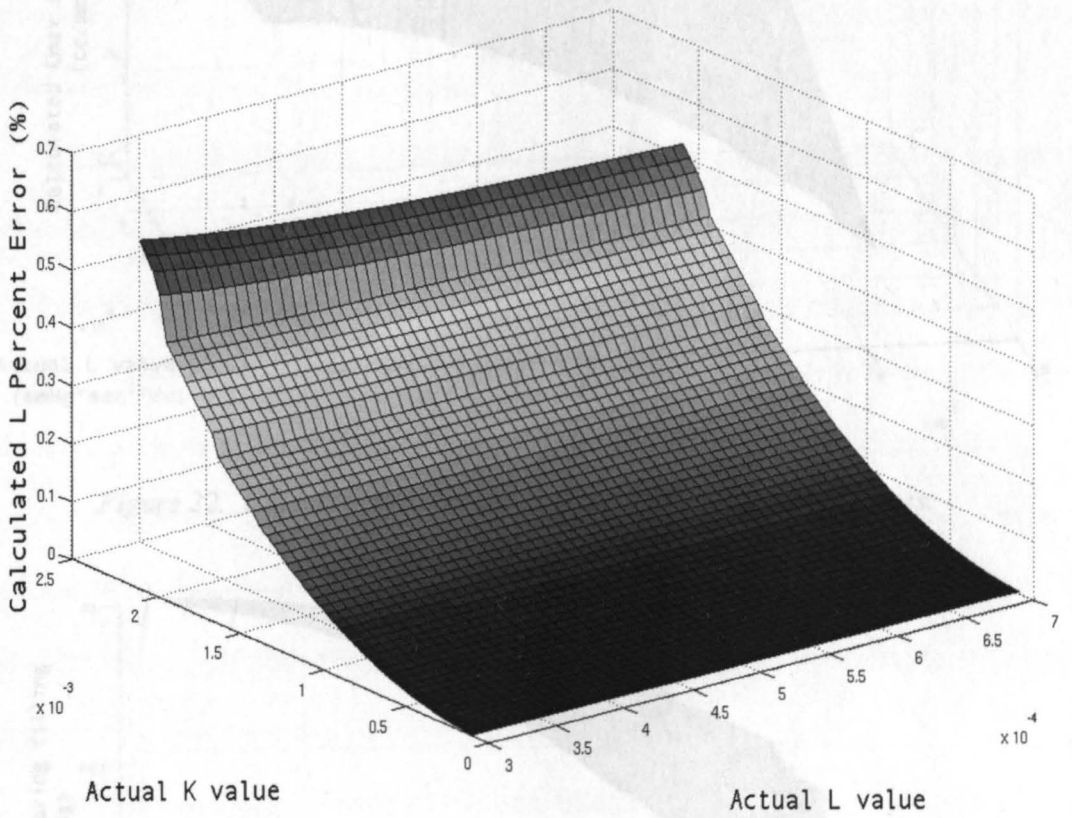


*Figure 21. Calculated Percent Error in L for Different Assigned Values of k and L.*

*Over the assigned parameter matrix of k and L values, the percent error in L looks to remain constant as L changes, and depends on the value for k*

Rotating the surface plot of Cmax to plot Cmax vs k, as shown in Figure 23, shows that while changes in L do play a role in accounting for a small part of the error, the majority of the error is related to the changes in k. As k increases, the percent error shown in Figure 21 increases and the calculated Cmax in Figure 22 and Figure 23 decreases.

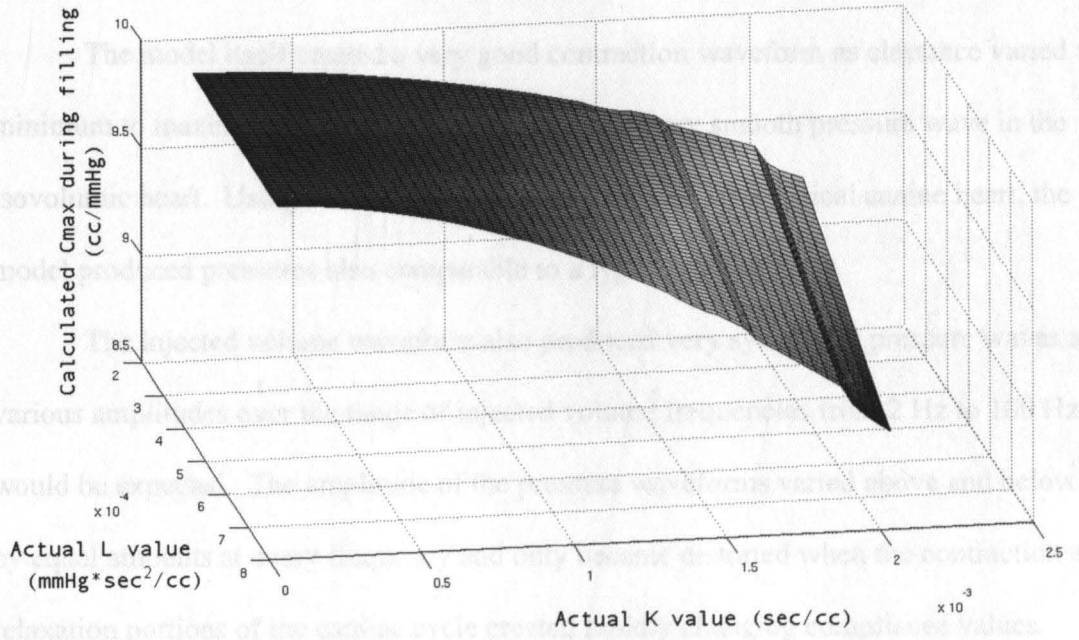


*Figure 22. Calculated Maximum C(t) for Different k and L Values.*

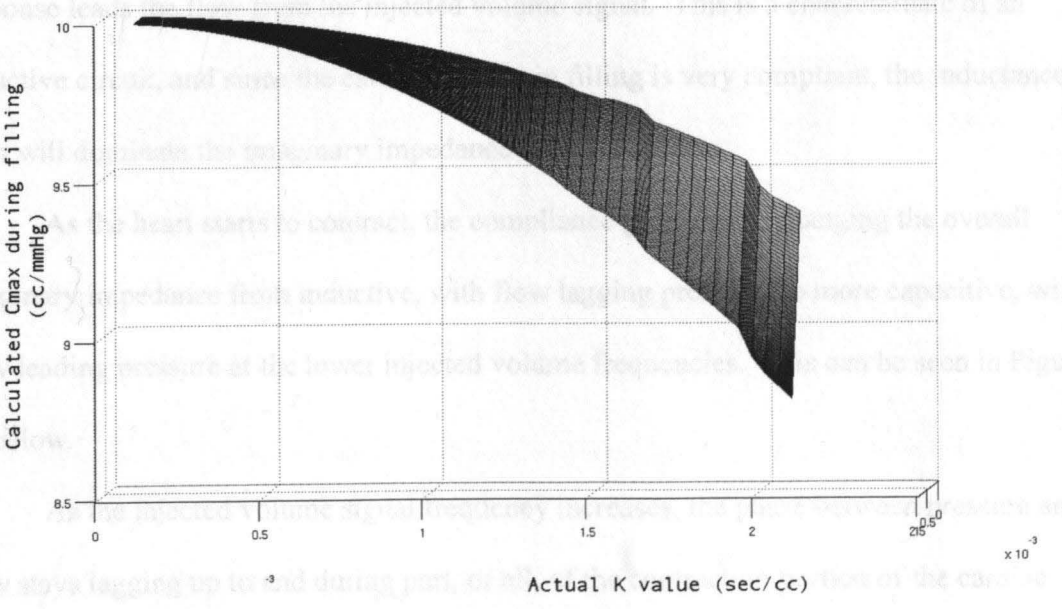


*Figure 23. Calculated Maximum C(t) for Different k and L Values Rotated.*

*The calculated maximum C(t) value is dependent on k values as shown when rotated. Only when L values become large does L begin to show effects.*

Model operation

The model itself created a very good contraction waveform as elastance varied from minimum to maximum and back again, producing a very smooth pressure wave in the isovolumic heart. Using values of elastance and volume for a typical canine heart, the model produced pressures also comparable to a typical canine heart.

The injected volume waveform also produced very symmetric pressure waves at various amplitudes over the range of injected volume frequencies from 2 Hz to 100 Hz, as would be expected. The amplitude of the pressure waveforms varied above and below zero by equal amounts at every frequency and only became distorted when the contraction and relaxation portions of the cardiac cycle created rapidly changing compliance values.

At a given frequency, the phase response during filling shows that the pressure response leads the flow from the injected volume signal. This is a characteristic of an inductive circuit, and since the cardiac system in filling is very compliant, the inductance term will dominate the imaginary impedance during this time.

As the heart starts to contract, the compliance goes down, changing the overall imaginary impedance from inductive, with flow lagging pressure, to more capacitive, with flow leading pressure at the lower injected volume frequencies. This can be seen in Figure 24 below.

As the injected volume signal frequency increases, the phase between pressure and flow stays lagging up to and during part, or all, of the contraction portion of the cardiac cycle. The flow lagging the pressure shows the increased inertial effect of the inductive element at the high frequencies as shown in Figure 25 below.

During the contraction portion of the cardiac cycle, the generated pressure waveform increases in amplitude compared to the filling portion due to the non-linear

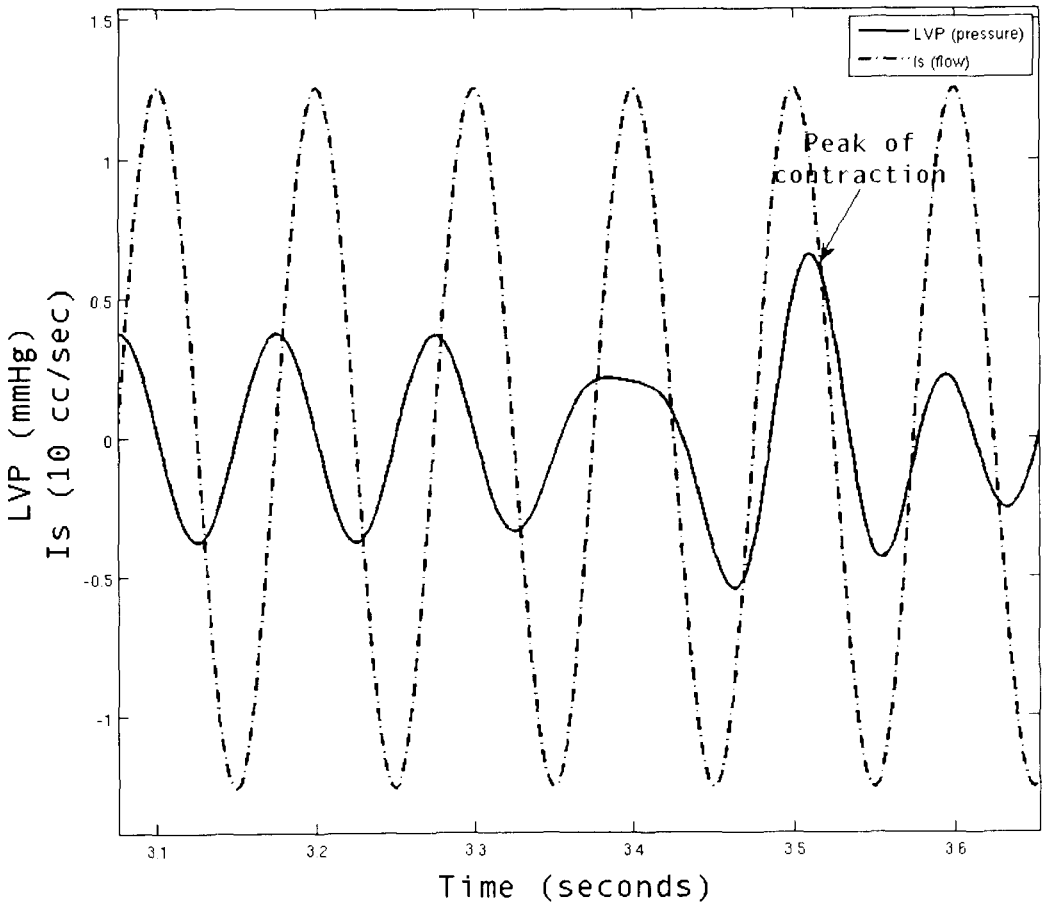


*Figure 24. Pressure and Flow Waveforms at Low Frequencies Showing the Phase Difference During Filling and Contraction.*

resistive term, k*LVP. As the LVP value increases, the resistance to flow increases, requiring more pressure to produce the same flow, Is, from the model. This can be seen in Figure 9 above, with a 22 Hz injected volume signal.

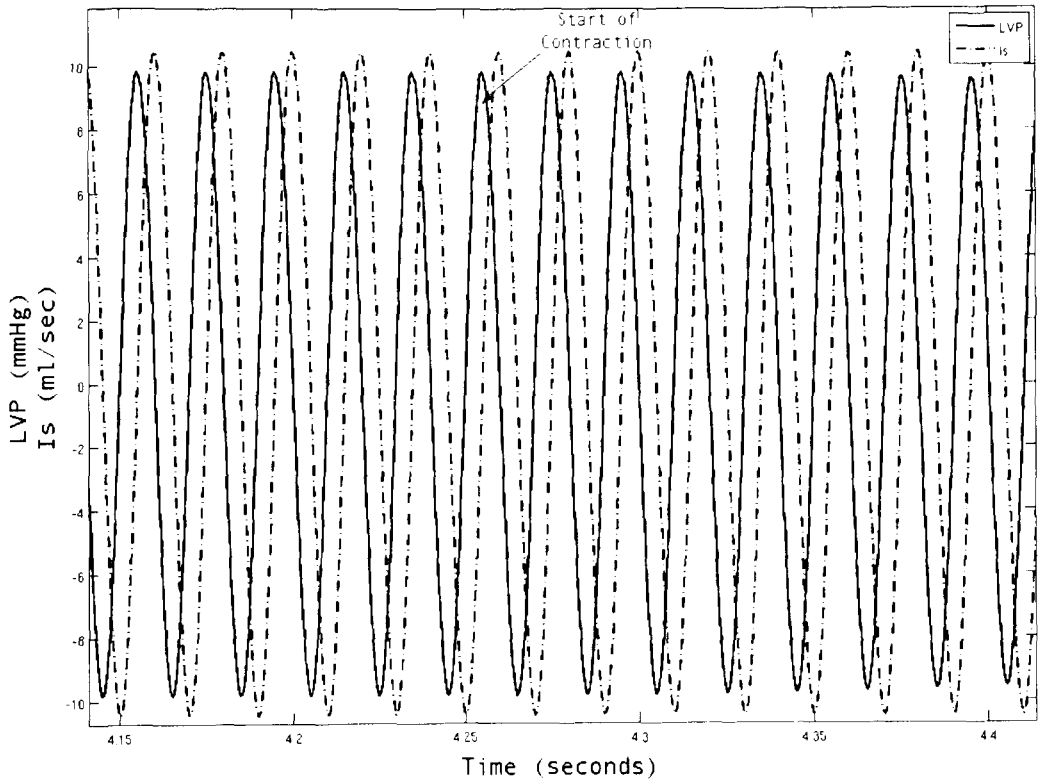


*Figure 25. Pressure and Flow Waveforms at High Frequencies.*
*This shows the flow is always lagging the pressure in phase, indicating an inductive system.*

Noise was also a significant problem to investigate. With the pressures and volumes possible in a clinical setting, adding noise to the measured values is also important. Using a 10 Hz and a 50 Hz injected volume signal frequencies, noise of 0.2 mmHg was added to the LVP signal of the 50 Hz signal. The 50 Hz LVP signal has an amplitude of approximately 10 mmHg, so 0.2mmHg would be a noise level of 2%, and in line with the pressure variability of solid state pressure transducers. Additionally, a 1 ml/sec flow random error was added to the flow signal at 50 Hz. The amplitude of the 50 Hz flow signal without noise is approximately 60 ml/sec, and a 1 ml/sec noise added on top

would be a 1.7% random error.

Without noise, the analysis of the measured flow and pressure waveform at 10 Hz and 50 Hz produced the calculated values of 0.00020001 sec/cc for k, and .00050002 mmHg*sec^2/cc for L, and a filling Cmax of 9.9868 cc/mmHg. The plot of the C(t) waveform is shown in Figure 26.

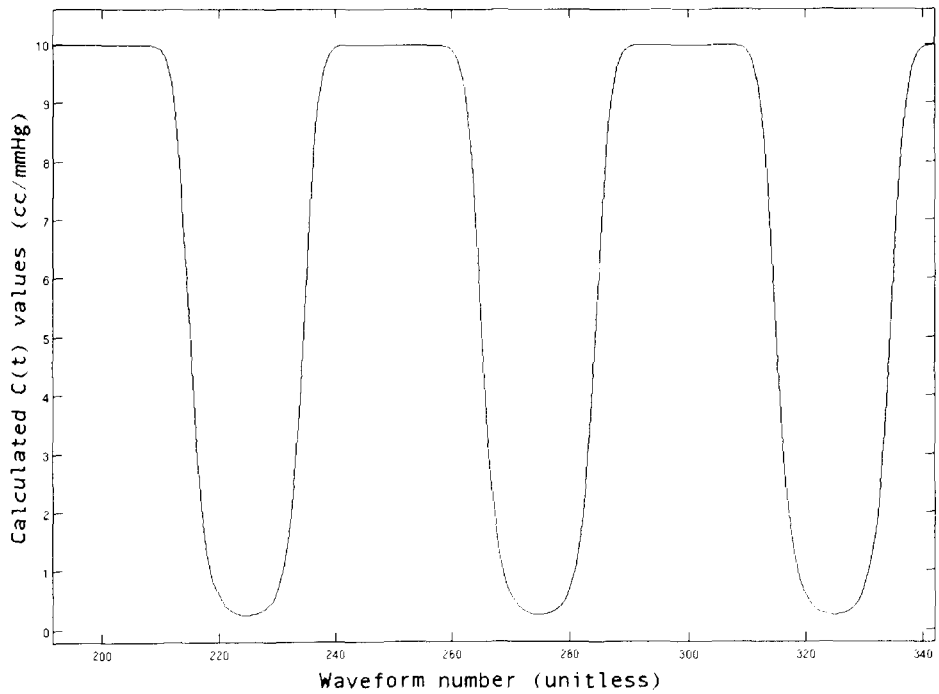


*Figure 26. Calculated C(t) for Noiseless Wave. Using non-noisy data, the calculated cardiac cycle elastance values stay very smooth and accurate.*

With noise added to the flow and LVP waveforms, the calculated values were not very different, but produced a much more random C(t) waveform. The calculated value of k was 0.00019961 sec/cc, L was 0.0005002 mmHg*sec^2/cc, and Cmax was calculated to be 9.9162 cc/mmHg. For both analyses, the actual value of k was 0.0002 sec/cc, L was

0.0005 mmHg*sec^2/cc, and Cmax was 10 cc/mmHg.

The numerical analysis produced very small errors in all three calculated values, but the major difference appeared in the waveform of C(t), as shown in Figure 27.

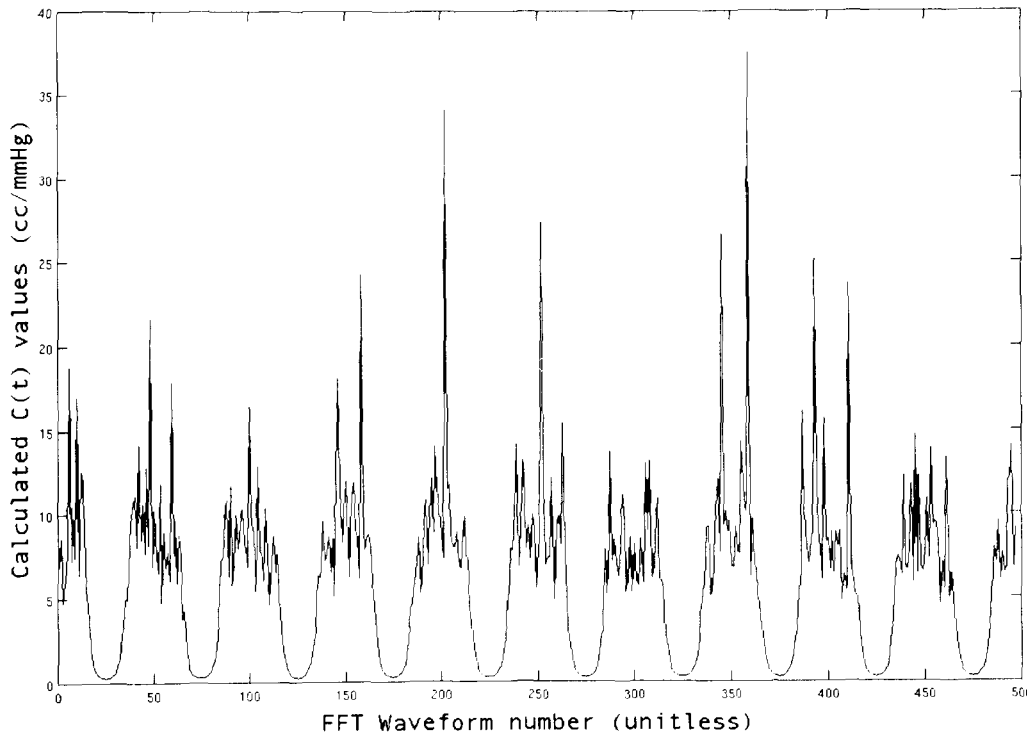


*Figure 27. Calculated C(t) With Added Noise to LVP and Flow Waveforms. When the noise is added to the flow and pressure waveforms, the calculated values of C(t) become less accurate and have large variations. However, the calculated single point values for Cmax, k and L had very little error when using approximately 2% noise.*

In general it still looks like the calculated C(t) resembles the actual value of 10 cc/mmHg during filling, but it is very hard to make that claim due to the wide variation in values. The maximum contractile value for C(t) remains 0.25 cc/mmHg, showing that noise is handled better during contraction than it is during filling.

Analyzing all of the results produced some unexpected situations that where hard to understand at first. Sometimes the model correct model behavior produced results that did not intuitively make sense, and raised questions about the validity of the model. After further analysis, it was determined that the model was working correctly, and the intuitive thinking had to be adjusted.

One interesting lesson learned from the model is that the inductance term causes the flow to lag the pressure at every portion of the cardiac cycle for higher frequencies, obscuring the contraction effects. The phase delay between the flow and the pressure looked very close to 90 degrees lagging, and seemed to remove the resistive element of the impedance as well by visual inspection. This did not fit the intuitive thinking that the phase shift should be less than 90 degrees, and should change over the contraction. However, resistive impedances were calculable at all frequencies to a high degree of accuracy, even the high frequencies where the pressure and flow waveforms looked only inductive, and the contraction was still visible as in Figure 26.

At very low frequencies, the pressure and flow phase responses showed a shift from lagging to leading during the contractile portion, but the next lesson learned was that there were not a sufficient number of injected volume waves to accurately resolve the time varying compliance to a high enough accuracy. The small number of injected signal waves to analyze in a given cardiac cycle dramatically lowered the accuracy of the calculations of every lumped-parameter model element for the cardiac model, from less than 1% error to as much as 10% error depending on the frequency and where the calculated C(t) values

appeared in time. This showed that, at a minimum, there is a starting frequency where accuracy increases to an acceptable level.

A good minimum frequency for accurate calculations for every lumped-model parameter was found to be around 20 Hz. Templeton used 22 Hz in 1974 although his reasons for selecting that frequency were never fully explained, but it provided a good capacitive result with minimal inductive interference. This frequency was of interest in the thesis, along with others in the range of 10 Hz to 60 Hz, for both mathematical and practical reasons. However, it is important to note that a single frequency cannot calculate both the inductive and capacitive terms of the imaginary impedances.

The inductive impedance begins to dominate the imaginary impedance at around 10 Hz for the typical canine cardiac values used. Campbell used frequencies up to and including 100 Hz for the isolated rabbit heart in 1997, and saw the amplitude of the generated pressure response increase as frequency increased.

Using the frequency and volume values from the model used for this thesis, it has been learned that the volumes required to get low error estimations can be very small. Using the model with larger volume changes at high frequencies actually decreases the accuracy of the calculated cardiac model elements due to the large amplitudes of pressure and flow. Even small volumes at high frequencies produce very large pressure responses due to the inductive impedance and the non-linear resistive element as the heart contracts.

The hypothesis that it is possible to calculate the lumped-parameter cardiac model values by injecting small volume perturbations into an isovolumic heart does appear to hold true for a range of volumes and frequencies.

## Future Work

With the isovolumic model verified to be consistent with a canine heart, and the analysis shown to work well at extracting the lumped-parameter model values, the next step would be to adapt the equations to allow for an ejecting cardiac cycle. To implement the theory in a practical application, the theory should be able to work in undefined situations, or both isovolumic and ejecting cardiac cycles.

Adding the differential equations for the ejecting and filling parts of the cardiovascular system will allows the model to more accurately resemble a practical situation, and then verifying the model and conducting these same analysis techniques for the ejecting system may allow for a more universal implementation of the theory.

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## APPENDIX A: MATLAB CODE

Matlab code to generate LVP waves at different frequencies.

```
clear

[B1,A1]=butter(2,.02);  %set up filter for finding extrema
OPTIONS=odeset('MaxStep',1e-3);  % set up ODE solver state
t=0:.0001:10;   %time step and length

cat_num=[ '1' '2' '3' '4' '5' '6' '7' '8' '9' 'a' 'b' 'c' 'd' 'e' 'f'];
% set frequencies to run
freq_num=[2 4 5 8 10 16 20 25 40 50 80 100 125 200 250];


L=.0005;
k=.0002;
L1=0;


jjj=2   % set volume size

v1= jjj/10;

%get standard PISO without perturbations

[a0 b0]=ode23(@eject3,t,[5,0,0.1],OPTIONS,100,0);

Pe0=b0(:,1);

[vol0 Is0]=GetV(t,100,0);
dis0=fiveptder(Is0,10000);
LVP0=(Pe0+L*dis0)./(1-k*Is0');

% get LVP waves including the volume perturbations
for jj=1:length(freq_num)

    f1=freq_num(jj);

    [a1 b1]=ode23(@eject3,t,[5 0 0.1],OPTIONS,f1,v1);

    Pe1=b1(:,1);

    [vol1 Is1]=GetV(t,f1,v1);
    dis1=fiveptder(Is1,10000);
    LVP1=(Pe1+L*dis1)./(1-k*Is1');

    eval(['Pe_' num2str(jj) '=Pe1;']);
    eval(['Is_' num2str(jj) '=Is1;']);
    eval(['LVP_' num2str(jj) '=LVP1;']);
```

```
    clear x1 x2 x3 x4 x5 a2a a4a lvp z phase zz2 Rx Iy x6 deltat

    [x1 x2 x3 x4]=extrema(filtfilt(B1,A1,Is1));   %use extrema to find
the peaks
    x5=sort(x2);  % sort the peaks in time

    deltat=floor(10000/f1);     %this is how long a period is in the
signals

    x6=length(x5)-3;
        %this is how many waves are in the signals - remove last 3


    LVP=LVP1-LVP0;  % subtract the PISO to get the pressure from the
volume changes only
    mLVP=LVP1;  %keep the true LVP wave to get mean LVP for k extraction

    Is=Is1;

    m1=zeros(deltat,x6);
    n1=zeros(deltat,x6);
    p1=zeros(deltat,x6);


    for i=2:x6
        for j=1:deltat


            m1(j,i-1)=Is(x5(i)+j-1);     %set up flow matrix
            n1(j,i-1)=LVP(x5(i)+j-1);    %set up Pressure matrix
            p1(j,i-1)=mLVP(x5(i)+j-1);   %set up mean lvp matrix
        end
    end

    for i=1:x6
        lvp(i)=mean(p1(1:deltat,i));     %calculate mean lvp
    end

    for i=1:x6
        press1=n1(1:deltat,i);
        flow1=m1(1:deltat,i);
        z(1:deltat,i)=(fft(press1))./(fft(flow1));      % resultant dp/dv
signal
        phase(1:deltat,i)=unwrap(angle(z(1:deltat,i)));        % phase of
dp/dv
        zz2(1:deltat,i)=abs(z(1:deltat,i));                     %
magnitude dp/dv
        Rx(i)=zz2(2,i)*cos(phase(2,i));            % real part of dp/dv
        Iy(i)=zz2(2,i)*sin(phase(2,i));            % imaginary part of
dp/dv
    end

    eval(['Iystore' num2str(jj) '=Iy;']);
```

```
    kys=Rx./lvp;     % k = Real impedance divided by mean lvp
    [oo op]=find(isnan(kys)==0);     %extract non numerical values

    kdata(jj)=median(sort(kys(op)));     %sort the numbered values
    Iys=Iy/(2*pi*f1);                %calculate L values
    [oo op]=find(isnan(Iys)==0);     % extract non numerical values

    Lfound(jj)=median(sort(Iys(op)));    % find median value and call that
L
    Lerror(jj)=abs(Lfound(jj)-L);        %calculate error in L
    if (Lfound(jj)>L1)
        L1=Lfound(jj);
    end
    % store data and calculate C(t)
    eval(['cdata' num2str(jj) '=-1./(2*pi*f1*(Iy-
2*pi*f1*Lfound(jj)));']);
    eval(['cTheorydata' num2str(jj) '=-1./(2*pi*f1*(Iy-2*pi*f1*L1));']);


end
```

Matlab code to do Monte Carlo analysis with or without noise.

```
% use monte carlo to test for K and L values

% volume is 0.2 ml

%use capacitors3c.m to generate standard frequencies

Pe1=Pe_5;   %pick Pe for frequency 10 Hz
Pe2=Pe_10;  %pick Pe for frequency 50 Hz

Is1=Is_5;   %pick flow signal at 10 Hz
Is2=Is_10;  %pick flow signal at 50 Hz

%take derivatives of the flow
dis1=fiveptder(Is1,10000);
dis2=fiveptder(Is2,10000);

% set up empty arrays for faster operation
kerror1=zeros(100,100);
kerror2=zeros(100,100);
calcmax=zeros(100,100);
Lerror1=zeros(100,100);
Lerror2=zeros(100,100);
lval1=zeros(100,100);
lval2=zeros(100,100);
kval1=zeros(100,100);
kval2=zeros(100,100);


for ii=1:100

    k=.0004+(ii-1)*.000004; %set up values for k
    ii          %create progress marker

    for jj=1:100

        L=.0003+(jj-1)*8e-6;    %set up values for L

        LVP1=(Pe1+L*dis1)./(1-k*Is1');  %create 10Hz LVP from Pe and k,L values
        LVP2=(Pe2+L*dis2)./(1-k*Is2');  %create 50Hz LVP from Pe and k,L values

        %use the following to add noise to the waveforms
        lvpnoise=rand(size(LVP2))*.2-.1;    %add .2mmHg noise to LVP
        isnoise=rand(size(Is2))*2-1;        %add 2ml/sec noise to flow

        LVP2=LVP2+lvpnoise;
        Is2=Is2+isnoise;


        clear x1 x2 x3 x4 x5 a2a a4a lvp z phase zz2 Rx Iy x6 deltat Iy10 Iy50

        [x1 x2 x3 x4]=extrema(filtfilt(B1,A1,Is1));
        x5=sort(x2);

        deltat=floor(10000/10);     %this is how long a period is in the signals

        x6=length(x5)-3;
            %this is how many waves are in the signals - remove 2
```

```
%this is the same as the generating code
LVP=LVP1-LVP0;
mLVP=LVP1;

Is=Is1;

m1=zeros(deltat,x6);
n1=zeros(deltat,x6);
p1=zeros(deltat,x6);

for i=2:x6
    for j=1:deltat

        m1(j,i-1)=Is(x5(i)+j-1);
        n1(j,i-1)=LVP(x5(i)+j-1);
        p1(j,i-1)=mLVP(x5(i)+j-1);
    end
end

for i=1:x6
    lvp(i)=mean(p1(1:deltat,i));
end

for i=1:x6
    press1=n1(1:deltat,i);
    flow1=m1(1:deltat,i);
    z(1:deltat,i)=(fft(press1))./(fft(flow1));      % resultant dp/dv
signal
    phase(1:deltat,i)=unwrap(angle(z(1:deltat,i)));      % phase of
dp/dv
    zz2(1:deltat,i)=abs(z(1:deltat,i));                  % magnitude
dp/dv
    Rx(i)=zz2(2,i)*cos(phase(2,i));              % real part of dp/dv
    Iy(i)=zz2(2,i)*sin(phase(2,i));              % imaginary part of dp/dv
end

Iy10a=sort(Iy);
Iy10=Iy;
eval(['Iymonte10_k' num2str(ii) '_L' num2str(jj) '=Iy;']);
zi1=Iy10a(70);
rx1=Rx(1:length(Rx)-2);
lvp1=lvp(1:length(lvp)-2);

k1=median(sort(rx1./lvp1)); %single frequency can calculate k
kval1(ii,jj)=k1;

%end of 10Hz, onto 50 Hz

clear x1 x2 x3 x4 x5 a2a a4a lvp z phase zz2 Rx Iy x6 deltat

[x1 x2 x3 x4]=extrema(filtfilt(B1,A1,Is2));
x5=sort(x2);

deltat=floor(10000/50);      %this is how long a period is in the signals

x6=length(x5)-3;
```

```
        %x6=floor(100000/deltat)-8;        %this is how many waves are in the
signals - remove 2
        % x7=diff(x5(2:length(x5)-2));


        LVP=LVP2-LVP0;
        mLVP=LVP2;

        Is=Is2;

        m1=zeros(deltat,x6);
        n1=zeros(deltat,x6);
        p1=zeros(deltat,x6);


        for i=2:x6
            for j=1:deltat


                m1(j,i-1)=Is(x5(i)+j-1);
                n1(j,i-1)=LVP(x5(i)+j-1);
                p1(j,i-1)=mLVP(x5(i)+j-1);
            end
        end

        for i=1:x6
            lvp(i)=mean(p1(1:deltat,i));
        end

        for i=1:x6
            press1=n1(1:deltat,i);
            flow1=m1(1:deltat,i);
            z(1:deltat,i)=(fft(press1))./(fft(flow1));      % resultant dp/dv
signal
            phase(1:deltat,i)=unwrap(angle(z(1:deltat,i)));        % phase of
dp/dv
            zz2(1:deltat,i)=abs(z(1:deltat,i));                     % magnitude
dp/dv
            Rx(i)=zz2(2,i)*cos(phase(2,i));             % real part of dp/dv
            Iy(i)=zz2(2,i)*sin(phase(2,i));             % imaginary part of dp/dv
        end

        Iy50a=sort(Iy);
        Iy50=Iy;
        eval(['Iymonte50_k' num2str(ii) '_L' num2str(jj) '=Iy;']);
        zi2=Iy50a(420);
        rx2=Rx(1:length(Rx)-2);
        lvp2=lvp(1:length(lvp)-2);

        k2=median(sort(rx2./lvp2)); %single frequency can calculate k
        kval2(ii,jj)=k2;

        k1error(ii,jj)=k1-k;     %find k errors
        k2error(ii,jj)=k2-k;

        %use the two equations two unknown method to solve for cmax
        cmax=(50/10-10/50)/(2*pi*10*zi2-2*pi*50*zi1);
        calcmax(ii,jj)=cmax;

        %use cmax to find L
```

```
        Lfound1=(zi1+1/(2*pi*10*cmax))/(2*pi*10);
        Lfound2=(zi2+1/(2*pi*50*cmax))/(2*pi*50);

        lval1(ii,jj)=Lfound1;
        lval2(ii,jj)=Lfound2;

        Lerror1(ii,jj)=Lfound1-L;    %calculate L error
        Lerror2(ii,jj)=Lfound2-L;

        %store everything
        eval(['C10_k' num2str(ii) '_L' num2str(jj) '=-1./(2*pi*10*(Iy10-
2*pi*10*Lfound1));']);
        eval(['C50_k' num2str(ii) '_L' num2str(jj) '=-1./(2*pi*50*(Iy50-
2*pi*50*Lfound1));']);

    end

end
```

Matlab code for the ODE solver

```
function [dy] = eject3(t,y,f1,v1)

%global f1 v1

Pe=y(1);
% Is=y(2);
% E=y(3);
% f1=y(4);
% v1=y(5);

t=mod(t,1);  %generate time from 0 to 1


[E dE]=GetE(t); % use time to get the elastance values
[V Is] = GetV(t,f1,v1); %use time to get the volume value


dPe=E.*(Is+(Pe./E^2)*dE);    %differential equation to solve

Is1=Is; %use Is to integrate flow to check volume

dy = [dPe; Is1; dE];
% only dPe is solved for, but Is1 and dE are used to check the integration
end
```

Matlab code to generate elastance and the derivative

```
function [E dE] = GetE(t)

t = mod(t, 1);  %get time between 0 and 1
a=t-.5; % shift time
tt=2*(t-.5);    %create a new time between 0 and 1

%create the equation for elastance based on normal distribution curve
E = 1/(sqrt(2*pi))*exp(-1/2.*(7*tt).^2)*8/.8 +.1;

%create derivative equation
dE=-8/(.8*sqrt(2*pi)).*tt.*exp((-1/2.*(7*tt).^2))*49*2;


end
```

Matlab code to generate injected volume and flow signals

```
function [V dV] = GetV(t,f1,v1)



t = mod(t, 1);  %get time between 0 and 1

% volume is a sine wave at the specified freq and amp
V = v1*sin(2*pi*f1*t);

%flow is the derivative of the volume signal
dV=2*pi*f1*v1*cos(2*pi*f1*t);

end
```

Code to find maximum and minimum extremes – downloaded from Mathworks.

```
function [xmax,imax,xmin,imin] = extrema(x)
%EXTREMA   Gets the global extrema points from a time series.
%   [XMAX,IMAX,XMIN,IMIN] = EXTREMA(X) returns the global minima and maxima
%   points of the vector X ignoring NaN's, where
%    XMAX - maxima points in descending order
%    IMAX - indexes of the XMAX
%    XMIN - minima points in descending order
%    IMIN - indexes of the XMIN
%
%   DEFINITION (from http://en.wikipedia.org/wiki/Maxima_and_minima):
%   In mathematics, maxima and minima, also known as extrema, are points in
%   the domain of a function at which the function takes a largest value
%   (maximum) or smallest value (minimum), either within a given
%   neighbourhood (local extrema) or on the function domain in its entirety
%   (global extrema).
%
%   Example:
%      x = 2*pi*linspace(-1,1);
%      y = cos(x) - 0.5 + 0.5*rand(size(x)); y(40:45) = 1.85; y(50:53)=NaN;
%      [ymax,imax,ymin,imin] = extrema(y);
%      plot(x,y,x(imax),ymax,'g.',x(imin),ymin,'r.')
%
%   See also EXTREMA2, MAX, MIN

%   Written by
%   Lic. on Physics Carlos Adrián Vargas Aguilera
%   Physical Oceanography MS candidate
%   UNIVERSIDAD DE GUADALAJARA
%   Mexico, 2004
%
%   nubeobscura@hotmail.com

% From        : http://www.mathworks.com/matlabcentral/fileexchange
% File ID     : 12275
% Submited at: 2006-09-14
% 2006-11-11 : English translation from spanish.
% 2006-11-17 : Accept NaN's.
% 2007-04-09 : Change name to MAXIMA, and definition added.


xmax = [];
imax = [];
xmin = [];
imin = [];

% Vector input?
Nt = numel(x);
if Nt ~= length(x)
 error('Entry must be a vector.')
end

% NaN's:
inan = find(isnan(x));
indx = 1:Nt;
if ~isempty(inan)
 indx(inan) = [];
 x(inan) = [];
 Nt = length(x);
```

```
end

% Difference between subsequent elements:
dx = diff(x);

% Is an horizontal line?
if ~any(dx)
 return
end

% Flat peaks? Put the middle element:
a = find(dx~=0);                % Indexes where x changes
lm = find(diff(a)~=1) + 1;      % Indexes where a do not changes
d = a(lm) - a(lm-1);            % Number of elements in the flat peak
a(lm) = a(lm) - floor(d/2);     % Save middle elements
a(end+1) = Nt;

% Peaks?
xa  = x(a);             % Serie without flat peaks
b = (diff(xa) > 0);     % 1  =>  positive slopes (minima begin)
                        % 0  =>  negative slopes (maxima begin)
xb  = diff(b);          % -1 =>  maxima indexes (but one)
                        % +1 =>  minima indexes (but one)
imax = find(xb == -1) + 1; % maxima indexes
imin = find(xb == +1) + 1; % minima indexes
imax = a(imax);
imin = a(imin);

nmaxi = length(imax);
nmini = length(imin);

% Maximum or minumim on a flat peak at the ends?
if (nmaxi==0) && (nmini==0)
 if x(1) > x(Nt)
  xmax = x(1);
  imax = indx(1);
  xmin = x(Nt);
  imin = indx(Nt);
 elseif x(1) < x(Nt)
  xmax = x(Nt);
  imax = indx(Nt);
  xmin = x(1);
  imin = indx(1);
 end
 return
end

% Maximum or minumim at the ends?
if (nmaxi==0)
 imax(1:2) = [1 Nt];
elseif (nmini==0)
 imin(1:2) = [1 Nt];
else
 if imax(1) < imin(1)
  imin(2:nmini+1) = imin;
  imin(1) = 1;
 else
  imax(2:nmaxi+1) = imax;
  imax(1) = 1;
 end
```

```
 if imax(end) > imin(end)
  imin(end+1) = Nt;
 else
  imax(end+1) = Nt;
 end
end
xmax = x(imax);
xmin = x(imin);

% NaN's:
if ~isempty(inan)
 imax = indx(imax);
 imin = indx(imin);
end

% Same size as x:
imax = reshape(imax,size(xmax));
imin = reshape(imin,size(xmin));

% Descending order:
[temp,inmax] = sort(-xmax); clear temp
xmax = xmax(inmax);
imax = imax(inmax);
[xmin,inmin] = sort(xmin);
imin = imin(inmin);


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```

Matlab code to find 5 point derivative

```
function [dxdt]=fiveptder(x,fs);

% Computes the derivative using algoritm from Numerical Analysis, 2ed.,
Burden, Faires, Reynolds; pg.130
% fiveptder(x,fs)
% x is the input signal for derivative calculation
% fs is the sampling frequency
% computes numerical derivative dx/dt

dt=1/fs;
%We need the time derivative of AoF so what follows is a numerical 5-
point derivative
dxdt=zeros(length(x),1);

for i = 3:length(x)-2
dxdt(i)=[1/(12*dt)] * [x(i-2) - 8*x(i-1) + 8*x(i+1) - x(i+2)];
% previous algoritm is from Numerical Analysis, 2ed., Burden, Faires,
Reynolds; pg.130
end
```