2-2013

Multiscale Modeling of Human Addiction: a Computational Hypothesis for Allostasis and Healing

Yariv Z. Levy
University of Massachusetts Amherst, yariv.levy@a3.epfl.ch

MULTISCALE MODELING OF HUMAN ADDICTION: A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS AND HEALING

A Dissertation Presented

by

YARIV Z. LEVY

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

DOCTOR OF PHILOSOPHY

February 2013

Computer Science

MULTISCALE MODELING OF HUMAN ADDICTION: A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS AND HEALING

A Dissertation Presented

by

YARIV Z. LEVY

Approved as to style and content by:

_____
Andrew G. Barto, co-Chair

_____
Jerrold S. Meyer, co-Chair

_____
Sridhar Mahadevan, Member

_____
Neil E. Berthier, Member

_____
Lori A. Clarke, Department Chair
Computer Science

DEDICATION

To my parents,

to my family,

and to my friends.

ACKNOWLEDGMENTS

I express my deepest gratitude to my co-Advisors, Professor Andrew G. Barto and Professor Jerrold S. Meyer. Professor Barto taught me why essence is the most elegant art of science, and Professor Meyer planted the seeds which bloomed.

I am grateful to the other members of my committee, Professor Sridhar Mahadevan and Professor Neil E. Berthier. Professor Mahadevan encouraged me to be meticulous, and Professor Berthier showed me how a good question can lead to a better answer.

I also express my deepest gratitude to Professor Dino J. Levy who taught me the fundamentals of drug addiction and encouraged me throughout my work. I was also guided and encouraged by Professor Hava T. Siegelmann during the early stages of my research.

I was fortunate to meet and interact with many colleagues, fellows, and teammates during the course of my stay at University of Massachusetts Amherst. I thank them for their curiosity, encouragement, and support.

I wish to thank the staff of the Department and of the University, including the Computer Science Administrative assistants, the Computer Science Computing Facility, the UMass Amherst Libraries, and the UMass Physical Plant Division. Their help was essential for successful completion of my PhD.

My work was supported in part by the National Science Foundation under NSF Grant #CNS-0619337. Any opinions, findings, conclusions or recommendations expressed here are the author's and do not necessarily reflect those of the sponsor.

ABSTRACT

MULTISCALE MODELING OF HUMAN ADDICTION: A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS AND HEALING

FEBRUARY 2013

YARIV Z. LEVY

B.Sc., ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE

M.Sc., ECOLE POLYTECHNIQUE FEDERALE DE LAUSANNE

Ph.D., UNIVERSITY OF MASSACHUSETTS AMHERST

Directed by: Professor Andrew G. Barto and Professor Jerrold S. Meyer

This dissertation presents a computational multiscale framework for predicting behavioral tendencies related to human addiction. The research encompasses three main contributions. The first contribution presents a formal, heuristic, and exploratory framework to conduct interdisciplinary investigations about the neuropsychological, cognitive, behavioral, and recovery constituents of addiction. The second contribution proposes a computational framework to account for real-life recoveries that are not dependent on pharmaceutical, clinical, and counseling support. This exploration relies upon a combination of current biological beliefs together with unorthodox rehabilitation practices, such as meditation, and proposes a conjecture regarding possible cognitive mechanisms involved in the recovery process. Further elaboration of this investigation leads on to the third contribution, which introduces a computational hypothesis for exploring the allostatic theory of addiction. A person engaging in drug

consumption is likely to encounter mood deterioration and eventually to suffer the loss of a reasonable functional state (e.g., experience depression). The allostatic theory describes how the consumption of abusive substances modifies the brain's reward system by means of two mechanisms which aim to viably maintain the functional state of an addict. The first mechanism is initiated in the reward system itself, whereas the second might originate in the endocrine system or elsewhere. The proposed computational hypothesis indicates that the first mechanism can explain the functional stabilization of the addict, whereas the second mechanism is a candidate for a source of possible recovery.

The formal arguments presented in this dissertation are illustrated by simulations which delineate archetypal patterns of human behavior toward drug consumption: escalation of use and influence of conventional and alternative rehabilitation treatments. Results obtained from this computational framework encourage an integrative approach to drug rehabilitation therapies which combine conventional therapies with alternative practices to achieve higher rates of consumption cessation and lower rates of relapse.

TABLE OF CONTENTS

Page

LIST OF TABLES

Table Page

LIST OF FIGURES

Figure Page

CHAPTER 1

INTRODUCTION

Use and misuse of addictive substances has been an ongoing phenomenon throughout the history of mankind from early civilizations to the present. While addiction has been widely regarded as detrimental and even criminal, science and popular beliefs have recently converged to consider addiction as a disease (1,2). Advances in social sciences, psychology, pharmacology, and physiology are continually providing new insight into the nature of addictive drugs and the consequences of their consumption. Extensive computational research has been conducted which deals with the neuropsychological, cognitive, behavioral and recovery aspects or scales of drug addiction. In the present document these scales presented in Figure 1 are defined as follows:

- The neuropsychological scale describes the ongoing activity of the relevant neural structures, which include the brain's reward system;
- The cognitive scale outlines the processing and integration of the neural activity, mimicking regions of the frontal cortex;
- The behavioral scale delineates the conduct of an individual, with respect to itself and the surrounding society;
- The recovery scale refers to possible interventions which prevent maladaptive behavior (i.e., the tendency to consume a drug).

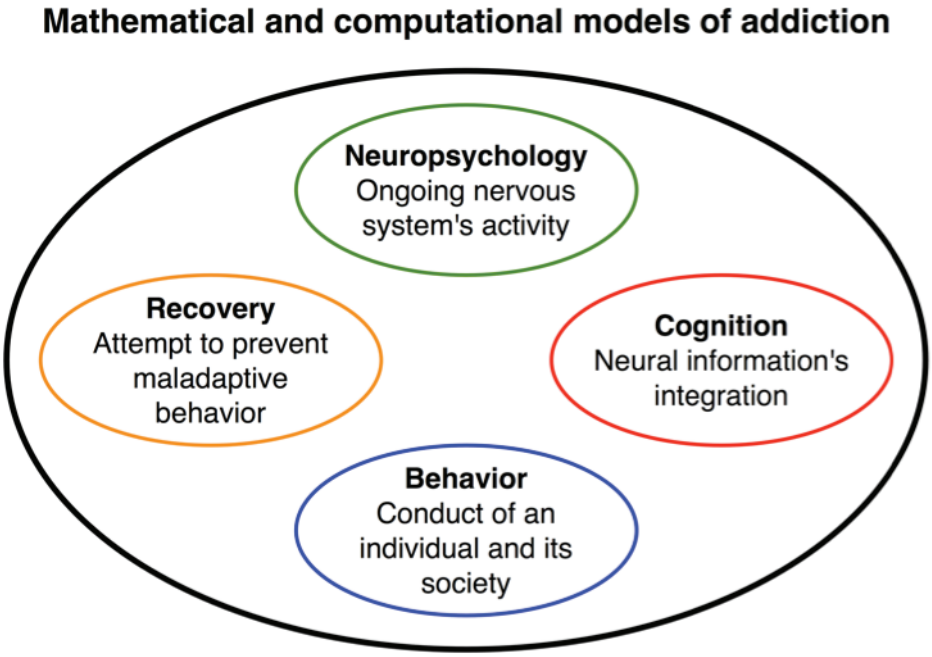

Figure 1: Neuropsychological, cognitive, behavioral and recovery scales are the four aspects considered in mathematical and computational models of addiction. Actual models of addiction commonly embrace one or two of these aspects.

Up to now, mathematical and computational models of addiction have considered only one or two of these scales. Effective use of the knowledge from these diverse facets to understand and treat drug addictions presents a daunting challenge: many aspects of this complex phenomenon are interrelated and time dependent. Moreover, a trade-off between a model's mathematical properties and its biological rationality should be found: a pertinent computational framework shouldn't be excessively complex, while allowing the model to simulate a significant diversity of behavioral profiles.

In the present dissertation, computational methods are used to integrate all four archetypal aspects of drug addiction into a comprehensive and translational multiscale model combining neuropsychological, cognitive, behavioral, and recovery observations, toward the prediction of drug-seeking behavior. It is expected that the results of this research will expand the understanding of substance addiction, with particular emphasis on cognitive correlations of the allostatic theory of addiction (3).

This chapter starts with an historic overlook of human drug dependency, continues with a glimpse of how computer science is deployed in biological investigations, and concludes with a description of the scientific contributions provided by this dissertation. Chapter 2 gives a background of the biological modeling of drug addiction; and Chapter 3 discusses previous formal models. In Chapter 4 are outlined the formal procedures engaged in developing the new formal framework discussed in this dissertation. Chapter 5 puts forward a cognitive learning mechanism as a necessary apparatus for emulating natural recoveries from drug addiction, where no pharmacological or behavioral interventions are employed. Chapter 6 computationally explores the allostatic theory of addiction and provides behavioral predictions with respect to cognitive correlates. Finally, Chapter 7 includes summary and conclusions of this dissertation.

1.1 Historical account of addiction in humankind

The lawful or illegal consumption of substances such as caffeine, alcohol, amphetamines, barbiturates, cocaine, and opium alkaloids can be traced back about 7000 years. The earliest documented evidence of addictive substance availability can be traced back to the Sumerian, Ancient Egyptian, and Ancient Chinese civilizations, involving opium, alcohol, and theine (caffeine[1]).

Around the year 5000 B.C. in Mesopotamia, the Sumerian civilization developed agriculture which significantly increased land productivity and the need to store sustenance surpluses. This prosperity led to the establishment of community life with permanent places of residence, as well as the need for a higher level of social organization and labor division. This new socio-economic organization facilitated cultural development and the invention of phonetic writing. The Sumerian written character for opium was associated with *"rejoicing"* (4).

By about 3500 B.C., the nearby Ancient Egypt civilization had new architectural techniques, a system of mathematics, a system of medicine, the first known ships, glass technology, and the earliest evidence of alcohol production in the form of a papyrus describing a brewery (5).

In a different part of the world sometime later in about 2000 B.C., the ruler of Ancient China, Shen Nong, known as the Emperor of the Five Grains, taught his people how to cultivate cereals, which led to the decrease in slaughtering of animals. The Emperor discovered many medicinal herbs and was accustomed to

[1] Theine was shown to have the same composition as caffeine in 1868. (Not to be confused with Theanine.)

boiling his water before drinking. It is believed that on one occasion some herbal leaves fell into his boiling water, he drank the brew, and he liked it (6).

Western civilization dates back to Ancient Greece and Ancient Rome, which were endowed not only with schools of art, philosophy, and rhetoric, but also with knowledge of the curative properties of plants and their euphoric characteristics. These societies had practical knowledge of the hallucinatory and temporary psychotic effects in opium poppies, ergot[2], mushrooms, and deadly nightshade[3] (7). The epic poet Homer cited the intoxicating, pain-relieving and sleep-inducing properties of these substances in *The Iliad* and *The Odyssey*, while the classical Roman poet Virgil mentioned them in *The Aeneid* (4).

Opium, alcohol and theine (caffeine) were known substances from the earliest time of the human civilization and their use has been celebrated, studied, and debated ever since.

More recently in 1821, the Englishman Thomas De Quincey wrote *"Confessions of an English Opium Eater"* (8,9), an account of his controlled laudanum[4] consumption and the effects on his life. At that time, it was not uncommon and even socially acceptable among Romantic writers to use opioids for both recreational and medical purposes. Some years later, from 1839 to 1842 and from 1856 to 1858, Britain declared two *Opium Wars* on China: under the pretext of enforcing anti-opium laws issued by the Chinese Emperor. These laws,

---

[2] A group of fungi used as a source of certain alkaloids.
[3] A plant used as a recreational drug because of the vivid hallucinations and delirium that it produces.
[4] Defined by the New Oxford American Dictionary as *"an alcoholic solution containing morphine, prepared from opium and used as a narcotic painkiller"*.

which were intended to decrease the large quantities of opium imported from India to China, indirectly affected British trading policy and eventually provided the pretext for Britain's military pursuit of commercial imperialism (10).

The first international alcoholism congress was held in Paris in 1878, and 28 years later the first international association for drug regulation was founded in Lausanne, Switzerland. Alcohol was never considered for international regulation, but opioids were. In the early 1900s, the Shanghai Opium Commission was established, and before World War I it became a global regulatory system. This control institution evolved into a preclusive authority during World War II (10).

The history of addictive substance use and abuse in the United States dates back almost 150 year to the American Civil War. Wounded veterans were legally given morphine-containing bundles for pain relief, and the first legal measure against substance abuse that was at least partially instigated by this medical practice dates back to 1875 when San Francisco opium dens were made illegal. Towards the end of the 19th century, substances such as morphine, laudanum, and cocaine were being legally used for pain relief and other medical purposes (e.g. heroin based cough syrup, cocaine toothache drops, etc.), the problem of addiction started to be recognized, and commercial drug regulation was begun. In 1906 the management of drug labeling was enforced with the passage of the Pure Food and Drug Act; in 1914 the legal distribution and use of opioids and cocaine became regulated by the Harrison Act; in 1920 the 18th

Constitutional Amendment banned most alcohol sales until 1933 (Prohibition); and in 1970 the Drug Enforcement Administration was created by the Controlled Substances Act in response to the growing availability and consumption of illegal drugs and increasing problems with addiction. The Anti-Drug Abuse Acts of 1986 and 1988 increased funding for drug treatment and rehabilitation and provided for the creation of the Office of National Drug Control Policy with responsibility for coordinating the national drug control policy (11,12).

A major shift occurred during the early 1950s when the World Health Organization (WHO) declared alcoholism as a disease. Already around 1870, the American Association for the Cure of Inebriates defined alcoholism as a disease. Even earlier, during the Age of Enlightenment, drunkenness was discussed as a disease (11,13). These views faded until the late 1990s, when the National Institute on Drug Abuse (NIDA) presented neuroscience and behavioral science evidence to promote this concept to the general public, politicians, and healthcare professionals (1). It was in 2004 that the WHO defined substance dependence as a disorder of the brain (14). Presently, addiction is considered a *"bio-psycho-social-spiritual disorder"* (2,15).

The use of addictive substances affects a very large portion of the population. Of the three substances discussed above (opium, alcohol, and theine-caffeine), caffeine is by far the most commonly used psychoactive substance, consumed daily by approximately 80% of the world's adult population (~3.5 billion). Moreover, it is estimated that 15-21 million people used opiates at

least once in 2007 and that about 76 million persons were diagnosed with alcohol use disorders in 2004. Other addictive substances in wide use include cocaine, amphetamines-group substances, and ecstasy-group drugs, with estimated worldwide use in 2007 between 16 and 21 million, 16 and 51 million, and 12 and 24 million, respectively. In the USA, these translate into a cost of approximately $181 billion for illicit drugs, $168 billion for tobacco, and $185 billion for alcohol (16,17,18). It should be noted that these estimates include only direct costs and disregard social, economic, and health implications associated with other factors such as deaths due to overdose or other complications from drug use (19).

1.2 Maturing out of addiction and natural recoveries

Nowadays, untreated recoveries from drug abuse are referred as *"natural recoveries"* (20,21). The first phenomenological instances were noticed in narcotics users and were referred as *"maturing out of addiction"* by Winick (22). Similar observations were successively noted and investigated also for other substances of abuse, such as alcohol and cocaine (23).

In 1962, Winick popularized the phenomenon of maturing out of narcotics addiction. His studies revealed cases where regular users of opium derivatives such as heroin, and of synthetic opiates such as meperidine, ceased to use the addictive substance without any psychological or pharmacological treatment (22). In 1980, Maddux and Desmond presented in the same venue an investigation discussing the possible overestimation present in the statistics of the original

study, and proposed further data to increase the accuracy of the description of this phenomenon (24).

In the two decades between theses studies, a number of studies were undertaken whose results were exceedingly dissimilar, arguing against a unified theory describing this type of phenomenon. The graph presented in Figure 2 plots the percentage of addicts becoming narcotics-abstinent against the follow-up period of the correspondent study, for 10 representative studies of maturing out of addiction listed in Table 1 of (25). The present dissertation focuses on the studies of Winick (red circle) and of Maddux and Desmond (blue plus sign), by integrating them and utilizing them within a computational framework to study natural recoveries from addiction in humans.

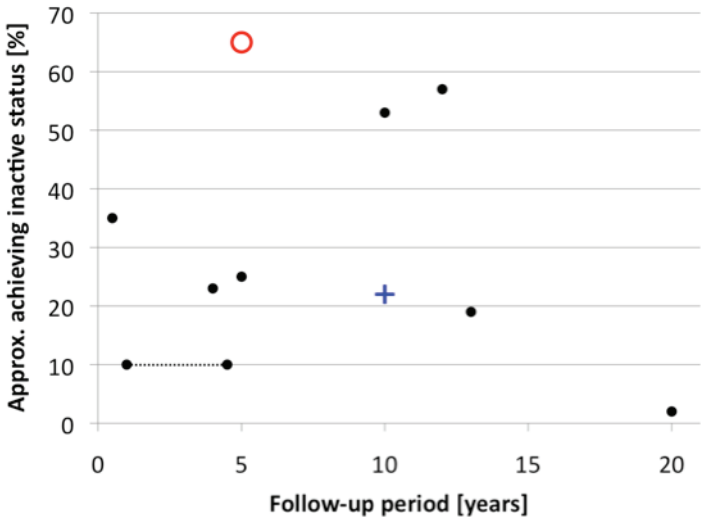

Figure 2: Recapitulation of 10 investigations of maturing out from heroin addiction undertaken between 1962-1980. These data were reported in (25). The percentage of former addicts achieving inactive status is plotted as a function of the investigation's lengths. The red circle corresponds to data in (22), the blue plus sign to data in (24), and the two united black dots to a study for which the follow-up period of the patients was distributed in the range 1 to 4.5 years.

1.3 Contributions

This dissertation presents three main contributions. The first one is a five-step procedure to convey biological and sociological correlates of addiction into a reliable computational framework. The second contribution encompasses a theoretical examination of unexplained cessation from drug consumption in the absence of medical and professional support, a phenomenon known as *maturing out of addiction* (22). The third and most significant contribution is a computational hypothesis to account for the allostatic theory of addiction (3). The present dissertation relates to the field of Computational Biology, which the National Institute of Health defines as

> *"... the development and application of data-analytical and theoretical methods, mathematical modeling and computational simulation techniques to the study of biological, behavioral, and social systems"* (26).

First contribution. The five-step procedure illustrated in Chapter 4 consists of formalization, expansion, qualitative validation, dynamical property analysis, and sensitivity analysis. The biological processes previously described by Levy[5] and Siegelmann in (27) are used to define the experimental framework of the computational model at the center of this dissertation. The formalization of these biological processes, presented in (28) and Appendix A, is organized into a multiscale model of drug addiction which includes four levels of observations:

[5] Dino J. Levy

neuropsychological, cognitive, behavioral, and recovery. Such formal organization, advanced in (29), promotes the clarity of the model and strengthens the interdisciplinary perspective on this disease. In order to enhance the biological plausibility of the experimental framework previously described by Levy[5] and Siegelmann (27), the model is enhanced with a more realistic behavioral scale. This elaboration, detailed in (29), is a demonstration of the model's expandability. In particular, the compulsion component of the model is enhanced to include elements of the incentive-sensitization theory of addiction, and the inhibition component of the model is enhanced to include developmental and biosocial elements (29). A conventional quantitative evaluation of the model is not possible to perform because the measure of several parameters defining the model is not available at this time. Instead, a qualitative validation of the model qualitative done to the extent possible was performed which involves computational simulations mimicking real-life patterns of drug abuse and their qualitative assessment. Initial explorations of qualitative validation are detailed in (29,30) and further developed in (31,32). The dynamic behavior of the system is assessed by testing how the framework converges toward a particular state of healthy or maladaptive behavior, and by examining how changes in the virtual subject's state influence fluctuations of the predicted behavior toward drug consumption, as described in (30). A sensitivity examination of the model, which considers both its phenomenological and mathematical characteristics, illustrates in (31) how a portion of the model could undermine the entire framework if not

properly calibrated. A functional constraint and a visualization tool are proposed as a means to identify and control this possible issue (31).

This first contribution addresses a fundamental step of modeling: the framework's validation. According to Zeigler et al. (33), the validation step typically requires a significant correspondence between experimental data and computational simulations to *"check if the model is in error"*. The discussed five-step procedure analyzes and evaluates the model in order to provide as strong an argument as possible in favor of the system's validity.

Second contribution. The preliminary recovery scale presented in (28) is enhanced to connect current drug-related neurological beliefs related to the neural plasticity of the brain's frontal cortex (34) with sociological studies describing natural recoveries from opioids (22,24). This contribution, detailed in Chapter 5 and in (32), results in a theoretical look at how episodes of maturing out of addiction may be triggered by non-conventional treatments (e.g., mindfulness-based cognitive techniques) emulated through a hypothetical learning mechanism. Even though speculative, this contribution provides support for the biological hypothesis that there is a cognitive learning mechanism, in the prefrontal cortex, which influences decision-making processes associated with drug abuse (32). This contribution constitutes a proof of concept in line with past and current opinions encouraging stronger interactions between social, natural,

and formal sciences for characterizing a disease such as drug addiction (35,15,36).

Third contribution. The third and main contribution of this dissertation is a computational hypothesis related to allostasis (3), a neuroscientific theory outlining how the brain's reward system reorganizes as drug intake progresses. The computational framework discussed in this dissertation is further elaborated to incorporate a pharmacokinetic/pharmacodynamic animal model of allostasis previously developed by Ahmed and Koob (37). This expansion corresponds to a theoretical translation of the animal model discussed in (37) toward human application. The augmented model, detailed in Chapter 6 and (38), assesses mood variations and drug consumption rates of a virtual subject, while providing biologically plausible and testable hypotheses related to allostasis in humans.

CHAPTER 2

BACKGROUND: BIOLOGICAL MODELS OF ADDICTION

The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) defines two types of maladaptive substance use: *"substance abuse"* and *"substance dependence"* (39). Both definitions include distinctive behavioral aspects. Substance abuse can manifest itself in reckless, negligent, unreliable, delinquent, or confrontational behavior. Substance dependence can present itself in eager, greedy, perfervid, zealous, or gluttonous behavior towards the addictive drug. Typically the word *addiction* refers to substance dependence. The transition from substance abuse to addiction is characterized by a significant increase in the time and energies invested by an individual to come into possession and use, or recover from the substance, along with the increase of the subject's tolerance to the drug and correspondent enlargement of its consumed amount. Patterns of drug use not only depend on the maladaptive state of the individual but also on the particular substance. Drugs such as nicotine and opiates are usually taken by humans according to a schedule, whereas others including alcohol, cocaine, and amphetamines may be taken intermittently. The common behavioral patterns encountered by a drug user include recreational, binge, regular or heavy use, recovery, and relapse. These behavioral patterns are defined by the aggregation of biological, psychological, and social elements, which jointly establish the

individual's state driving the desire or willingness to engage with the addictive drug.

Researchers investigating the elements responsible for substance dependence began to evaluate and estimate the inherent features of addiction by observing natural phenomena such as medical conditions, psychological deviations, and social awareness.

In 1968, Siegler and Osmond described seven models of drug addiction: one medical model, one socio-psychological model, and five moral models (40). The medical model considers the addict as a patient and addiction as a chronic disease which can be caused by contact with an addictive drug, but where predisposition factors and relevant chemical processes are unknown. As written by Siegler and Osmond, the socio-psychological model considers the addict as a *"victim of social forces beyond his control"* (40), an individual with strong personality problems related to substance dependencies and influenced by social class, neighborhood, age, and mental health. The five moral models are the retributive, deterrent, restitutive, preventive, and restorative models. These frameworks respectively describe the addict as a convicted criminal, a bad example, a debtor, a failure in moral education, or a wrongdoer, and the set of causes to become an addict include moral failure and lack of deterrence or moral instruction.

Twelve years later, in 1980, the National Institute on Drug Abuse (NIDA) published its 30th Research Monograph with a collection of articles providing a

more comprehensive perspective of drug addiction. This collection considers 43 different theories of addiction which together encompass more than 13 distinct centers of interests such as psychiatry, psychology, sociology, biomedical sciences, neurosciences, etc. (41).

In their 2005 book on psychopharmacology, Meyer and Quenzer describe the most prominent views of addiction: the physical dependence model, the positive reinforcement model, the incentive-sensitization model, the opponent-process model, the allostatic model, and the disease model (11). These six models and a more recently developed view of addiction, the impaired response inhibition and salience attribution (I-RISA) model (34), are described below.

The neuropsychological scale of the model at the center of this investigation relates to the physical dependence and disease models, the cognitive scale relates to the positive reinforcement and the I-RISA models, and the behavioral scale relates to the allostatic and, by extension, the opponent-process models.

2.1 The physical dependence model

The physical dependence model describes addiction in terms of relapse and comprises two concepts related to withdrawal symptoms, which are the unpleasant physical reactions that generally occur after ceasing to take an addictive substance. The first concept relates to relapse as mean to alleviate physical reaction to abstinence that typically occurs shortly after the drug has

been discontinued. In this case, relapse occurs when the addict which is struggling to cope with distressing withdrawal symptoms resumes drug intakes to alleviate this pain. The unwanted pain is removed, but the subject is once again exposed to addiction. The second concept delineates cases of relapse due to conditioned withdrawal, which usually occurs after the addict has been drug-free for a significant time. In this case, physical reactions to abstinence occur in particular places, and hence the subject develops a classical conditioning between addictive substance and location. Even after a long drug free period, a former addict may be subject to drug cravings which arise when in previously drug-conditioned locations. Research related to the physical dependence model emphasizes how brain regions including the amygdala, the anterior cingulate cortex, and the basal ganglia are particularly active during conditioned withdrawal episodes.

There are two main critiques of the physical dependence model. First, there are no insights into the processes that occur when the subject experiences drugs for the first time. This model can explain the maintenance of an addiction, but cannot account for the changes that occur to the addict-to-be. Second, this model assumes strong physical dependence on the abused substance, and thus fails to consider drugs such as cocaine which do not produce a strong physical dependence (11).

2.2 The positive reinforcement model

According to this model, the euphoric state experienced after drug intake reinforces actions that preceded the substance administration. In other words, repeated drug intake induces a desire by the subject to experience again the euphoric state and to engage again in the course of actions that led to the drug intake. Furthermore, in case of an attempt to cease using the substance, the subject will experience a craving caused by the overwhelming desire to attain again the feeling of wellbeing caused by the drug.

Behavioral studies focused on the development of this model used rodents and primates. For a limited amount of time each day, the test subject was given free access to intravenous drug injections administered through an accessible lever. A precise amount of drug was injected into the bloodstream of the subject when the bar was pressed. The action of pressing the lever can provide the drug: for example, one dose of drug is delivered for every five lever presses. Thus it was possible to measure the relative strength of substance reinforcement effects. This reinforcement eventually reached its upper limit (threshold) when the animal stopped pressing the lever, presumably because the reward acquired to achieve this action did not justify the effort: the effort required for receiving the actual drug (reward) was too large with respect to the drug dose provided. For the same ratio between real and empty injections, an animal was generally found to have a higher perseverance to press the lever when the dose provided in the actual drug injection was higher. While clearly illustrating the role of positive reinforcement, this model neglects the social effects of drug abuse, which can have negative

real life consequences in the career of a drug user, family breakups, professional and financial problems, health issues, engagement in criminal activities, etc. (11).

2.3 The incentive-sensitization model

The incentive-sensitization theory of addiction is grounded on the distinction between drug liking and drug wanting or, more specifically, between the euphoric sensation that arises while taking a drug and the powerful desire to take the drug again. This theory, formulated by Robinson and Berridge (42), states that during the establishment of the addictive state, the *"wanting"* level of a subject strongly increases, while the *"liking"* level stays constant or even slightly decreases (42,43,44). The discrepancy between these two processes is believed to originate at the level of neural pathways within the brain. Since it is known that the mesolimbic dopamine pathway can be sensitized by repeated intakes of addictive substances, this framework justifies the hypothesis for which this particular neural circuit could be more important to drug wanting rather than for drug liking. The psychological process called *"incentive salience"*, which leads the subject to a wanting state, may be caused by long-lasting neuroadaptations and could explain why it is difficult for a former addict to avoid relapse episodes. While supported by strong experimental data from both animal and human studies, the accuracy of this model might substantially benefit by considering additional psychosocial factors interacting with the biology of addiction (11).

In the computational model presented in this document, the incentive-sensitization theory partially defines the behavioral scale: the compulsive component within that scale is described as the average of the *"wanting"* and the *"liking"* processes.

2.4 The opponent-process model

The opponent-process model for drug addiction is also relevant to motivation in general. Similar to the incentive-sensitization model, it involves two processes which are different instead of complementary.

In the early 1970s Solomon and Corbit introduced the opponent-process theory of motivation to describes how the affective homeostatic state of an individual is maintained by

> *"... many systems in the brain, the business of which it is to suppress or reduce all excursions from hedonic neutrality, whether those excursions be appetitive or aversive, pleasant or unpleasant"* (45).

This psychological framework considers the emotional reaction to a stimulus as the sum of two elements: an a-process which occurs immediately after the event, and a b-process which begins after a slight delay at a slower rate with a reversed hedonic magnitude. Drug intake initially causes large and positive a-processes that gradually diminish due to the subject's increasing tolerance to the substance. The corresponding b-processes are minor at first, but their intensity and duration grow with continued use of the substance. The opponent-

process framework properly predicts that repetitive drug intake can diminish the euphoric state originated by an addictive substance and eventually cause withdrawal symptoms, but it fails to account for the transitions in the gradual development of a dependency whereby in initial stages drugs are experienced to *feel high* but subsequently become used to *feel normal*. This model assumes that the hedonic homeostatic state of an addict persists and remains unimpaired over time even though every drug intake perturbs it. In other words, the baseline around which the a- and b-processes fluctuate remains constant.

2.5 The allostatic model

The principle of allostasis was established to enhance the homeostatic model whereby the well-balanced functional state of a living being is sustained by the constant conservation of the organism's inner environment. Each divergence from the normal state of the organism is counterbalanced by negative feedback mechanisms which support the reinstatement of original setpoints. Instead, the allostatic model advances that the internal state of the organism continuously adapts to the surrounding natural world, attaining functional stability through the adaptation of physiological thresholds (46). Allostasis, as defined by Sterling and Eyer,

> *"... provides for continuous re-evaluation of need and for continuous readjustment of all parameters toward new setpoints"* (46).

In humans, this continuous adaptation to the environment is reached by means of neural and endocrine processes that are able to take priority over homeostatic regulations (46).

According to the hypothesis put forward by Koob and colleagues, a drug addict attains the allostatic state by means of the chronic deviation of their hedonic baseline. The addict's physiological state is maintained operative by means of this affective adaptation, rather than by reinstatement of the original homeostatic balance. Symptoms of allostasis are manifested by changes in the addict's mood or state of mind (3). The concept of allostasis enhances the opponent-process model with neurobiological findings and similarly, but more comprehensively, accounts for the transitions in the gradual development of a dependency whereby drugs are first experienced to *feel high* but subsequently to *feel normal*. The allostatic framework of addiction relies on changes observed in the subject's nervous and endocrinal systems which occur as addiction perpetuates, causing continuous and progressive distortions of the subject's affective state (47). The *raison d'être* of these distortions is to guarantee the functional stability of the organism while its hedonic homeostatic state is corrupted.

The hedonic effect of an addictive substance on the brain's reward system is orchestrated by within-system neuroadaptations and between-system neuroadaptations (48). Experimental observations show that rats undergo a continuous degradation of hedonic valence during extended periods of cocaine

consumption (49). Similarly, the negative hedonic valence of the individual is increased by within-system and between-system neuroadaptations, and chronically impacts the person's mood (3). Initial drug consumption disrupts the normal synaptic physiology of the reward system (50) which aims to reinstate its equilibrium by means of within-system neuroadaptations (48). Within-system adaptations act at the molecular or cellular level defining the brain reward circuitry (51) and increase the magnitude of the ideal threshold of the reward (37). For instance, if the effect of the consumed drug of abuse relies on the availability of a particular neurotransmitter, within-system adaptations will diminish its amount within the reward system (52). With repeated drug administration the reward system becomes accustomed to extended activations of the within-system component, which eventually causes withdrawal symptoms during periods of abstinence (48). Dopamine in the nucleus accumbens (NAc) and extended amygdala plays an important role in within-system adaptations (53). As consumption further advances, the brain's expectation for future rewards increases and within-system neuroadaptations become progressively inadequate and eventually fail to provide the individual with a well-adjusted functional state.

Due to deficiencies of within-system adaptations, brain structures different than the one defining the reward system are recruited through the deployment of between-system neuroadaptations to further counterbalance the effect of the drug (48). These brain structures, delineated by Koob and Le Moal, embody the *"anti-reward systems"* (54). Between-system adaptations increase the baseline

reward threshold (37) and originate in the brain stress system (48). For example, if a drug has a particular effect on the reward circuit, between-system activations could promote a hormonal response leading to the opposite effect (52). The corticotropin-releasing factor operating in the amygdala, stria terminalis, and ventral tegmental area (VTA) plays an important role in between-system adaptations (53).

2.6 The disease model

The disease model has been accepted as a valid perspective on addiction after a few failed introductory attempts, as discussed in the historical overview above. Jellinek's research about alcoholism published in 1960 began this successful ascent by proposing a straightforward definition of alcoholism and a corresponding taxonomy (55,56).

Jellinek's description of alcoholism includes two characteristics:

> *"... one is drinking and the other is damage (individual or social, or both) incumbent upon the drinking"* (55).

This interpretation was received as a significant upgrade of the precursor moral model that considered the addict an individual with weak mental and moral qualities. The proposed classification includes five grades of alcoholism which in increasing order of severity are: alpha, beta, gamma, delta, and epsilon alcoholism. These five categories are organized with respect of three main questions:

- What causes a person to become an alcoholic?
- What are the processes involved?
- What are the implicated damages?

The recognized causes encompass psychological, physiological, socio-cultural, and economical domains; the involved processes embrace tolerance, loss of control, physical versus psychological dependence, nutritional and physical habits; and the damages include physical and/or mental, and socio-economic types (55).

Jellinek's classification of alcoholism provided an early distinction between *"chronic alcoholism"* (up to beta alcoholism) correlated with physical and behavioral consequences of long-term alcohol use, and *"alcohol addiction"* (starting from gamma alcoholism) related to craving and lack of control (55).

Nowadays the disease model is a main reference in scientific research, professional treatments, self-help groups, and also mass media. Early disease models considered the addict as a human being inclined to the use and misuse of drugs mostly because of an inherited susceptibility, and are referred to as susceptibility models. With the blooming of neuroscientific investigations it became apparent that long-term drug use causes significant changes in the structure and functioning of the addict's brain. These findings supported the evolution of susceptibility models into exposure models, which consider the

changes occurring at the neural substrate level of a long-standing drug user as accountable for the addictive behavior of the subject (11).

The advancement that the field of neuroscience underwent from the late 1970s drove the adaptation of the disease model into the *"brain disease"* (1) model, as expressed by Leshner in the late 1990s. Investigations relaying on laboratory animal data and on human brain imaging techniques promoted the understanding of the substance abuse cycle, including involved ionotropic and metabotropic mechanisms (50). The enhanced neurobiological comprehension of the addict's states (e.g., loss of control, drug craving, and withdrawal symptoms) promoted and delineated new pharmacological treatments and facilitated the progress of health practices related to addiction (57).

The brain disease model of addiction positively influences society, heath care, and research, even though a recent study warns about a possible adverse effect: the progressive instauration of a view of addiction exclusively centered on brain studies (58). Such an exclusive view could diminish important contributions from fields such as psychology or sociology which are equally significant towards a better understanding of this phenomenon. Moreover, assigning to an addict the category of a person with a brain disease could result in an increased ostracism among human beings addicted to drugs (59). An interdisciplinary attitude including features ranging from neuroadaptations to socio-economic context, including biological, psychological, and social elements, was discussed as a pragmatic candidate to avoid such unwanted outcome (36).

2.7 The impaired response inhibition and salience attribution model

In their 2002 review, Goldstein and Volkow describe neuroimaging studies that support a new conceptualization of addiction, designated as I-RISA. In addition to the limbic system, until that point believed to represent the essential neural structure involved in addiction, the authors discuss the involvement of another brain region: the frontal cortex. The I-RISA model hypothesizes two processes to explain how the state of an addict cycles with a positive feedback from drug intoxication to drug craving, to compulsive drug administration, to drug withdrawal, and again to intoxication. Goldstein and Volkow state that these two processes are the

> *"... loss of self-directed/willed behaviors to automatic sensory-driven formulas" and the "attribution of primary salience to the drug of abuse at the expense of other available rewarding stimuli"* (34).

The first process relies on observed changes within the mesolimbic and mesocortical dopaminic pathways which suggest that an addict expresses a different response inhibition with respect to a healthy individual. Presented with the same stimulus (a drug of abuse), the neural substrate of the addict will facilitate the behavior leading to the immediate reward (drug intake), whereas the neural substrate of the healthy individual will more carefully ponder such immediate reward since it is potentially harmful in a longer term.

The second process depends on the alterations observed within the orbitofrontal and anterior cingulate cortices (regions active in cognitive, emotional, and decision-making processes) which suggest that an addict and a healthy individual have contrasting saliencies while attributing reward values to emotional matters (34).

Even though prefrontal cortex and anterior cingulate gyrus consistently show activation during drug intoxication, cocaine abusers experiencing craving express a higher neural activity and a different glucose metabolism in these brain regions than do healthy individuals. Withdrawing cocaine users exhibit a lower cerebral blood flow than healthy subjects in the prefrontal and lateral frontal cortices, and as the cessation period become longer; they also exhibit a higher glucose metabolism in the orbitofrontal cortex and in the striatum, as opposed to healthy subjects.

With respect to a healthy individual, the neural differences observed in addicted subjects suggest that an addict is more likely to experience cognitive distortions leading to a misjudged reward evaluation for drug intakes to the disadvantage of non-drug stimuli. With respect to the computational model advanced in the present investigation, the I-RISA view of drug addiction supports the conjecture of a cognitive level which integrates neural activities that define the subject's drug-seeking behavior.

CHAPTER 3

RELATED WORK: COMPUTATIONAL MODELS OF ADDICTION

Technological advances and the consequent increase in the quality and quantity of data describing multiple characteristics of addiction have enabled researchers to use mathematical and computational tools to further advance the study of drug abuse. Computational techniques are widely accepted as valid tools to describe and predict processes associated with drug dependences (60), as well as other mental (61) and physical (62) diseases.

It has been recently proposed (63) that existing computational models of addiction which consider dopaminergic signaling as having an essential role can be organized into three different families: quantitative pharmacological models, abstract models of dopamine functions, and knowledge repository models. Here this categorization of formal models is expanded to include two additional families – epidemiological and economic models – which do not explicitly take into consideration the dopaminergic effects, but are pertinent to comprehensively understanding how computational descriptions of addiction can further advance this field of study. Hereafter these five categories, shown in Figure 3, are described and discussed. For the most part, these computational models take into consideration one or two of the scales of observations described in Figure 1. A pragmatic approach to integrate all these scales into one formal framework is discussed at the end of this chapter, and resides in knowledge repository models.

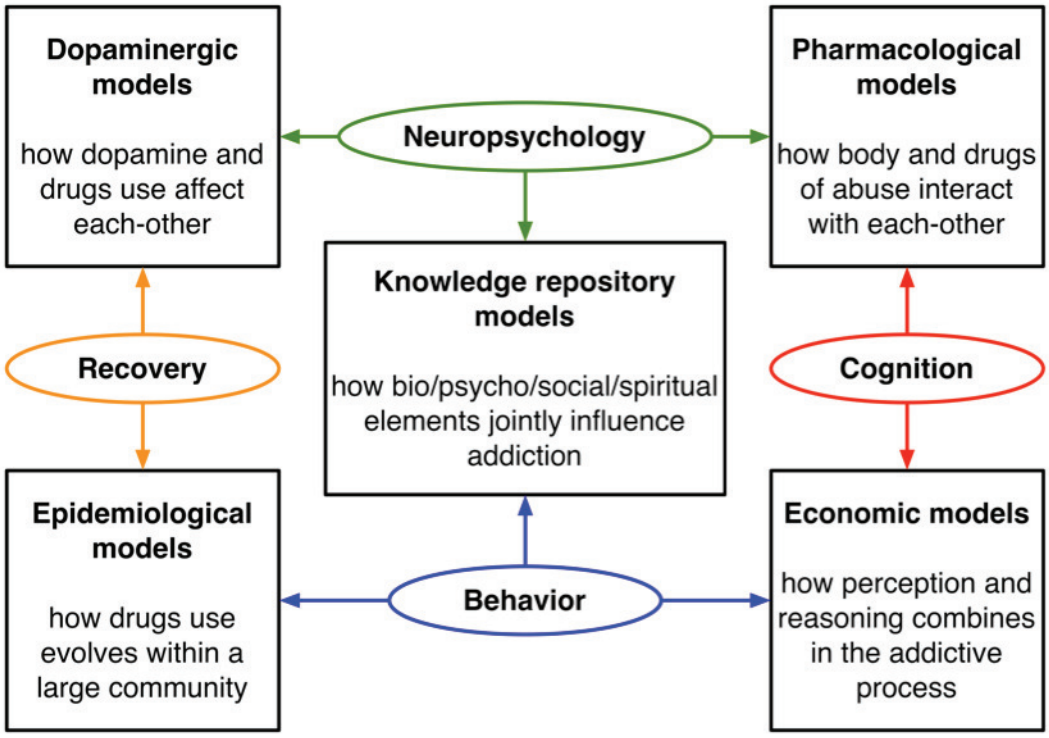

Figure 3: Epidemiological, economic, pharmacological, dopaminergic, and knowledge repository models of addiction. Current models are mostly concerned with two scales of observations (neuropsychology, cognition, behavior, and recovery).

3.1 Epidemiological models

Epidemiological models provide a tool to predict how classes of drug takers behave, and could qualify as a useful framework to assist professionals in the formulation of treatment and prevention strategies. A model in this family consists of a system of differential equations describing over time the size of a subset within the studied population, and is mainly used in the field of

mathematical epidemiology. As described by Diekmann and Heesterbeek, this field is

> *"... about translating biological assumptions into mathematics, about mathematical analysis aided by interpretation and about obtaining insight into epidemic phenomena when translating mathematical results back into population biology"* (64,65).

An epidemiological model proposed in 2000 uses three nonlinear differential equations to describe the dynamics of tobacco use, recovery, and relapse. This model considers a constant population, divides it into smokers, potential smokers, and smokers who have quit smoking permanently. It describes their respective rates of change with respect to time (65,66). More recently, the introduction of two new classes of mild and chain-smokers, as well as the impact of smoking-related illnesses, have extended this model. That study shows how the number of smokers decreases when chain-smokers stay no longer than 1.5 years in this class before reverting to the mild-smoking class. Similarly, the number of smokers decreases if mild-smokers stay as such for no longer than 1.5 years (67). A deeper analysis of the original model reveals four states of equilibria, only one smoking-free (68).

One of the first epidemiological models of opiate addiction using ordinary differential equations appeared in 2007 (69). Mathematical epidemiology principles, more specifically compartmental model structures, were applied in order to identify the parameters that policy-makers should modulate in order to maximize the effectiveness of prevention and treatment resources. This study

concluded that increased drug-use would prevail when the probability of becoming a heroin user is greater than the sum of the cessation probabilities. The cessation probabilities describe situations such as treatments, natural or drug-related deaths, and spontaneous recoveries. To reduce the total number of heroin users within the population, the probability of becoming an addict is identified as more significant than the ratio of users accessing treatments. While assuming that all individuals have the same level of susceptibility, this study reinforces a foregone conclusion that prevention is better than cure (69). Using realistic parameters, this model has a stable equilibrium which indicates the exclusion of an epidemic in heroin use (70). Similar frameworks have been developed for alcohol addiction (71,72,73).

3.2 Economic models

Conventional economic theory is based upon a fundamental assumption that an individual acts so as to maximize his/her personal level of satisfaction with respect to the available resources. The level of satisfaction is called *utility*, the available resources are called the *budget*, and the behavioral phenomenon is called the *utility maximization* (74). Economists became interested in drug addiction by first studying topics related to product consumption and habit formation. In the standard model of consumption, exclusively current consumption affects utility rather than past and future consumption. More recent studies consider such temporal component as a fundamental element in

decision-making processes, which is labeled *temporal discounting* (75). The reward, or utility, of an action was initially described as a time-dependent exponentially decaying function. This expansion originated the current categories of economic models for addictive behavior, which include the myopic (or irrational), imperfectly rational, and rational models (76).

The myopic model considers that an addicted individual's preferences change over time as a consequence of past experiences and other factors such as advertisements (e.g., a drug prevention campaign) and a drug's price. The imperfectly rational model assumes two competing natures of the individual, one that will consistently try to quit using the drug, and another that will regularly encourage drug use. In the context of cigarette smoking, as described by Chaloupka and Warner,

> *"... everybody behaves like two people, one who wants clean lungs and long life and another who adores tobacco"* (77).

The rational addiction model proposed by Becker and Murphy in 1988 (78) is the most popular of the three models, especially for the analysis of cigarette consumption, where an individual is assumed to consistently plan the maximization of utility over time, with current consumption influenced by present, past, and future budget constraints. Under this framework, addiction is represented as a strong habit (78).

The field of behavioral economics, where conventional economic theory meets and unites with psychological correlates, is interested in how people

behave in reality rather than what an idealized *"rational"* person would do. For example, in 1999 Bickel et al. (79) empirically showed that the temporal discounting of real-life nicotine addicts is better approximated by a hyperbolic function, rather than by a traditional exponential function. In fact, a smoker discounts cigarettes more rapidly than financial rewards and, unexpectedly, a non-smoker and an ex-smoker have similar discount rates for monetary rewards (79).

More recently, the integration of behavioral economics together with correlates of neuroscience originated the field of neuroeconomics. In 2005, Bechara suggested that addiction is

> *"... the product of an imbalance between two separate, but interacting, neural systems that control decision making: an impulsive, amygdala system for signaling pain or pleasure of immediate prospects, and a reflective, prefrontal cortex system for signaling pain or pleasure of future prospects"* (80).

According to this view, denoted as the *"competing brain regions hypothesis"* (75), the consumption of an addictive drug induces an increase in the activity of the impulsive system and a decrease in the activity of the reflective system. The addict's temporal discounting of the addictive drug and, as a consequence, the addict's substance consumption rate are influenced by the interaction of these systems (75).

3.3 Quantitative pharmacological models

Pharmacological models of drug addiction consist of a pharmacokinetic (PK) unit and a pharmacodynamic (PD) unit. PK/PD models are mainly applied to cocaine self-administration. As expressed by Holford and Sheiner, the first component characterizes *"what the body does to the drug"*, whereas the latter component delineates *"what the drug does to the body"* (81). The PK component is relevant when the relationships between the drug's concentration and effects are known, whereas the PD component is pertinent for a constant concentration of the drug since it does not consider the temporal factor within the concentration-effects relationships (82). More specifically:

- The PK module delineates the evolution of drug concentrations in the brain over time using an open model[6] composed of a central or blood compartment and a peripheral or brain compartment (83);
- The PD component describes the facilitation of the reward system's gain using the inhibitory maximal effect (E_{max}) model which describes the drug's effects in terms of the it's concentration (84).

One of the earliest quantitative pharmacological models of cocaine self-administration, presented in 1999, predicts the PK and PD of drug self-administration in rats (85). The main conclusion of this study concerned how rats cease cocaine use when the substance concentration is maintained above the

[6] In a PK/PD open model the animal's body is considered as a unique homogeneous agent which absorbs the substance instantaneously and eliminates it as time passes.

satiety threshold. In particular, a rat will no longer undergo cocaine self-administration when its inner drug concentration is at a certain level (86).

A more recent PK/PD model from 2000 also incorporated the *theory of receptors* dating from the early 1900s (87). This model describes the pertinent endogenous chemical signaling, more specifically, the receptor pharmacology and the timing properties characterizing them (88).

A more comprehensive quantitative model of cocaine self-administration further developed the allostatic framework, discussed in Chapter 2, by proposing a PK/PD model that accounts for the correlation between compulsive drug intake and a chronically deviated baseline reward threshold in laboratory rats (37). Simulations based upon this framework successfully replicate patterns of intravenous cocaine self-administration observed in laboratory rats. More details of this PK/PD model, presented by Ahmed and Koob in 2005 (37), are discussed in Chapter 6.

3.4 Abstract models of dopamine functions

Dopaminergic models of addiction are derived from the artificial intelligence paradigm, presented by Sutton and Barto (89), known as temporal difference reinforcement learning (TDRL). The main objective with this family of models is to characterize the functioning of dopamine in the brain.

The TDRL framework (89), inspired by behavioral psychology, aids an artificial agent in learning to maximize a numerical reward signal in a given

environment. The *temporal difference* component drives the learning process of the agent by relying on the difference of consecutive predictions of reward related to the agent's environment (90). In such models, an autonomous intelligent agent learns from experience how to select actions in order to maximize future rewards. The agent's decision-making process for action selection is based upon the strength of the predicted future reward discounted by the expected time to the reward (89,90).

In 1986, Schultz (91) recorded the activation of dopaminergic neurons of a monkey in three different settings: (i) the animal is not trained and is provided with an unexpected reward; (ii) the animal is trained to receive a reward after a previously activated cue (e.g., visual or auditory stimulus); and (iii) the trained animal is presented with the activation cue but receives no reward. Barto (92) and Houk et al. (93) proposed in 1995 a model based on TDRL in which dopamine encodes prediction errors. In particular, the experimental results of Schultz (91) demonstrated that: (i) dopaminergic neurons strongly activate when the monkey receives an unexpected reward; (ii) when the primate has learned that a visual or auditory cue is precursor of an upcoming reward, dopaminergic neurons fire when the cue is presented to the animal instead of when the reward is received; and (iii) the dopaminergic neurons of a trained animal presented with the learned cue are inactive when the expected reward becomes available.

Barto (92) and Houk et al. (93) presented the first instance of this model's class in terms of a particular TDRL architecture, called the Actor-Critic

architecture, to computationally describe dopaminergic neurons in the basal ganglia. The Actor-Critic framework relates to an agent composed by two components: the Actor, which controls the agent's actions in relation to its environment; and the Critic, which provides the Actor with evaluative feedback about the undertaken actions (92). In 1996-97, Montague et al. (94) and Schultz et al. (95) also proposed a computational model where dopamine acts as a *"predictive reward signal"* (96), while using a slightly different TDRL architecture than the one previously proposed by Barto (92).

The investigations presented in (92,93) and (95) emphasize how the firing rates of dopamine neurons in the midbrain mimic the error term of the TDRL framework. The TD error notifies the computational agent about the difference between the expected and the actual reward. These studies suggest that the phasic activity of dopaminergic neurons within the animal's neural substrate code the internal representation of the monkey's reward prediction errors. A predicted reward that has a higher or lower value than expected drives the policy revision of the agent. This, in turn, translates to the monkey thereby changing the strategy for the next actions.

In 2004, Redish presented a computational model of cocaine addiction based on a modified TDRL framework (97). The effects of the substance are simulated by a synthetic positive signal that relates to the dopamine increase experienced by the subject after a drug intake. The introduction of such synthetic signal as part of the TD error function prevents the predicted and actual rewards

from being equal, and therefore precludes the agent from learning a policy other than taking the drug. In other words, this model just eliminates negative prediction errors. In such context, addiction is described as a monotonic process which prevents recovery. Experimental results published in 2007 by Panlilio et al. (98) refute Redish's hypothesis that each drug intake leads to a reward larger than the expected reward for that intake.

A subsequent study by Dezfouli et al. (99) reports in 2009 a TDRL framework which employs an average reward algorithm (100) and does not consider addiction as a monotonic process towards drug use. The unlearning of seeking behavior is tackled, but the model cannot describe reinstatement.[7] As pointed out by the authors, the model's validation through experimental data remains difficult because of its theoretical nature.

3.5 Knowledge repository models

The top-down approaches of the epidemiological and economic models and the bottom-up approaches of the pharmacological and dopaminergic models are not, by themselves, sufficient to create a computational framework which comprehensively describes the addiction process. The former relies on psycho-social factors that affect the addictive behavior of a population, whereas the latter focus on physiological and neurological evidence to understand the process of addiction. The common interest of both approaches is to understand animal

[7] Reinstatement may be the homolog of the human experience of relapse.

behavior (human, primate, or rodent) related to substance use and abuse. A new family of biologically plausible models has recently emerged, named knowledge repository (KR) models, which attempts to describe drug addiction as comprehensively as possible (101).

Bobashev et al. (101) first expressed this view in their summary of the *2006 College on Problems of Drug Dependence workshop*. The objective of a KR model is to amalgamate findings obtained from investigations that focus on different scales of observation to advance a comprehensive understanding of substance addiction. The exemplification of a KR model of addiction described by the authors embraces a wide variety of different factors (e.g., socioeconomic components, interpersonal relationships, life-changing events, presence of chronic diseases, physiological and cognitive features, etc.) which may be correlated in order to simulate plausible behavioral trajectories that illustrate archetypal patterns of drug use and misuse (e.g., initiation and escalation of drug use, recovery, relapse, etc.). The principal characteristic of a KR model resides in the consideration of a multi-scale standpoint that corresponds to a conceptual framework that is increasingly supported by the scientific community studying addiction (60,102).

In 2006, Gutkin et al. (103) present the first KR model for nicotine addiction, which describes the acquisition and maintenance of drug-taking behavior by means of two modules: one that characterizes action-selection, and another that describes the signaling of receptors of dopaminergic neurons. The

major hypothesis is that dopaminergic neurons of the ventral tegmental area (VTA) are affected by nicotine, which initiates molecular changes in the glutamate-based learning process within the dorsal striatum. In other words, nicotine in the VTA acts as a multiplier of the dopaminergic neural signaling that evaluates a reward related to substance intake. This evaluation modulates the synaptic plasticity in the dorsal striatum area through glutamate neurons modeled as a stochastic winner-take-all network which regulates the actual action of nicotine self-administration. This investigation also integrates a dopamine-dependent learning rule differentiating between phasic and tonic dopamine neurotransmissions (103).

With respect to the abstract models of dopamine functions discussed in Section 3.4, this KR model is relatively similar in terms of neural correlates that are modeled, but differs in the computational tools used to describe the system. Abstract models of dopamine function deploy the computational paradigm of TDRL where the correspondences between mathematical parameters and biological means are not always recognized. Instead, KR models as the one discussed above use *ad hoc* dynamical systems, where the biological processes of interest are translated into mathematical language.

The KR model of Gutkin et al. (103) was later discussed in terms of how nicotine and the neurotransmitter acetylcholine impact the addictive process by combining the neural dynamics of the VTA with the activities of specific nicotinic ACh receptor subtypes (104). This investigation suggested furthering the

exploration of nicotinic acetylcholine receptor mechanisms that are influenced by nicotine and, in turn, alter the dynamic properties of the reward neural circuitry (104).

In terms of the scales of observation presented in Figure 1, and as shown in Figure 3, the KR model for nicotine addiction discussed above (103) includes neuropsychological and behavioral elements (63). The former layer takes into account how dopaminergic signals from the ventral pathway influence the glutamatergic learning processes in the dorsal striatal structures of the brain (103) and combines the neural dynamics of the VTA with the activities of specific nicotinic ACh receptor subtypes (104). The latter layer is a stochastic function contingent on the neural activity of the considered brain areas (103).

The multi-layer approach of KR models may provide pertinent insight for the interdisciplinary study of addiction. Health care professionals, sociologists, psychologists, pharmacologists, physiologists, etc. can use such models to computationally evaluate new hypotheses based on their own expertise, while taking into account state-of-the-art knowledge from other domains.

In 2008, a review relying on a system biology perspective emphasized the possible impact that formal frameworks might provide to the study of mental disorders (61). This survey discussed how the relationship between empirical and formal methods could be enhanced; presented modeling approaches that should be considered; reviewed software that may ease formal translations; identified signal pathways within the neural and molecular scales; and concluded

that a better understanding of mental disorders linking the molecular level to the whole system may be achieved by adopting a formal standpoint.

In 2009, the same venue published a review by Tretter et al. (102) discussing from a systems biology standpoint the onset of addiction while considering three scales of observations: behavior, the brain's networks connectivity, and molecules inside the brain's cells. The authors formally assessed these distinct levels by providing biological architectures of their structures and exploratory mathematical formulations of their dynamics. Moreover, the authors proposed a skeleton for a qualitative view of the brain to include these three scales of observations and predict drug consumption patterns.

3.6 Relations to the model advanced in this dissertation

This section describes how the computational model at the center of this dissertation relates to the five categories of models shown in Figure 3 and discussed in the present chapter.

Epidemiological models. Epidemiological models are more pertinent to the field of Public Heath than the KR model presented in this dissertation, and they can be helpful in making decisions about regulations related to drug use and abuse (e.g., laws, taxes, etc.). These models aim to describe how addiction spreads within a population, whereas the model presented in this dissertation is

intended to describe the processes that drive an individual to abuse an addictive substance.

A significant difference between these two types of modes resides in the characterization of an individual. Epidemiological models generally assume uniform drug vulnerability within the population, whereas the computational model presented in this dissertation includes a large number of parameters which can describe a large variety of virtual subjects. This difference underlies the broad conclusions of the studies discussed in Section 3.1 (e.g., prevention is better than cure).

Epidemiological models consider two of the four scales of observations encompassed in the KR model presented in this dissertation: the behavioral and the recovery scales.

Economic models. Conventional economic models of addiction treat drug consumption as a rational or irrational behavior, and provide important insight into how price, opportunity cost, and income influence substance abuse. These models mainly consider that an addict's aim is to maximize hedonic reward.

The main difference between these models and the model at the center of this dissertation relates to economic factors. In the model presented here they are not explicitly taken into consideration but instead they are more broadly considered by means of a process describing influences that social rules have on individual behavior.

Conventional economic models consider two of the four scales of observations considered in the KR model discussed in this dissertation: behavioral and cognitive. Recently, the neuroeconomics community started to join conventional economics and abstract models of dopamine functions in order to better understand decision-making processes. This will eventually enhance economic models with a neuropsychological and a recovery scale.

Quantitative pharmacological models. PK/PD models arise from the field of clinical pharmacology and aim to understand the effects of a drug with respect of specific dosing regimens. This family of models is centered on the cellular level of an organism. As such, PD/PK models describe how different concentrations of a pharmaceutical drug influences an organism.

The main contribution of this dissertation is based on the connection of a KR and a PK/PD model of addiction. In particular, the computational hypothesis for allostasis presented in Chapter 6 is crafted by integrating the multiscale model of addiction discussed in Chapters 4 and 5, together with the PK/PD animal model of addiction presented by Ahmed and Koob (37). The study presented in Chapter 6 connects a KR and a pharmacological model of addiction, while providing testable hypotheses about how to increase the success rates of current addiction treatments in humans.

Pharmacological models of drug addiction generally consider two of the four scales of observations included in the model advanced in this dissertation: neuropsychology and cognition.

Abstract models of dopamine functions. The family of abstract dopamine models is valuable for proposing testable hypotheses about dopaminergic structures and functions within the brain. Dopaminergic models use practical implementations of the TDRL paradigm to match experimental observations related to dopamine.

The main challenge for these models is to create a connection between computational theory and real brain systems. In particular, TDRL frameworks are used to describe dopaminergic functions in the animal brain, but some of the involved computational parameters still require a clear correspondence with real brain correlates. Moreover, these models are exclusively based on the neurotransmitter dopamine, which has a significant role in the process of addiction but is not the only involved compound.

The KR model discussed in this dissertation takes into account the influence of dopamine in the process of addiction, while integrating additional factors which are significant for a more comprehensive understanding of this disease. The KR model discussed herein does not include a TDRL apparatus. Nonetheless, a possible location where the discussed KR model can be united with dopaminergic models is indicated in Chapter 6.

Abstract models of dopamine functions encompass two of the four scales of observations considered in the KR model discussed in this dissertation: neuropsychology and recovery. As mentioned earlier, recent neuroeconomics studies combine dopaminergic models with conventional economic models, and

will eventually enhance dopaminergic models with a behavioral and cognitive scale.

Knowledge repository models. The model at the center of this dissertation is a KR model aiming to describe drug use and abuse by integrating within the same formal framework multiple layers of observations. With respect to the foundational KR model by Gutkin et al. (103), which includes studies of neuropsychology and behavior, the model presented in this dissertation encompasses the four scales of observations discussed in Chapter 1, namely: neuropsychological, cognitive, behavioral, and recovery scales.

CHAPTER 4

FIVE-STEPS TOWARD A COMPUTATIONAL MODEL

The formal framework advanced in this dissertation is, in terms of Bobashev et al. (101), a knowledge repository (KR) model of addiction. The proposed computational framework integrates into a unique apparatus four different scales of observations to provide a more comprehensive view of drug addiction, as illustrated in Figure 4. The neuropsychological scale relies on quantitative studies of neural processes involved in addiction; the cognitive scale is a computational hypothesis whose rationale is endorsed by experimental findings; and the behavioral scale relies on quantitative observations about neural development, on established theories about addiction, and on the possible impact that social rules may have on addictive behaviors. The recovery scale is a biological speculation that may be supported by the empirical observations discussed in Chapter 1, known as *maturing out of addiction* (22) or as *natural recoveries* (105,20), which are remission instances from abusive drug consumption that occur without any behavioral or pharmacological interventions and that are so far unexplained.

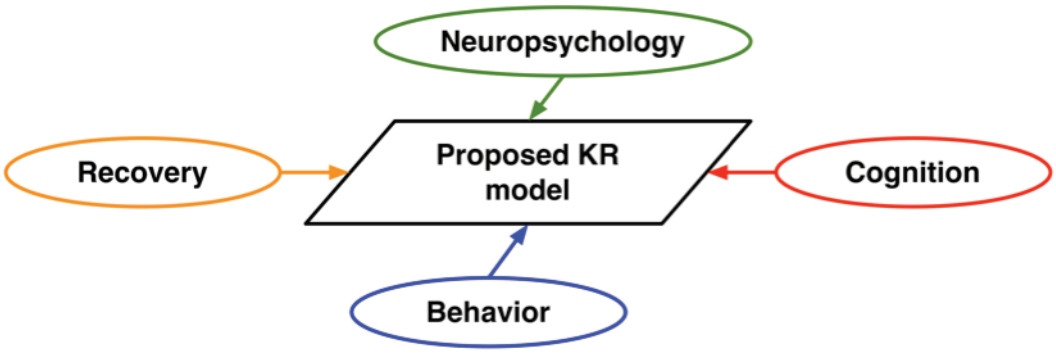

Figure 4: The knowledge repository (KR) model presented in this dissertation takes into account the four scales of observations, namely neuropsychology, cognition, behavior, and recovery.

In terms of modeling and simulation theory, these four scales of observations outline the experimental frame of the model. Zeigler et al. (33) define the experimental frame as a collection of data of interest and against which model validity will be examined.

The computational model advanced in this dissertation intends to describe drug addiction as the aggregate of the relevant collection of data outlined by Levy[5] and Siegelmann (27), and elaborated by Levy et al. (29,32,38): neural activities resulting from drug use; the mediation of mental processes converting these activities into decision-making; the related sociocultural and educational influences; and the intervention of rehabilitative means.

This chapter outlines the five steps undertaken with the objective of providing a simulator capable of predicting archetypal instances of observations contained in the experimental frame. The five steps are formalization, demonstration of expandability, qualitative validation, analysis of dynamics, and sensitivity analysis. This formal course of action results in a framework

appropriate for the comprehensive study of addiction aiming to encourage hypothesis-driven research. Within this line of research, in Chapter 5 is presented an exploratory hypothesis relating the brain's cognitive mechanisms to natural recoveries. Furthermore, and aiming to support translational research for drug addiction, in Chapter 6 are studied the connections between the allostatic theory of addiction (presented in Chapter 2) and current practices of rehabilitation.

4.1 Formalization of the biology underlying addiction

This initial step includes the creation of the conceptual diagram describing the model, the development of mathematical definitions characterizing it, and their implementation within a computational framework.

The formalization phase is intended to present the system architecture with the relevant processes classified according to four scales of observation: neuropsychology, cognition, behavior, and recovery. This step facilitates the initiation of the mathematical definitions of the model's processes and their implementation within a computational framework, while easing communication among the multidisciplinary community for which this research is intended.

In the natural world, the processes subject to modeling operate in continuous time. During the formalization phase these natural processes are each mathematically approximated by discrete time functions, such as functions of a discrete variable geometrically increasing or decreasing; functions of a

discrete variable with decreasing values throughout activation. These functions are defined largely through weighted sums and sigmoid functions. These mathematical definitions are crafted to restrain the model's parameter search space while allowing a large diversity of dynamics to arise. In addition, parameter values are constrained to biological data to the extent possible.

During the formalization process, a basic learning rule inspired by the weights adaptation of a perceptron was proposed and demonstrated to be a necessary condition for making this framework effective in the emulation of a recovery process. These learning rules and demonstrations are discussed in Chapter 5 and in (32).

A KR model of addiction was established which includes four scales of observation. The outcomes of the formalization phase are detailed in (28,30); in Chapters 5 and 6 of this dissertation, which include conceptual diagrams; and in Appendix A, which includes mathematical definitions.

4.2 Demonstration of expandability

Expandability is an important feature of a model if its plausibility is to be improved over time. Practically any biological entity can be observed at different scales of observation. For example, the study of an organism's nervous system includes granularities ranging from units of angstrom to meter (30). Any level of observation is potentially a pertinent source of knowledge towards a more accurate description of the studied system. Moreover, expandability is a suitable

property for a computational model prepared to include new scientific insights without compromising the whole framework underlying the model.

> ***Hypothesis:*** *the presented KR computational model of addiction is expandable in terms of the levels of observation defining it.*

Levy[5] and Siegelmann (27) considered as constant two main processes of their model: inhibition and compulsion. To strengthen the model's rationale, the present model extends these constant signals into dynamical processes. The inhibition process is defined to include social and developmental factors, and the compulsion process is designed to mimic the incentive-sensitization theory of addiction.

This contribution demonstrates the model's expandability in terms of its levels of observations and further incorporates additional biological details. The evaluation of this expansion is immediate: on the one hand, the non-monotonic and relapse properties of the systems are preserved; on the other hand, these expansions allow characterizing virtual subjects of different ages and living in various environments. This expansion was presented by Levy et al. (29).

An additional demonstration of expansion is presented in (38) and in Chapter 6, where the integration of a pharmacokinetic/pharmacodynamic module into the model increases its scope without compromising the framework.

The hypothesis of the model's expandability was demonstrated. The discussed model's elaborations augment the computational description of

addiction toward a more comprehensive portrayal, while verifying that pre- and post- expansion outcomes are consistent with each other.

4.3 Qualitative validation

As described by Zeigler et al. (33), the validation step requires a significant correspondence between experimental data and computational simulations. Usually, a computational model of a biological system is designed to mimic a specific set of data that are measured in a particular experimental frame.

The computational model at the center of this dissertation relies on qualitative descriptions of processes defining addiction. These descriptions are grounded on animal studies, human observations, or even common sense. A classical quantitative validation is not suitable because the model is meant to mimic behavioral trajectories of a virtual human subject by integrating a multitude of features characterizing addictive drug use and abuse rather than, for example, to precisely correlate firing frequencies and responsiveness of neurons within a particular area of a particular brain.

Qualitative processes included in the discussed model include the level of negative consequences (or pain), the negative emotional state (or stress), current craving for the drug, the saliency of drug cues, as well as several external triggers such as sudden traumas, strong stressful events, drug priming, and acute cues (106), which details are presented by Levy et al. (29,32,38).

Hypothesis: *the KR model of addiction presented in this investigation is qualitatively valid for a useful range of human behaviors.*

Within this context, the validation of the present model relies on qualitative and rational arguments which emphasize the model's ability to mimic real-life patterns of behavior related to substance use and abuse. Preliminary qualitative validations were presented in (29,30) while considering limited drug consumption and relapse. Simulations of archetypal behavioral patterns of drug consumption such as escalation of drug use; conventional treatments (e.g., nicotine patches for smoking); and alternative medical cures (e.g., meditation) are discussed in Chapters 5 and 6 of this dissertation, and presented in (32,38).

The validity hypothesis is problematic to prove because of the high-dimensionality of the computational model and its large number of parameters. The simulations provided in Chapters 5 and 6 account for a demonstration of validity by providing appropriate simulations for representative behavioral patterns defined within the system's experimental framework.

Qualitative validation of the KR model at the center of this dissertation was demonstrated to the extent possible.

4.4 Dynamical properties analysis

The computational model at the center of this investigation considers addiction as a non-monotonic disease. In other words, the addictive state of a virtual subject described by the model is assumed to be a reversible process. In

terms of dynamical system, this assumption considers the existence of an addictive state able to evolve into a healthy state as a consequence of a slight perturbation of the system. More specifically, the addictive state described by the model should not be an attractor. A dynamical system analysis of the model's output could reveal otherwise.

> ***Hypothesis:*** *the KR model of addiction presented in this investigation is able to describe non-monotonic cases of addiction.*

In the analysis conducted in (30), no steady states were found in simulations related to behavioral patterns of drug consumption. Also no evidence was found which attests to the existence of fixed points in the trajectory of the model's output.

A deeper analysis of these simulations suggests that the processes defining the neuropsychological scale of the model do not prevent the addicted virtual subject from regaining a healthy behavioral state. These analyses demonstrate that a less-healthy virtual subject (i.e., an agent more likely to consume drugs) expresses fewer fluctuations and less flexibility in drug-seeking behavior than a more-healthy virtual subject (i.e., an agent less prone to drug intake). The dynamical analysis step presented in (30) supports the possibility of a computational intervention that simulates rehabilitation, as discussed by Siegelmann et al. (28), and by Levy et al. (32,107).

The proposed KR model of addiction was shown to be able to describe non-monotonic cases of addiction.

4.5 Sensitivity analysis

During the framework's formalization step, the mathematical definitions of the processes were crafted to minimize the number of parameters, while allowing the simulation to mimic a variety of behavioral profiles. Nevertheless, the number of the model's parameters is large. Many of these parameters arise from mathematical constraints rather than from natural observations. The effect of such parameter on the model's output should be analyzed in order to avoid the framework's corruption.

Sensitivity analysis was applied to identify such possible parameters. A suitable technique was found in a one-factor-at-a-time (OAT) analysis, where all the parameters are methodically examined for different values to understand how they affect the model's output (108). A classical OAT approach necessitates systematically testing one parameter against the others. Given the large number of parameters employed in the model's formal description, such approach would have consumed excessive resources. Aiming to optimize resources while taking advantage of the classical OAT procedure, the model's mathematical features were examined with respect to the natural processes they are meant to describe. For example, the parameters defining the geometrically increasing or decreasing processes within the model are intended to describe real-life features which have different rates of change for different nonfictional subjects. Because these functions are bounded, the values of their parameters are not undermining the

framework's dynamics toward a particular outcome. In other words, and as shown in Figure 5 and detailed in (31), the framework's structure was analyzed while simultaneously considering both the phenomenological and mathematical properties of the model, to identify possible sources of destabilization. Such structural analysis recognized one potentially problematic parameter, which may bias the virtual subject toward an unchanging behavioral trajectory: to always or to never consume the substance.

To avoid this bias, a safe set of possible values for this potentially problematic parameter was proposed in form of a function dependent upon other pertinent parameters of the model. To test such functional control, several simulations were undertaken with different values of this potentially problematic parameter, and the corresponding outputs were analyzed (31).

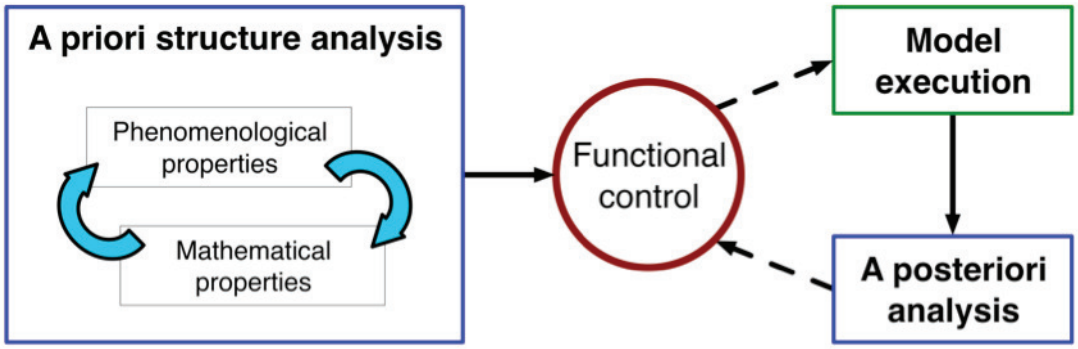

Figure 5: Prior to execution, the model's phenomenological and mathematical inter-correlations were analyzed, and when necessary a functional control was crafted and refined by analysis of the model's output. Modified from (31).

In more detail, the majority of processes within the neuropsychological and behavioral scales of the model are exponential functions that are explicitly restricted to remain within a bounded interval (e.g., [0,1]) and include a number of parameters defining their rates of change. These processes are not inclined to destabilize the framework's output even though increasing or decreasing at different paces.

A hyperbolic tangent function is used within the cognitive scale to scale a process into a specific interval (e.g., [–1,1]). This hyperbolic tangent includes a parameter which is a mathematical requisite rather than a biologically inspired component. Algebraic analysis of this particular parameter shows that, under defined conditions, the virtual subject's state could become biased toward a consistent drug consumption or abstinence. This issue was discussed in (31), where it was shown that the introduction of a functional control can limit the model's bias toward a particular behavior of the virtual subject.

The objective of identificating sensible parameter values was attained, and the possible control for such parameter values was demonstrated. The details of the sensitivity analysis are presented by Levy et al. (31).

4.6 Concluding remarks

The five-step procedure described in the present chapter generates a computational framework whose features may be pertinent to hypothesis-driven research about substance use and abuse. The computational definitions of the

processes composing the model are reported in Appendix A of this dissertation. The biological descriptions of these processes are reported in (29,32,38) and in Chapters 5 and 6 of this dissertation.

In particular, Chapter 5 presents a computational speculation about maturing out of addiction, whereas Chapter 6 provides plausible insight about addiction by further elaborating the model to include two theories discussed in Chapter 2: the allostatic model and the impaired response inhibition and salience attribution model.

CHAPTER 5

HYPOTHESIS-DRIVEN FRAMEWORK FOR MATURING OUT

The computational model resulting from the five-step procedure discussed in Chapter 4 is presented and deployed in this chapter. The aim of this contribution is to provide a theoretical and biologically plausible computational description for the unexplained phenomenon of maturing out of addiction (22).

Most of this chapter reports the investigation discussed in (32)*.*

5.1 A Multiscale Model of Addiction

In this chapter, a systemic model is advanced, as shown in Figure 6, which aims to characterize the comportment of a human through its tendency toward drug-seeking behavior. This computational framework was defined and qualitatively validated (29), its dynamics and sensitivity were analyzed (30,31), and its recovery scale initiated (28).

The model shown in Figure 6 comprises neuropsychological, recovery, cognitive, and behavioral elements. The neuropsychological scale incorporates internal and external processes describing the neural ongoing activity that depends on time t (in hours). Internal processes include the level of negative consequences such as poor health or social relations, $P(t)$, the level of negative emotional state, $S(t)$, the level of drug craving, $D(t)$, and the saliency of drug-

associated cues, $Q(t)$. The external processes characterize sudden experiences that, when activated, instantly influence the subject's neural activity. These are: drug-associated cues, $A_Q(t)$, that may be triggered by an event such as visiting a *drug buddy*; painful traumas, $A_P(t)$, that may cause an addict to stop taking drugs immediately for a period of time; strong stressful episodes, $A_S(t)$, that may lead a former addict into immediate drug-use; and drug priming, $A_D(t)$, such as social drinking, that may bring the virtual subject into drug-use again. The output of the model, $G(t)$, depends on both internal and external processes. The process $G(t)$ defines a feedback loop to the neuropsychological scale. The behavioral scale includes the model's output $G(t)$, which is a qualitative evaluation of a virtual subject's tendency for drug-seeking, and arises from the antagonism between inhibitory and compulsory elements. Negative values of $G(t)$ correspond to maladaptive behavior, whereas positive ones account for healthy behavior. For the sake of clarity, the processes of inhibition and compulsion are considered constants even though explicit time dependencies of these processes were previously defined (29).

The cognitive scale complies with the definition by Bourgine and Stewart:

> *"A system is cognitive if and only if sensory inputs serve to trigger actions in a specific way, so as to satisfy a viability constraint"* (109).

This scale is established as a mediator between low and high level of behavioral control. In a perceptron-like architecture, the neuropsychological processes are weighted and integrated to define the degree of rationality, $rd(t)$,

which drives the virtual subject's cognitive state, $cs(t)$, toward a more inhibited or a more compulsive behavior. The recovery scale is a computational hypothesis which relies on the definition of natural recovery, for which the addict ceases using the drug *"without the help of treatment intervention"* (105), suggesting a recovery process solely impacting the cognitive scale (no pharmacological or behavioral interventions). The recovery process is designated as a sudden cognitive change which, when induced, makes achievable a drug abstinence period that may or may not endure. The recovery scale affects the virtual subject's cognitive state by two mechanisms: a direct intervention on the virtual subject's rationality estimation, and a modulation of the internal and external processes weights. The second mechanism can endure and aims to emulate cognitive learning (i.e., the neural plasticity in the prefrontal cortex). In the next section are presented the formal descriptions of the cognitive and recovery scales. Computational definitions of the neuropsychological and behavioral scales are reported in (29) and in Appendix A.

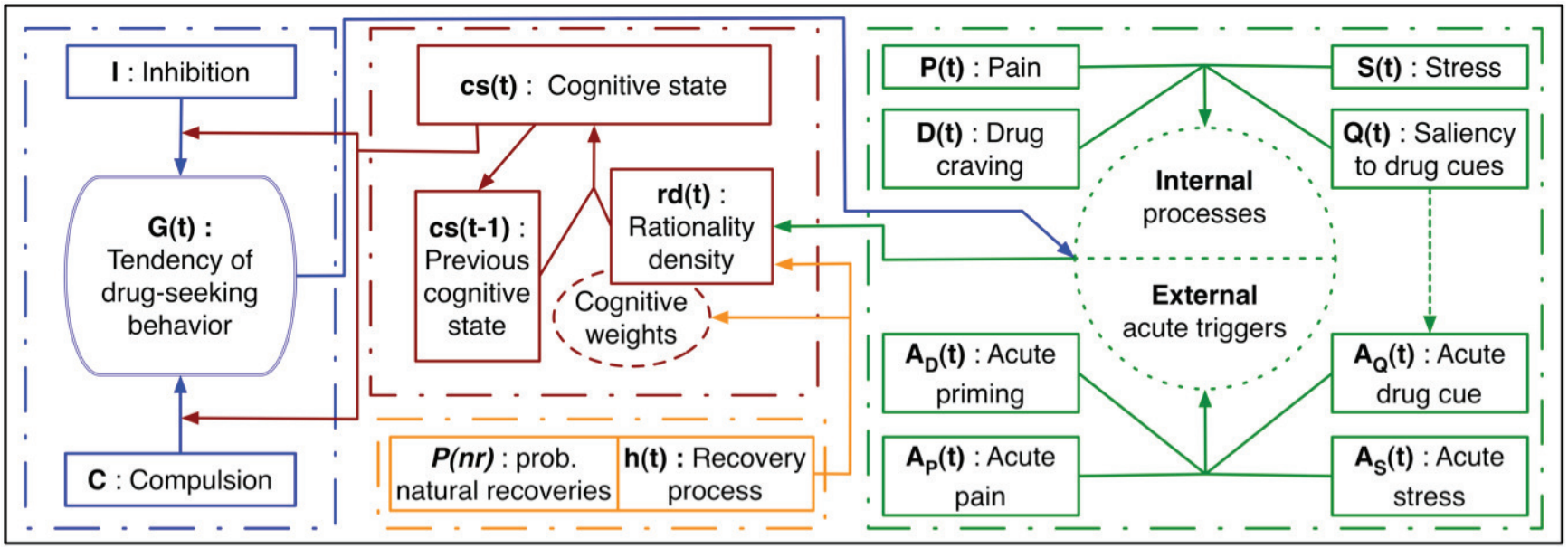

Figure 6: Diagram of the computational model, where the output of the model $G(t)$ represents the tendency for drug-seeking behavior. The levels of observations represented include the neuropsychological scale in green, the recovery scale in orange, the cognitive scale in red, and the behavioral scale in blue.

5.2 Methods

This section presents the details of the cognitive and recovery scales, as well as the data used to emulate instances of the recovery process.

The rationality density, $rd(t)$, is defined as a weighted sum of the neuropsychological and recovery processes:

$$\begin{aligned} rd(t) = \quad & \omega_S(t)\cdot S(t) + \omega_P(t)\cdot P(t) + \omega_D(t)\cdot D(t) + \\ & + \omega_{AS}\cdot A_S(t) + \omega_{AP}\cdot A_P(t) + \omega_{AD}\cdot A_D(t) + \\ & + Q(t)\cdot A_Q(t) + \omega_h \cdot h(t). \end{aligned} \qquad \text{Eq. 1}$$

The weights ω for the processes $P(t)$ and $A_P(t)$ are in $\mathbb{R}^+$, whereas the other weights are in $\mathbb{R}^-$. This rationality estimate drives the cognitive state of the virtual subject, $cs(t)$:

$$cs(t) = \frac{1}{2}\tanh\left(\alpha\cdot cs(t-1) + \beta\cdot rd(t) + \gamma\right) + \frac{1}{2}, \qquad \text{Eq. 2}$$

where of α, β, and γ are constants and the model's sensitivity to their values is discussed in (31).

The recovery process, $h(t)$, equals 1 if it is active, and 0 otherwise. The active state of the recovery process is determined by *trigger events* that occur at any time step t with a probability that depends on the subject's age, together with a *duration process* that determines the active state's duration once triggered.

Letting $te(t)$ indicate the presence or absence of a trigger event at time step t (in hours):

$$te(t) = \begin{cases} 1 & \text{with probability } p(T) \\ 0 & \text{otherwise,} \end{cases} \qquad \text{Eq. 3}$$

where $p(T)$ depends on the subject's age T (in years) according to Equation 8 that is a smooth fit to the discrete data in Table 1.

The duration process, $d(t)$, accumulates trigger events by being increased by a positive constant, δ, whenever there is a trigger event, i.e., whenever $te(t) = 1$, and otherwise being decremented by 1 but bounded below by 0:

$$d(t+1) = \begin{cases} \delta \cdot d(t) & \text{if } te(t) = 1 \\ \max\left(0,\ d(t) - 1\right) & \text{otherwise.} \end{cases} \qquad \text{Eq. 4}$$

Given this, the recovery process is active whenever $d(t)$ is non-zero:

$$h(t) = \begin{cases} 1 & \text{if } d(t) > 0 \\ 0 & \text{otherwise.} \end{cases} \qquad \text{Eq. 5}$$

The effect of this is that if one assumes that at initial time t_0, $d(t_0) = 0$, then the recovery process becomes active upon the first occurrence of a trigger event and remains active for δ time steps after that, unless other trigger events occur while it is active, in which case the duration is increased by δ for each trigger event.[8]

[8] The author thanks A. G. Barto for his help with this formal description.

When a recovery process arises, it influences $rd(t)$ through two mechanisms. On the one hand, $h(t)$ has a direct effect on $rd(t)$ as defined in Equation 1. On the other hand, the cognitive weights ω of the processes $P(t)$, $S(t)$, and $D(t)$ provisionally change their values according to the relationship:

$$\omega(t) = \begin{cases} \kappa + \Delta & \text{if } h(t) = 1 \\ \kappa & \text{otherwise,} \end{cases} \qquad \text{Eq. 6}$$

where Δ is in $\mathbb{R}^-$ for $S(t)$ and $D(t)$, and in $\mathbb{R}^+$ for $P(t)$.

At the last active time step of a recovery process, $h(t)$, the temporary effect on ω of processes $P(t)$, $S(t)$, and $D(t)$ can become permanent with arbitrary probability θ (different for the three processes):

$$\kappa(t) = \begin{cases} \kappa + \Delta & \text{if } d(t) = 1 \text{ and with probability } \theta \\ \kappa & \text{otherwise.} \end{cases} \qquad \text{Eq. 7}$$

This equation aims to mimic neural plasticity within the cognitive cortex of the virtual subject and is referred to as *cognitive learning*.

5.2.1 Probability of a recovery process $P(T)$

In 1962, Charles Winick popularized the phenomenon of maturing out of narcotics addiction, revealing cases where regular heroin and synthetic opiate abusers ceased using the substance without any psychological or pharmacological treatment (22). In 1980, Maddux and Desmond discussed the possible overestimation of Winik's statistics, and proposed further data to

increase the accuracy of the study (24). Maddux and Desmond confirmed that the trends of age distribution for withdrawal initiations were consistent in both studies, and argued the possible overestimation due to the disregard of cessation onset rates in the base addict population.

In the present investigation, data reported in (22) and (24) are combined to quantify the likelihood of a narcotic addict to undergo a *maturing out* experience. Winick based his investigation on the number of addicts reported to the Federal Bureau of Narcotics in 1955 that were not reported again during a five-year period (22). As reported in Table 1, the probability for an addict to experience a maturing out experience is inferred (fourth column in Table 1). This probability is scaled using the subsequent results by Maddux and Desmond, which report the annual rates of abstinence onset in the base population (24). For simplification purposes, the age category *"All ages"* in (24) is considered to describe the age range from 0 to 19 years old, and the category *"40-49"* to additionally include ages exceeding 49 years old. The scaled cumulative distribution function for a maturing out event to arise can be approximated in terms of the age in years T of a virtual subject as:

$$p(T) = \frac{0.02359}{1 + e^{-0.154 \cdot T + 5.037}}. \qquad \text{Eq. 8}$$

Table 1: Data about the US narcotics users population in 1955 and the related former addicts population at the end of 1959. These data are used to calculate the cumulative distribution function (CDF) describing the occurrences of maturing out from narcotics addiction, which is subsequently scaled in accordance to new observations about the onset age of abstinence in the base population. AP = Number of active addicts in total addict population; FS = Number of former addicts in sample; AOA = Annual onsets of abstinence per 1000. Columns AP, FS, and AOA are reproduced from (22,24) with permission of the United Nations Office On Drugs and Crime (UNODC).

Age	AP	FS	CDF P(FS|AP)	AOA	CDF P(FS|AP) * AOA
< 20	1743 (3.8%)	13 (0.2%)	0.75%	23	0.17‰
20-30	24343 (53.6%)	2820 (39.0%)	12.33%	21	2.59‰
30-40	14058 (31.0%)	2857 (39.5%)	32.65%	22	7.18‰
> 40	5247 (11.6%)	1544 (21.3%)	62.08%	38	23.59‰

5.3 Results: plausible scenarios of drug-seeking and maturing out

Two scenarios are presented of a virtual subject denoted as B.T, who had a healthy mental and physical development and became an addict in her early adulthood. In the first set of simulations, the weights ω of the processes $P(t)$, $S(t)$, and $D(t)$ can only change their values according to Equation 6, whereas in the second set of simulations Equation 7 also applies. The graphs reported in this section represent the mean of 100 simulations of 600 time steps (~25 days) each and their corresponding standard errors of the mean for B.T. at the age of 35.

5.3.1 Baseline simulations

The baseline scenario is presented in Figure 7, where the computed profile of B.T.'s drug seeking-behavior, $G(t)$, is not influenced either from the direct or from the indirect effects of the recovery process. In these situations, the model's output $G(t)$ is steady at negative values, corresponding to maladaptive behavior. The internal processes have stable trajectories, and only the external processes $A_P(t)$ and $A_Q(t)$ occur, since $A_S(t)$ and $A_D(t)$ can not be triggered when $G(t)$ is negative.

5.3.2 Direct Influence of the Recovery Process

According to Equation 8, a 35 year old virtual subject can be exposed to at most 5 recovery processes within the year. In more details, $p(35) = 0.0144$ which corresponds to 5.27 expected recovery events within 365 days. Figure 8 shows the graphs corresponding to the processes defining B.T.'s profile. The recovery process $h(t)$ has a direct effect solely on her cognitive scale. In other words, the weights ω of the processes $P(t)$, $S(t)$, and $D(t)$, used to estimate the cognitive state, can only temporarily change their values, during an active process $h(t)$, but are not subject to any permanent alteration. There are 4 recovery processes that occur during these simulations, at $t \in \{120, 200, 210, 420\}$, which correspond to an immediate and strong change in the model's output $G(t)$. For a limited time, B.T. expresses healthy behavior because of the new value of the weights ω. During this period, the model's output $G(t)$ becomes positive, but this sudden change does not last for a sufficient time for B.T. to acquire a permanent healthy behavior, and her maladaptive behavior regains predominance when the active effect of $h(t)$ ceases.

5.3.3 Direct and Potentially Long-Term Influences of the Recovery Process

In the previous scenario, the direct effect of the recovery process by itself is not durable enough for the whole system to acquire the necessary dynamic allowing B.T. to start a potentially long-lasting period of abstinence. The non-monotonic property of this model (30) computationally grants B.T. a possible

lifelong rehabilitation, but the values of the constants defining the model that are necessary to achieve such a condition will correspond to a situation beyond biological plausibility (e.g., an event $h(t)$ lasting several months). In the simulations presented in Figure 9, the weights ω of the processes $P(t)$, $S(t)$, and $D(t)$, can permanently change their values once the active effect of $h(t)$ ceases accordingly to Equation 7. After completing the 3rd recovery process, B.T. expresses a fragile healthy behavior (positive $G(t)$ values), which is further consolidated by the 4th recovery process. This simulation exemplifies a plausible trajectory of an addict that starts an abstinence period within a period of about one month, as a result of 4 long-lasting recovery events, as for example could correspond to instances of non-traditional healing techniques to help overcoming addiction. Instances of these techniques were discussed in the late 1970s (e.g. meditation, faith healing, holistic medicine, etc.) (110), and more recently were at the center of two issues of the journal serving the Association for Medical Education and Research in Substance Abuse (e.g. *"attentional control"*, Mindfulness-Based Cognitive Therapy, etc.) (111,112).

The simulations presented in Figures 7 and 8 show the contrast between the progressions of a virtual subject in the absence and in the presence of recovery events, respectively. In both scenarios, maladaptive behavior persists. It is only when the virtual subject's cognitive learning is active, as described in Equation 7, that the virtual subject is able to maintain healthy behavior even after recovery events dissipate.

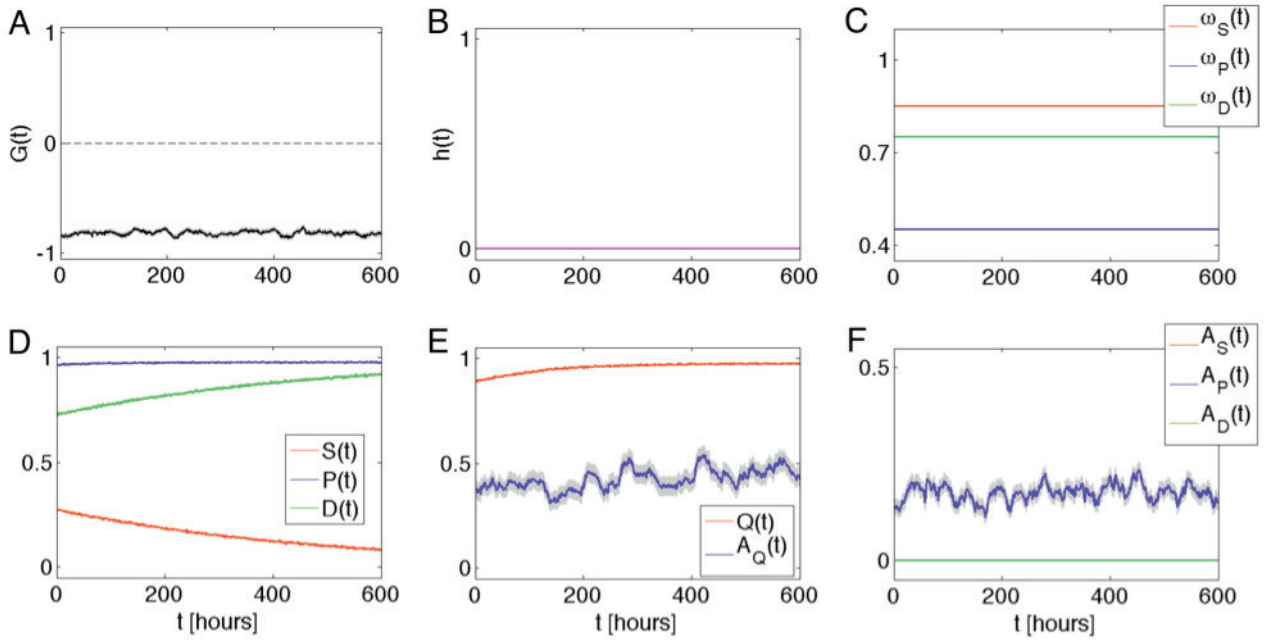

Figure 7: Mean and standard errors of the mean for 100 simulations of B.T.'s profile at 35 years old, 600 time steps long (25 days) without any effect of $h(t)$. (A) The drug-seeking behavior $G(t)$ is negative (maladaptive behavior). (B) The recovery process $h(t)$ is constantly zero. (C) The cognitive weights $\omega(t)$ are constant. (D) The internal processes $S(t)$, $P(t)$, and $D(t)$ are smooth. (E) The steady internal process $Q(t)$ and the its related external process $A_Q(t)$. (F) The external processes $A_S(t)$, $A_P(t)$, and $A_D(t)$. The processes $A_S(t)$ and $A_D(t)$ are overlapping (constantly equal to zero) since can not occur when $G(t)<0$.

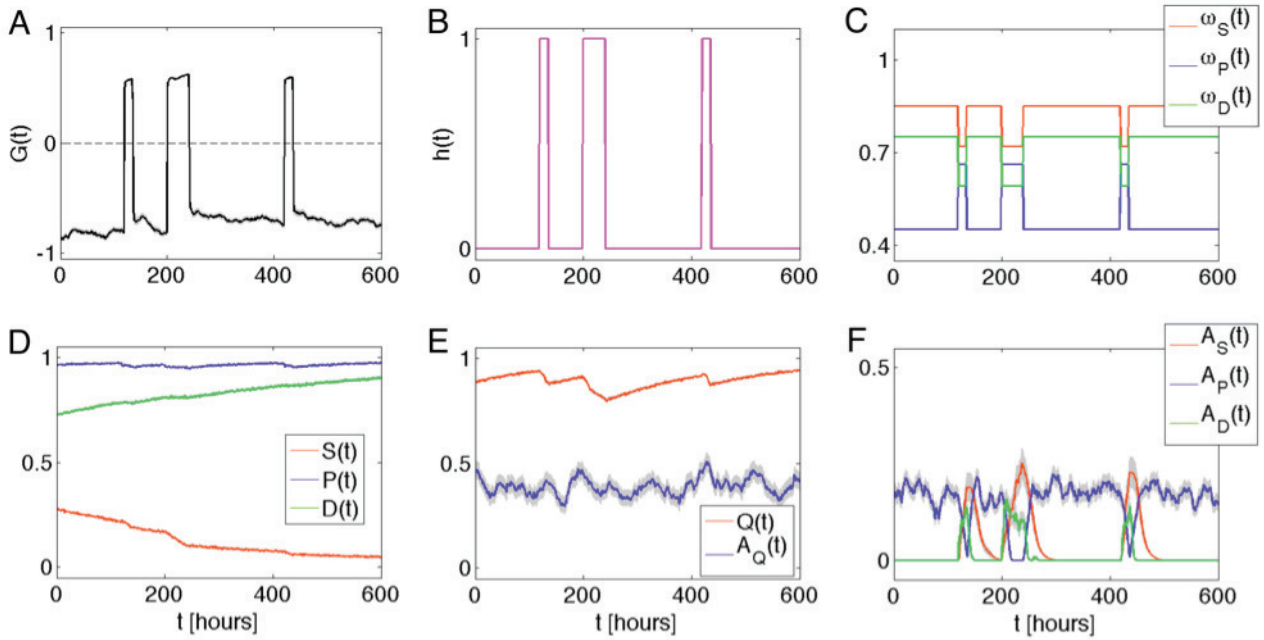

Figure 8: Mean and standard errors of the mean for 100 simulations of B.T.'s profile at 35 years old, 600 time steps long (25 days) under the direct effect of $h(t)$. (A) The drug-seeking behavior $G(t)$ is mostly negative (maladaptive behavior) and the effect of the recovery process $h(t)$ is strong enough to temporarily change it into positive (healthy behavior). (B) The recovery process $h(t)$ is activated at $t \in \{120, 200, 210, 420\}$. (C) The cognitive weights $\omega(t)$ change value when $h(t)$ is active. (D) The internal processes $S(t)$, $P(t)$, and $D(t)$ change behavior when $h(t)$ is active. (E) The internal process $Q(t)$ and the its related external process $A_Q(t)$ are influenced by $h(t)$. (F) The external processes $A_S(t)$, $A_P(t)$, and $A_D(t)$. The processes $A_S(t)$ and $A_D(t)$ occur only when $G(t)>0$, that in this scenario also corresponds to an active $h(t)$.

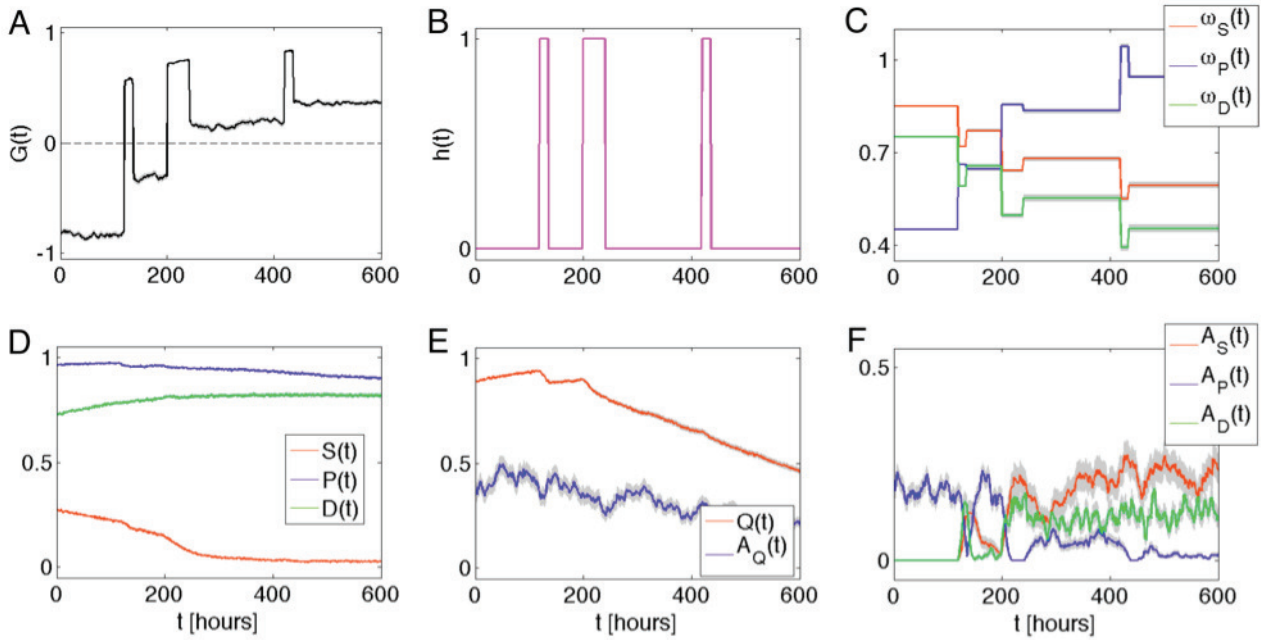

Figure 9: Mean and standard errors of the mean for 100 simulations of B.T.'s profile at 35 years old, 600 time steps long (25 days) under the effect of $h(t)$. (A) The drug-seeking behavior $G(t)$ starts as negative (maladaptive behavior) and the effect of the recovery process $h(t)$ allows its transition into positive values (healthy behavior). (B) The recovery process $h(t)$ is activated at $t \in \{120, 200, 210, 420\}$. (C) The cognitive weights $\omega(t)$ change value when $h(t)$ is active and are subject to a permanent change when an $h(t)$ event becomes inoperative. (D) The internal processes $S(t)$, $P(t)$, and $D(t)$ change behavior when $G(t)$ transition to positive values. (E) The internal process $Q(t)$ and the its related external process $A_Q(t)$ are influenced by $h(t)$ and the positive value of $G(t)$. (F) The external processes $A_S(t)$, $A_P(t)$, and $A_D(t)$.

5.4 Analysis: a cognitive learning mechanism to enable maturing out

The parameter γ in Equation 2 significantly influences the output of the model, and its value can be calculated to mathematically ensure that the virtual subject has no cognitive preference toward a particular behavior. This is exemplified in Figure 10 and detailed in (31). In Figure 10 are presented two identical virtual subjects which differ only by the magnitude of ω_P, whose values are $\omega_P = 0.55$ and $\omega_P = 0.75$ for Class 1 and Class 2, respectively. In the simulations presented in Figure 10 there is no recovery process and all weights are constant throughout the experiments. Three evaluations are presented with different values of γ, in particular, a profile biased toward maladaptive behavior ($\gamma = -1.3$), a profile biased toward healthy behavior ($\gamma = 3.3$), and a profile without prior cognitive bias (unbiased γ, $\gamma = -0.49375$). The evaluations with a biased γ express considerably less flexibility than the evaluation with the unbiased γ.

The simulations presented in this chapter show that a cognitive learning mechanism is a necessary but not sufficient condition for recovery: for some virtual subjects, cognitive interventions are successful in facilitating rehabilitation, whereas for some others they are not.

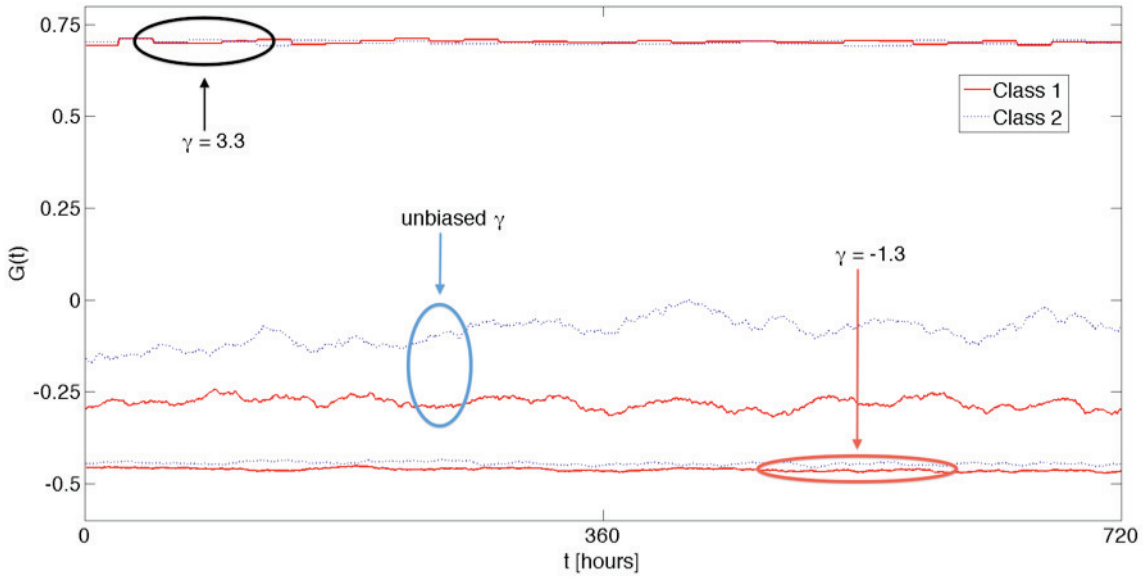

Figure 10: Simulations of a virtual subject having different cognitive inclinations. The profile biased toward maladaptive behavior has $\gamma = -1.3$, the profile biased toward healthy behavior has $\gamma = 3.3$, and the unbiased profile has $\gamma = -0.49375$. Classes 1 and 2 represents two virtual subject which have the same profile with exception the value of ω_P, which is $\omega_P = 0.55$ and $\omega_P = 0.75$, respectively. Slightly modified from (31).

Comparisons of simulations defined by an arbitrary γ with simulations using the unbiased γ, defined in (31), are presented in Figure 11. The unbiased γ ensures that the virtual subject's cognitive scale is able to range over maladaptive and healthy behaviors without becoming trapped into a particular state. The value of γ is the same for simulations presented in Figures 7-8, and the ones in Figure 9 labeled as *"B.T.'s original* γ*"*. All other parameters are equivalent for all simulations. In Figure 9 (A and D) there are no recovery processes $h(t)$; in Figure 11 (B and E) only direct influences of $h(t)$ are considered; and in Figure 11 (C and F) both Equations 6 and 7 apply. The baseline simulations presented in Figure 11 (A and D), which do not include any

recovery occurrences, show the cognitive predilection of B.T. toward a healthier behavior. B.T.'s original portrayal expresses a less accentuated likelihood of maladaptive behavior than its correspondent cognitively unbiased description. The computed behaviors involving solely the direct influence of the recovery process $h(t)$, compared in Figure 11 (B and E), describe a situation in which B.T. successfully abstains from drug use for a limited time, but the corresponding cognitively unbiased profile constantly preserves maladaptive behavior. The behavioral and neuropsychological characteristics of the subject make this abstinence difficult to preserve for B.T.'s original profile, and establish a challenging environment for her unbiased profile to reach a healthy behavior. The model's outcomes presented in Figure 11 (C and F) compare the original and unbiased profiles of B.T. when both the direct and the potentially long-term influences of the recovery process $h(t)$ are active. Both cases tend towards a healthier behavior, which is reached and maintained by the original profile but is barely touched by the unbiased profile.

The 2-D cross-correlations shown in Figure 11 D, E, and F provide an immediate look at the similarity between B.T.'s original profile and its correspondent cognitively unbiased alter ego, considering each simulation rather than the mean of several simulations. Without any recovery processes, the cross-correlation matrix has a smooth circular pattern (Figure 11D), which becomes distorted when only the local effect of the process $h(t)$ is active (Figure 11E), and substantially changes the motif for simulations operating the cognitive learning

described above (Figure 11F). These cross-correlation patterns suggest that the first and second case studies share a moderately similar dynamic, whereas they differ with respect to the dynamic of the third case study.

These results suggest that an addict may have the cognitive means to start an abstinence period which, depending on his or her neural substrate and natural surroundings, could persist over time.

The juxtaposition of the original and the unbiased profiles demonstrate that the cognitive learning mechanism discussed in this chapter is a necessary but not sufficient condition to guarantee recovery. This may provide a biologically plausible rationale to assist further explorations on how drug abusers respond to recovery practices including cognitive interventions.

5.5 Concluding Remarks

The fields of psychology and neuroscience provide us with a growing amount of evidence supporting the fundamental role of cognitive components in the course of an addict's life. A pivotal investigation demonstrates that cocaine craving is induced by neural correlates within the frontal cortex, rather than by the dopaminergic circuitry (113), and in a recent review paper, George and Koob propose the hypothesis for which

> *"drug addiction involves a failure of the different subcomponents of the executive systems controlling key cognitive modules that process reward, pain, stress, emotion, habits, and decision-making"* (114).

Heeding this belief, and supported by observations of natural recoveries, the framework presented here aims to describe a simplistic computational scheme necessary to counteract such cognitive deficiency. Even though the neural correlates of an addict's limbic system have been modified compared to the brain of a healthy individual, it seems biologically plausible to consider neural changes in the prefrontal cortex to account, at least partially, for a balancing mechanism reconditioning the brain's functions towards a healthy state.

The present investigation proposes formal arguments to support the hypothesis of a cognitive learning mechanism, defined in Equation 7, capable of influencing decision-making processes associated with drug abuse. The emulated abstinence onsets from drug abuse presented above are an initial attempt toward the localization of such a balancing mechanism. To advance this exploration, it would be interesting to emulate similar rehabilitation properties within a more elaborated biologically inspired cognitive architecture, as for example Leabra (115), Clarion (116), or GMU-BICA (117). To further enhance psychological plausibility of the model presented in this paper, components studied in pathological gambling (stressors, cognitive distortions, ruminations, and distractions) (118) could be incorporated and explored.

The framework presented in this chapter supports the view that mindfulness-based cognitive techniques can act as a catalyst for maturing out of addiction.

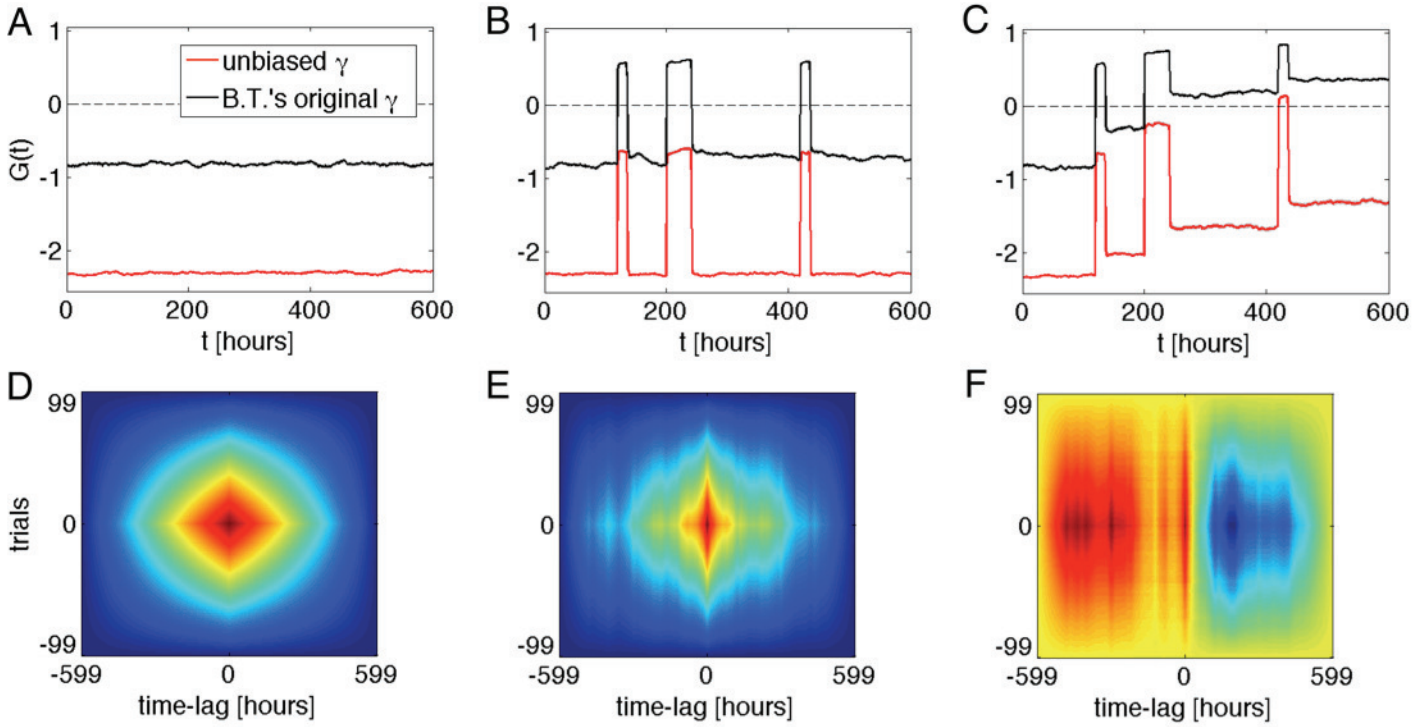

Figure 11: Comparison of simulations using the original and the cognitively unbiased values of γ. On the upper part are represented means and standard errors of the mean of the model's output $G(t)$ for 100 simulations of 600 time steps (25 days) each. On the bottom part are plotted the cross-correlations matrices comparing B.T.'s original profiles with its unbiased profile. In (A, D) the recovery process $h(t)$ is not active; in (B, E) $h(t)$ is active but can not induce a permanent change of the cognitive weights; and in (C, F) $h(t)$ is active and can potentially initiate a long-lasting period of abstinence by permanently modifying the cognitive weights values. In (D, E, F) the cross-correlation gradient progresses from red (high) to blue (low).

CHAPTER 6

A COMPUTATIONAL HYPOTHESIS FOR ALLOSTASIS

In the present Chapter, the KR framework supporting the hypothesis for *maturing out* discussed in Chapter 5 is modified and expanded to include a module relating the allostasis theory of addiction, which is based on pharmacokinetic and pharmacodynamic characteristics of drug use and abuse. The objective of this contribution is to provide a theory-based hypothesis that could be tested experimentally, possibly leading to an improvement in the understanding of this phenomenon.

This Chapter reports the investigation in (38).

The current investigation was undertaken to explore the allostatic framework of addiction, described in Chapter 2, by considering two computational hypotheses in which within-system and between-system adaptations are explicit time-dependent processes, and to introduce a computational estimation of mood change related to drug intake in human users. Motivated by animal observations (119), the within-system adaptations predicted by the presented model depend upon ongoing neural activities defining the virtual subject's current attitude towards drug use. Between-system adaptations rely on higher-order cognitive processes in accordance with the *"impaired response inhibition and salience*

attribution" (I-RISA) theory of addiction by Goldstein and Volkow (34), discussed in Section 2.7. For evaluation and validation purposes, an additional provisional assumption is formulated to predict the subject's mood as dependent on reward functions controlling behavior and on euphoric and dysphoric effects of the consumed substance.

6.1 Introduction

The allostatic theory of drug abuse describes how the brain's reward system evolves as substance misuse progresses. Neural adaptations arising from the reward system itself and from the antireward system provide the subject with functional stability, while affecting the person's mood. The present investigation proposes a computational hypothesis describing how a virtual subject's drug consumption, cognitive substrate, and mood interface with reward and antireward system neuroadaptations. Reward system adaptations are presumed interrelated with the ongoing neural activity defining behavior towards drug intake. These adaptations arise from brain areas that encompass the nucleus accumbens, ventral tegmental area, and prefrontal cortex (PFC). Antireward system adaptations are assumed to mutually connect with higher-order cognitive processes occurring within PFC, orbitofrontal cortex, and anterior cingulate cortex. The subject's mood estimation is a provisional function of reward components.

A knowledge repository model for allostasis is presented, which incorporates pharmacokinetic, pharmacodynamic, neuropsychological, cognitive, and behavioral components. Behavioral patterns of tobacco smoking exemplify the predictive properties of the framework. Three case studies are discussed: escalation of cigarettes consumption; conventional treatments similar to nicotine patches; and alternative medical practices comparable to meditation. Each computed profile comprises 100 simulations over a period of 160 days for a virtual subject encountering drugs on the fifth day. The primary outcome measures of the model include an estimate of the virtual subject's mood, and the daily account of drug intakes. The main limitation of this study resides in the 21 time-dependent processes which at the same time only partially describe the complex phenomena of drug addiction, and involve a large number of parameters which may underconstrain the framework.

Simulated patterns of drug intake, including escalation of drug use and rehabilitation, predict that reward system neuroadaptations account for mood stabilization, whereas antireward neuroadaptations delineate mood improvement and reduction in drug consumption. As an effort toward translational research in drug use and abuse, the discussed computational framework provides formal arguments encouraging current rehabilitation therapies to include meditation-like practices along with pharmaceutical drugs and counseling.

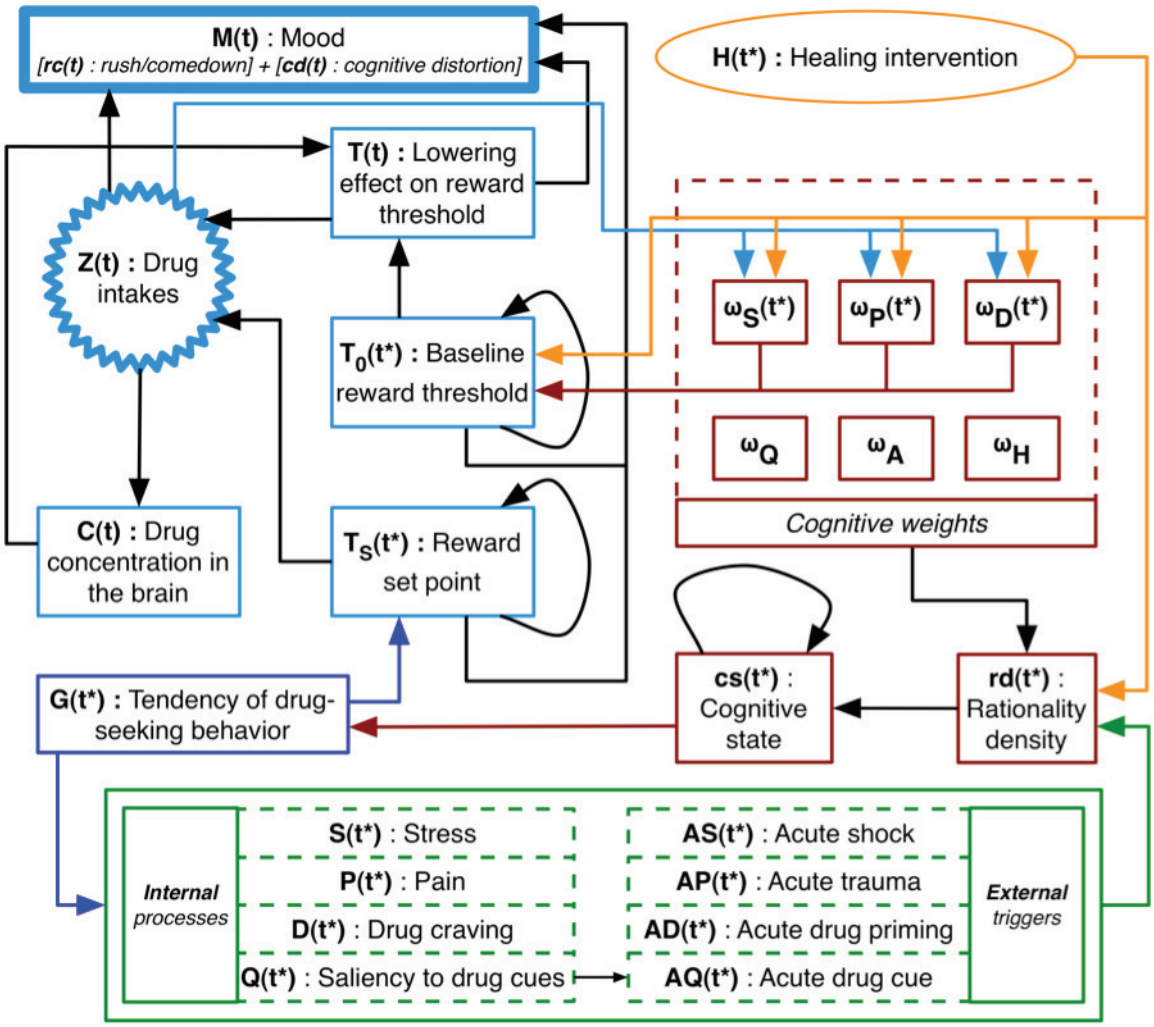

Figure 12: Diagram of the computational model. Time units differ: t is in minutes and t^* in hours. Output $M(t)$ is the mood estimation within the allostatic framework which combines the rush/comedown effect of the drug, $rc(t)$, with the virtual subject's cognitive distortion, $cd(t)$. Levels of observations include the neuropsychological scale in green, the cognitive scale in red, and the healing scale in orange (32), which are connected to the expanded PK/PD model (37) in light blue. The cognitive weights, which modulate the ongoing neural activity on the neuropsychological scale, define the tendency of drug-seeking behavior, $G(t^*)$. This predisposition influences the reward set point, $T_S(t^*)$, which together with the lowering effect on reward threshold, $T(t)$, defines decisions about drug intake, $Z(t)$. The cognitive weights influence the baseline reward threshold, $T_0(t^*)$, indirectly influence $T(t)$, and are affected by $Z(t)$. A healing intervention has a direct impact on both cognitive learning and $T_0(t^*)$, and an indirect effect on $T_S(t^*)$ associated with changes in the virtual subject's rationality density, $rd(t^*)$. The mood $M(t)$ is a combination of $Z(t)$, $T(t)$, $T_0(t^*)$, and $T_S(t^*)$.

6.2 Methods: Computational framework for allostasis

A pharmacokinetic/pharmacodynamic (PK/PD) model of allostasis for laboratory rats has been developed which relates compulsive drug intake to a chronically deviated baseline reward threshold (37). The PK component of this model represents how the rat's bloodstream and brain absorb the substance, and the PD component accounts for the threshold-lowering effect of the drug. The decision-making process defining the animal's future drug self-administration is controlled by the negative hedonic valence induced by the substance. Within-system alterations are represented by changes in the drug potency index in the PD component of the model, and between-system adjustments are described by variations of the baseline reward threshold. Simulations based upon this computational framework successfully replicate patterns of intravenous cocaine self-administration observed in laboratory rats, while relying on constant values to represent the within-system and the between-system adaptations (37).

In the present study, this animal model is translated toward human application by mathematically describing the within- and the between-system components as time-dependent functions, and by providing an estimation of the virtual subject's mood. This discrete-time model, which is shown in Figure 12, accounts for the behavioral, neuropsychological, and cognitive scales of observation in humans over time scales of minutes t and hours t^*, along with correlates of brain reward. The model produces computational predictions of drug intakes, $Z(t)$, and mood, $M(t)$. The provisional measure of M is an aggregate of

neural and psychological components. The former relies upon the direct rush/comedown effect of the drug, $rc(t)$, and the latter upon cognitive distortions, $cd(t)$, emulated as a function of current and previous hedonic adaptations. The Encyclopedia of Cognitive Behavior Therapy defines cognitive distortions as *"identifiable errors in thinking"* (120) which sustain pathologies related to alcohol and drug use (121) gambling (122,123), eating (124), and Internet use (125).

The behavioral scale includes the binary decision toward Z which depends on the arithmetical difference between the lowering effect on reward threshold $T(t)$ and the reward set point $T_S(t^*)$, similar to (37). The baseline reward threshold $T_0(t^*)$ influences T. The thresholds T, T_S, and T_0, are the reward components associated respectively with the inverse variation of the brain's reward sensitivity, the drug's evolving acute effect which is reminiscent of the intracranial self-stimulation paradigm (126), and the minimal drug effect providing the individual with a reliable outcome (*feel high*). The drug concentration in the brain is represented by $C(t)$, which depends on Z and influences T.

Two hypotheses are introduced to account for the time-dependency of within-system and between-system neuroadaptations. The first hypothesis was inspired by observations on rats (119) and relates to changes within T_S that are assumed contingent on the tendency for drug-seeking behavior, $G(t^*)$, estimated in (32). Accordingly, within-system adaptations are assumed to be dependent upon ongoing neural activities which define the current virtual subject's behavior towards drug use. G assesses the neural activity of brain regions sensitive to

addictive drugs. Healthy behavior (i.e., avoidance of drug use) corresponds to positive values of G, and maladaptive behavior (i.e., a tendency towards drug-seeking behavior) to negative values. Within-system alterations are included in the PD component of the model and represented by T_S as an alternative to the drug potency index discussed in (37). After the first drug intake, T_S is assumed to monotonically increase for healthy behavior and exponentially decrease for maladaptive behavior:

$$T_S(t^*+1) = \begin{cases} \lambda \cdot \left(1 - e^{-\beta \cdot d}\right) + T_S(t_c) & \text{if } G(t^*) \geq 0 \text{ and } \sum Z \geq 1 \\ T_S(t_c) \cdot e^{-\gamma \cdot d} & \text{if } G(t^*) < 0 \text{ and } \sum Z \geq 1 \\ T_S(t^*) & \text{otherwise,} \end{cases} \quad \text{Eq. 9}$$

where λ, β, and γ, are constants; t_c corresponds to the last time t^* where G changed its sign; d is a temporal unit-step counter reset to 0 when G changes its sign; and $\sum Z \geq 1$ denotes that at least one drug intake occurred up to time t^*. Within-systems neuroadaptations impact the allostatic state of the virtual subject by affecting M. At first only these adaptations take action, but cooperate with between-system neuroadaptations after the virtual subject experienced several drug intakes.

The estimation of G depends on internal processes (S, P, D, and Q) and external triggers (AS, AP, AD, and AQ), which define the neuropsychological scale of the model. The negative affective state of nervousness, anxiety, or stress $S(t^*)$ of an addict expands during withdrawal phases (127) due to changes occurring in

the brain reward and stress systems (3) including the VTA, the NAc, the amygdala, and the lateral hypothalamus (128). The level of burden or worry $P(t^*)$ related to a person's health state increases as a consequence of drug consumption (129).

The intensity of drug craving $D(t^*)$ strongly correlates with the level of extracellular dopamine in key brain areas. Animal experiments show how the concentration of dopamine in the NAc increases during acute drug consumption (130) and decreases during withdrawal (131). Human studies suggest that dopamine-related neural activity in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC) intensifies under the influence of drugs (132), and diminishes during long-term withdrawal (34).

Severe stressors $AS(t^*)$ such as electric foot-shocks for laboratory rats (133) and verbal scolding for humans (134) can lead to the reinstatement of maladaptive behavior. Acute distress events $AP(t^*)$ such as non-fatal overdoses for injection drug users (135) or coronary heart disease for smokers (136) may cause the individual to rapidly cease using the substance. After a period of abstention, rats (137) and humans (138) exposed to drug priming $AD(t^*)$ are more likely to stumble into relapse. Drug-associated cues linked to a particular environment $AQ(t^*)$ can reactivate drug-seeking behavior (139). The magnitude $Q(t^*)$ of these cues depends upon the drug-contingent neural mechanisms of learning and memory (140) that may facilitate the sensitization of incentive salience of drug cues leading to compulsive consumption (44).

The cognitive apparatus of the virtual subject transforms the ongoing neuropsychological activities into information accessible at the behavioral scale. Internal processes, external triggers, and healing interventions $H(t^*)$ are adapted by a set of time-varying cognitive weights $\omega_S(t^*)$, $\omega_P(t^*)$, $\omega_D(t^*)$, and constant parameters ω_Q, ω_A, and ω_H, to estimate the rationality density $rd(t^*)$ of the virtual subject. For the first number of drug intakes, the time-dependent cognitive weights ω_S, ω_P, and ω_D stochastically adjust and predispose the virtual subject toward maladaptive behavior, mimicking associative learning between the drug and its pleasurable effect. The cognitive state, $cs(t^*)$, translates rd to reflect the proportion between inhibition and compulsion driving the estimation of G.

The second computational hypothesis assumes that the baseline reward threshold T_0 depends upon higher-order cognitive processes. This is consistent with the I-RISA model (34) whereby between-system adaptations are considered to depend upon learning and memory functions. After a number of drug intakes, the cognitive substrate of the virtual subject starts to stochastically influence T_0 by means of ω_S, ω_P, ω_D and the healing intervention $H(t^*)$. Between-system alternations are conveyed by T_0, defined as a function of the cognitive time-dependent weights and H. The modulating influence of ω_S, ω_P, and ω_D on T_0 has opposite valence when a healing intervention occurs ($H = 1$) than when it does not ($H = 0$):

$$T_0(t^*+1) = \begin{cases} T_0(t^*) + \delta_{T0} \cdot \left(-2 \cdot H(t^*)+1\right) \cdot \\ \quad \cdot \left(\omega_S(t^*) - \omega_P(t^*) + \omega_D(t^*)\right) & \text{if } \sum Z \geq \alpha \\ T_0(t^*) & \text{otherwise,} \end{cases} \qquad \text{Eq. 10}$$

where δ_{T0} and α are constants, and $\sum Z \geq \alpha$ denotes the period subsequent to at least α drug intakes. Between-systems neuroadaptations adjust the virtual subject's allostatic state by altering M. These adaptations arise after α drug intakes and together with within-systems adaptations influences the virtual subject's mood.

The time-dependent cognitive weights emulate PFC, OFC, and ACC alterations that lead addicted persons and healthy individuals to manifest contrasting saliencies during affective events related to drug consumption (141,142). When active, healing interventions influence ω_S, ω_P, ω_D, and rd, inclining the virtual subject toward healthy behavior. Once H becomes idle, residual cognitive effects on these weights stochastically become permanent. Different occurrences of H delineate replacement therapies (e.g., nicotine replacement therapy) or complementary treatments (e.g., mindfulness meditation). Both techniques favorably support cigarette-smoking cessation (143,144). The first is simulated with an active H lasting several days, whereas the second by a sequence of active H's of much shorter durations.

Formal definitions of the processes in Figure 12 are included in the Supplementary Material (Appendix A).

6.2.1 Model validation and provisional assumption

Validation of the system dynamics model is divided into a structural module and a behavioral module (145). Both aspects were discussed in (37) for the PK/PD portion of the model of Figure 12 in terms of a sensitivity analysis of key parameters and output comparison with laboratory animal data. For the drug-seeking prediction part of the model, the structural identification and control of intrinsic bias was discussed in (31), and simulations of plausible scenarios for human psychoactive drug consumption were discussed in (32).

To further evaluate the validity of the present model, the virtual subject's mood is considered in addition to archetypal drug-seeking patterns. As mentioned above, mood alterations caused by an addictive substance are provisionally assessed as the aggregate of the drug's rush/comedown effect, $rc(t)$, and consequent cognitive distortion, $cd(t)$. The evolution of rc is defined as the summation of piece-wise sinusoidal functions each of one period with slightly exponentially decaying tails that initiate when a drug intake occurs. Cognitive distortions related to addiction are assumed to depend on the overall current reward state of the virtual subject which includes T, T_S, and T_0. Healthy individuals should not suffer from cognitive distortions: no current drug's effect on reward threshold, T, should arise, nor should any negative hedonic valences from within- and between-system neuroadaptations, T_S and T_0. The speculative cd combines the current reward state of the individual, the current activation of within- and

between-system neuroadaptations, alongside of previously experienced hedonic adaptations:

$$M(t) = rc(t) + cd(t)$$
$$\text{with } cd(t) = -T(t) + \gamma_M \cdot \Delta TSO(t^*) - \Delta TSO(t^* - 1) \text{ when } \sum Z \geq 1, \quad \text{Eq. 11}$$

where γ_M is constant; $\sum Z \geq 1$ denotes that at least one drug intake occurred up to t; and ΔTSO stands for the arithmetic difference between T_S and T_0. The formulation of cd is suggested by the temporal difference component employed in the first model of learning mechanism associated with dopaminergic neurons in the basal ganglia (92,93).

6.3 Results

Plausible real-life scenarios are illustrated in this section to simulate a virtual subject who is consuming abused substances. Three case studies narrating tobacco smoking are considered. The first depicts transitions from early to heavy smoking; the second considers conventional therapies (e.g., nicotine patches); and the third represents alternative medical treatments (e.g., meditation). Only cognitive correlates of conventional and alternative practices are emulated in the model at the center of this dissertation. In particular, only positive cognitive adaptations are emulated, even when emulating conventional therapies (for which the positive pharmacological effects are not emulated).

The simulation results include means for 100 simulations and standard errors of the mean corresponding to a period of 160 days with the drug becoming available on the fifth day. Changes in the allostatic state of the virtual subject are estimated through variations of the mood M.

When possible, parameters defining the simulations were chosen according to human studies. The rat brain apparent volume of distribution for cocaine used in (37) was replaced with an estimate for (S)-[11C]nicotine in humans (146). The number of drug intakes defining the initial associative learning reflected in ω_S, ω_P, ω_D, as well as the constant α in Equation 10, were chosen according to a clinical study by Difranza at al. (147) which classifies the progression of physical addiction into four stages: none (stage 1), wanting (stage 2), craving (stage 3), and needing (stage 4). Associative learning may arise until the needing phase, and the constant α relates to the craving phase. For nicotine, the four stages correspond to consumption rates of 2.2 ± 3.4, 4.4 ± 5.0, 8.6 ± 7.1, and 13.2 ± 7.7 cigarettes per smoking day (147), respectively. The minimum amount of time separating consecutive drug intake of 4 seconds in (37) was changed to 30 minutes. All other initial conditions of the present simulations were defined in accordance with (37) and (32). The values of the parameters used in the simulations are reported in Table 2.

The three considered case studies are presented in the next section and in Figure 13, where T_S and T_0 are constant. These settings correspond to the results presented by Ahmed and Koob in (37). The three case studies are

described in Sections 6.3.2 to 6.3.4, where Figures 14 to 19 each include three Evaluations: in the first both T_S and T_0 are time-dependent processes according to Equation 8 and Equation 9, in the second T_S is constant, and in the third T_0 is constant. The daily sobriety index is defined as the average number of simulated runs with at least one daily drug intake.

6.3.1 Baseline: constant reward set point and constant baseline reward threshold

This section presents simulations based on the model in Figure 12 while considering the reward set point, T_S, and the baseline reward threshold, T_0, as constants. This is comparable to the simulations of drug self-administration in rats presented by Amhed and Koob in (37) translated to humans.

Figure 13 reports simulations of the three case studies considered in this chapter, with experimental settings as discussed in Sections 6.3.2 to 6.3.4, when T_S and T_0 have constant values throughout the simulations instead of being the time-dependent functions defined by Equations 9 and 10. The first column corresponds to Case Study 1 (transition from early to heavy smoking); the second column to Case Study 2 (nicotine patch therapy); and the third column to Case Study 3 (practice of meditation). In Figure 13, line A reports the evolution of the cognitive weights ω_S, ω_P, and ω_D; line B the progression of T, T_S, and T_0; line C the prediction of mood M; and line D the average drug consumption and sobriety index.

The main difference between the simulated case studies in Figure 13 resides in the evolution of the cognitive weights ω_S, ω_P, and ω_D, which depends on the recovery process H. As detailed in the next sections, in Case Study 1 there are no H events, in Case Study 2 the occurrences of H are few and relatively long-lasting, whereas in Case Study 3 these are more frequent and of shorter in duration.

The three case studies express a similar evolution of the lowering effect on reward threshold, T, which is characterized by a loading phase (where the agent frequency of drug intake is high until satiety is reached) and a consequent maintenance phase (where the drug intake frequency becomes smaller and endures for the duration of the simulation). This is visible in Figure 13 (line B and correspondent close-up) and equates with the results of Ahmed and Koob (37).

The mood M steps down after the loading phase and does not express the chronic depression anticipated by Koob and Le Moal (3). The average drug consumption of the virtual subject is stable at ~12 cigarettes/day, and the sobriety index drops to 0% after the first intake.

The fine details for the simulations presented in Figure 13 can be found in Figure 20 (Appendix B). The tendency for drug-seeking behavior G, the internal (S, P, D, and Q) and external processes (AS, AP, AD, and AQ) are different across the three case studies. The simulations provided in this section are a frame of reference to assess Equations 9 and 10, and the simulations discussed in the remainder of this chapter.

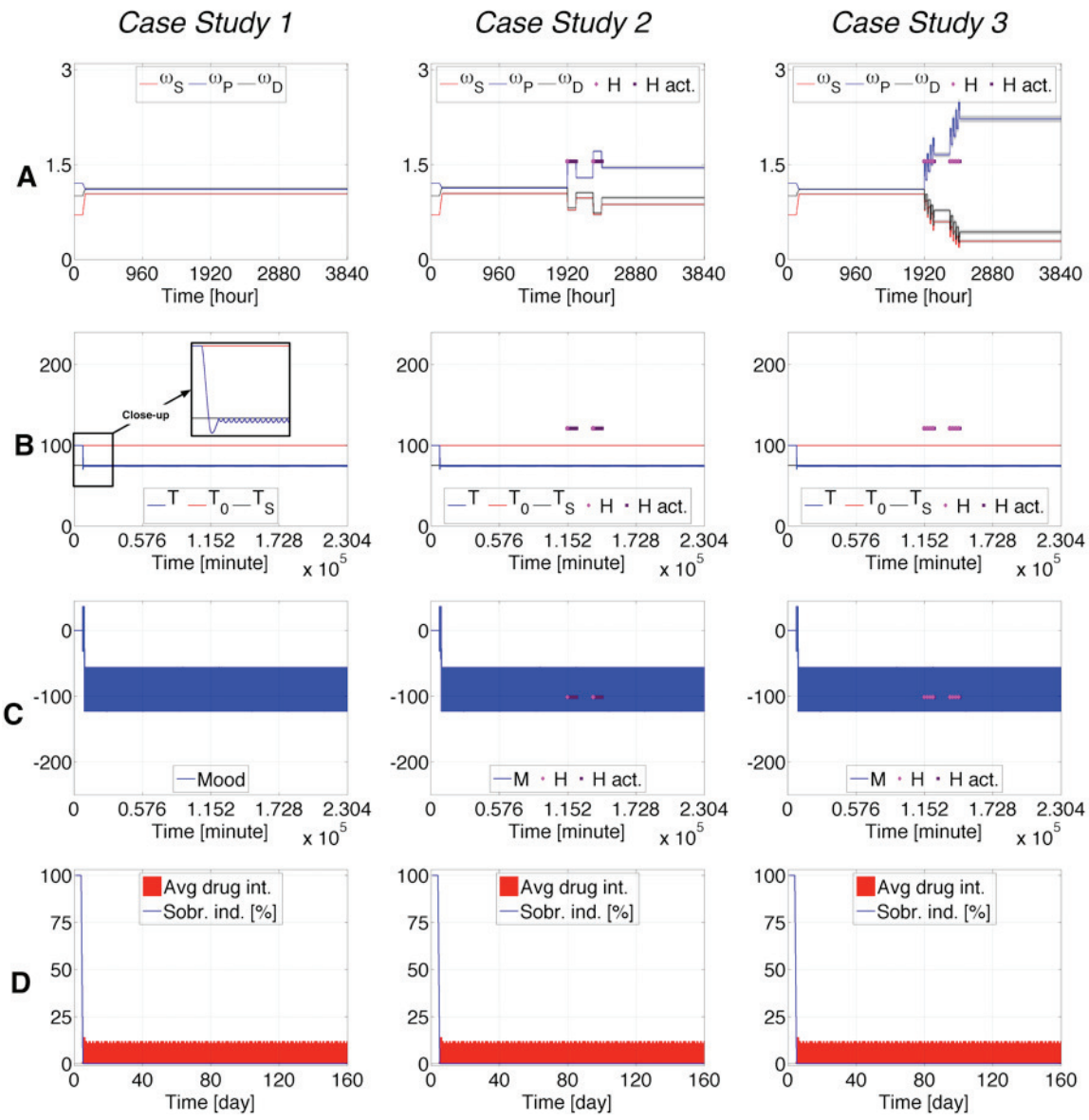

Figure 13: Baseline (T_S and T_0 are constant). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs and correspond to the three case studies discussed in this chapter. Line A shows the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); line B the progression of T (blue), T_S (black), and T_0 (red); line C the evolution of the subject's mood M; and line D the average number of drug intakes (red) and the sobriety index (blue). Further details of these simulations are reported in Figure 20.

6.3.2 Case Study 1: Allostatic state trajectory during escalation of drug consumption

This section discusses a virtual subject who engages in cigarette smoking five days after the simulation begins. Figure 14 presents the evolution of cognitive weights and reward components, whereas Figure 15 mood and health state assessments. In Evaluation 1, changes in ω_S, ω_P, and ω_D are gradual; T is at first weaker than T_S but eventually surpasses it, and T_0 continually increases; M increasingly oscillates around its downslope; the average drug consumption increases and the sobriety index diminishes. Upon completion of the simulation, this virtual subject is characterized by an average consumption of ~42 intakes/day (~2 packs) and a sobriety index of ~11%, comparable to a severe stage 4.

In Evaluation 2, the cognitive adaptations occur significantly faster than for Evaluation 1. T and T_S are approximately equal at first, but eventually T becomes larger than T_S as T_0 constantly increases. M abruptly decreases during the loading phase and subsequently manifests a negative trend enclosed by minor oscillations. The average consumption quickly increases and the virtual subject reaches a satiety state of ~48 cigarettes/day. Note that the number of intakes defining satiety is not an explicit constraint defined in the model. The sobriety index is consistently at zero.

In Evaluation 3, the evolution of the virtual subject's processes is very similar to the predictions for Evaluation 1, but T decreases and M has a less

negative downslope. This evaluation ends with ~34 intakes/day and ~25% sobriety.

Additional details can be found in the Supplementary Figures (Appendix B). Figure 21 includes the fine details for Case Study 1, and Figures 22 and 23 show how different probabilities defining changes in ω_S, ω_P, and ω_D influence the predicted consumption rates and mood downslope. If the first smoked cigarette within the simulations is considered as the first ever in the life of the virtual subject, then Figures 22 and 23 can be considered to relate to different rates of progression from recreational smoking toward heavy smoking.

Case Study 1 indicates that a virtual subject consuming drugs for the first time, or relapsing after a period of abstinence, undergoes a continuous negative shift in mood baseline which directly correlates with the strength of cognitive learning facilitating drug consumption. In addition, the virtual subject suffers growing mood swings during protracted consumption. When T_S is constant, the mood substantially decreases during the first number of drug intakes, and the virtual subject rapidly reaches the satiety consumption rate. With T_0 constant, the simulated mood has a weaker negative tendency and oscillates less.

This Case Study shows that escalation in drug consumption occurs together with chronic depression of mood. These simulations predict that the virtual subject's mood strongly drops when only between-system adaptations are operative, and moderately decreases when only within-system adaptations are operative.

6.3.3 Case Study 2: Allostatic state trajectory during conventional therapies

The profile presented in this section is similar to Case Study 1 but also includes healing interventions, H. Five-day long H events are activated at $t = 1920$ and $t = 2280$ [hours]. This is intended to emulate 25 days of a replacement therapy using a nicotine transdermal system for 2 five-day periods separated from each other by 15 days. Case Study 2, does not replicate the pharmacological effects of the replacement drug, but rather aims to mimic possible cognitive facilitations toward a healthy state which may be enabled by this drug.

All Evaluations for Case Studies 1 and 2 are similar until H is activated.

During the first therapeutic period in Figures 16 and 17, ω_S, ω_P, and ω_D are influenced by H to promote healthier behavior. This positive effect partially persists after the first period of therapy and is further strengthened by the second. In Evaluation 1, the activation of H causes a small upswing in T, a strong upswing in T_S, and a decrease in the upslope of T_0. The degradation of M becomes less accentuated after the treatment. The average drug consumption drops and the sobriety index rises while H is active. This experiment endpoint is comparable to an advanced stage 3 or an intermediate stage 4, with a consumption rate of ~14 intakes/day and a sobriety index of ~62%. In Evaluation 2, both T and T_0 reduce their upslope during the therapy, while the effect on M is negligible. The average consumption steadily increases ending at ~47 intakes/day, and the sobriety index drops to zero. In Evaluation 3, the

progression of the virtual subject's processes is similar to Evaluation 1 but somewhat slower. M stabilizes and becomes nearly constant after the therapy. This endpoint is ~8 intakes/day and ~81% sobriety.

Additional fine detail for Case Study 2 can be found in Figure 24 in the Supplementary Figures (Appendix B). Figures 25 and 26 show how different probabilities defining the influence of H affect the permanent predicted consumption rates. Higher probabilities lead the virtual subject to stage 1 or intermediate stage 2, whereas lower probabilities to advanced stage 4. The same sets of probabilities are tested when T_S is constant (Figures 27 and 28) and when T_0 is constant (Figures 29 and 30). For T_S constant, the virtual subject always gets to a satiety consumption rate, and reveals a shy positive trend in M for the highest probabilities along with a decrease in average consumption. For T_0 constant, M becomes constant after the therapy and its variations become smaller as the tested probabilities become higher.

Case study 2 shows how a few yet long healing interventions diminish the negative trend in the virtual addict's mood. Early indications of mood increase appear when healing signals are highly effective. When T_S is constant, curative effects on the mood are negligible, unless cognitive learning is exceptionally successful. Even though positive, the influences on mood for this extreme case are quite limited. With T_0 constant, the mood stabilizes after healing interventions and remains roughly constant.

This Case Study exemplifies the effect of prolonged healing interventions. These simulations predict that the virtual subject's mood continues to worsen in spite of therapeutic events when only between-system adaptations are operative. The predicted mood stabilizes as a consequence of healing periods when only within-system adaptations are operative.

6.3.4 Case Study 3: Allostatic state trajectory during alternative medical treatments

The profile in Figures 18 and 19 present a different type of healing intervention than in Case Study 2. At simulated times $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours], a fifteen hour H event is activated. This is intended to emulate 2 five-day healing periods during which the virtual subject undergoes four meditation practices separated by 40 hours. The benefits of each practice last for 15 hours, and the two healing periods are 10 days apart. Other than H event durations and activation times, all the parameters defining this Case Study are the same as in Case Studies 1 and 2.

During the first period of meditation, ω_S, ω_P, and ω_D strongly adjust. The enduring positive changes are additionally expanded after the second period of meditations. In Evaluation 1, T decreases before meditation, increases during meditation, and finally decreases again afterwards. There is an upswing of T_S when H is active. T_0 initially increases, becomes constant after the first healing session, and decreases after the second. After the first period of meditation, M

stops declining, and after it increases with reduced oscillation. The average drug consumption significantly decreases after the first healing period and further decreases after the second. The sobriety index robustly increases during the treatment. The endpoint of this evaluation corresponds to ~1 intake/day and ~97% sobriety, placing the virtual subject in stage 1 or early stage 2. In Evaluation 2, T variations are minors, and T_0 is a wide bell-shaped curve which maximal height corresponds to the healing periods. Activations of H first lead to stabilization of M, and then to its increase. The bell-shaped average drug consumption reaches its maximum and starts to decrease when H is active, finishing at ~12 intakes/day. The sobriety index starts to increase shortly after the end of the treatment reaching ~40% at the end of the simulation. Evaluation 3 is comparable to Evaluation 1 but M stabilizes after the therapy rather than increasing, and its final state is characterized by <1 intake/day and ~99% sobriety.

Additional details for Case Study 3 can be found in the Supplementary Figures (Appendix B). Figure 31 shows the fine details. Figures 32 and 33 illustrate how different probabilities defining the influence of H permanently impact the predicted consumption rates. Higher probabilities lead the virtual subject to cease using the drug, whereas lower probabilities to advanced stage 1 or intermediate stage 2. The same sets of probabilities are tested when T_S is constant (Figures 34 and 35) and when T_0 is constant (Figures 36 and 37). For T_S constant, the virtual subject always gets to its satiety consumption rate; and after

the treatment M increases. For T_0 constant, M tends to become constant after the therapy and its variations become smaller as the probability becomes higher.

Case study 3 displays how phasic healing interventions increase the mood of the virtual addict. This increase becomes very bold while healing signals have high effectiveness. Also, when T_S is constant, mood increases as a direct correlation of healing success. With T_0 constant, after healing interventions the mood stabilizes and becomes approximately constant.

This Case Study exemplifies the effect of brief healing interventions that follow one another at short intervals. These simulations predict that the virtual subject's mood increases as a result of curative events when only between-system adaptations are operative. The predicted mood stabilizes but does not improve after healing periods when only within-system adaptations are operative.

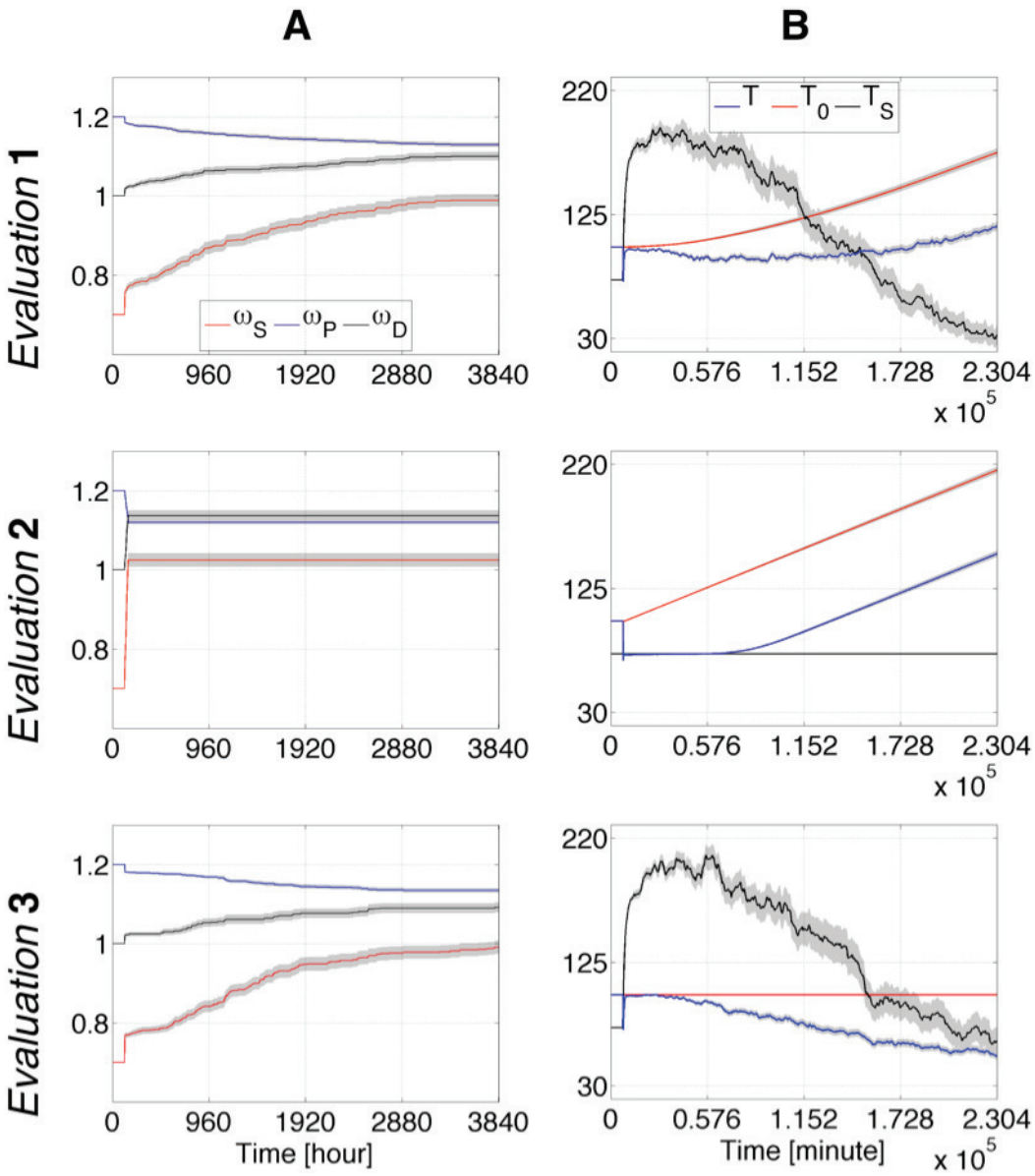

Figure 14: Case Study 1 (cognitive weights and reward components). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. Column A shows the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); and column B the progression of T (blue), T_S (black), and T_0 (red). The gray shades correspond to SEM. The time-scales are hours for column A, and minutes for column B. Further details of these simulations are reported in Figure 21.

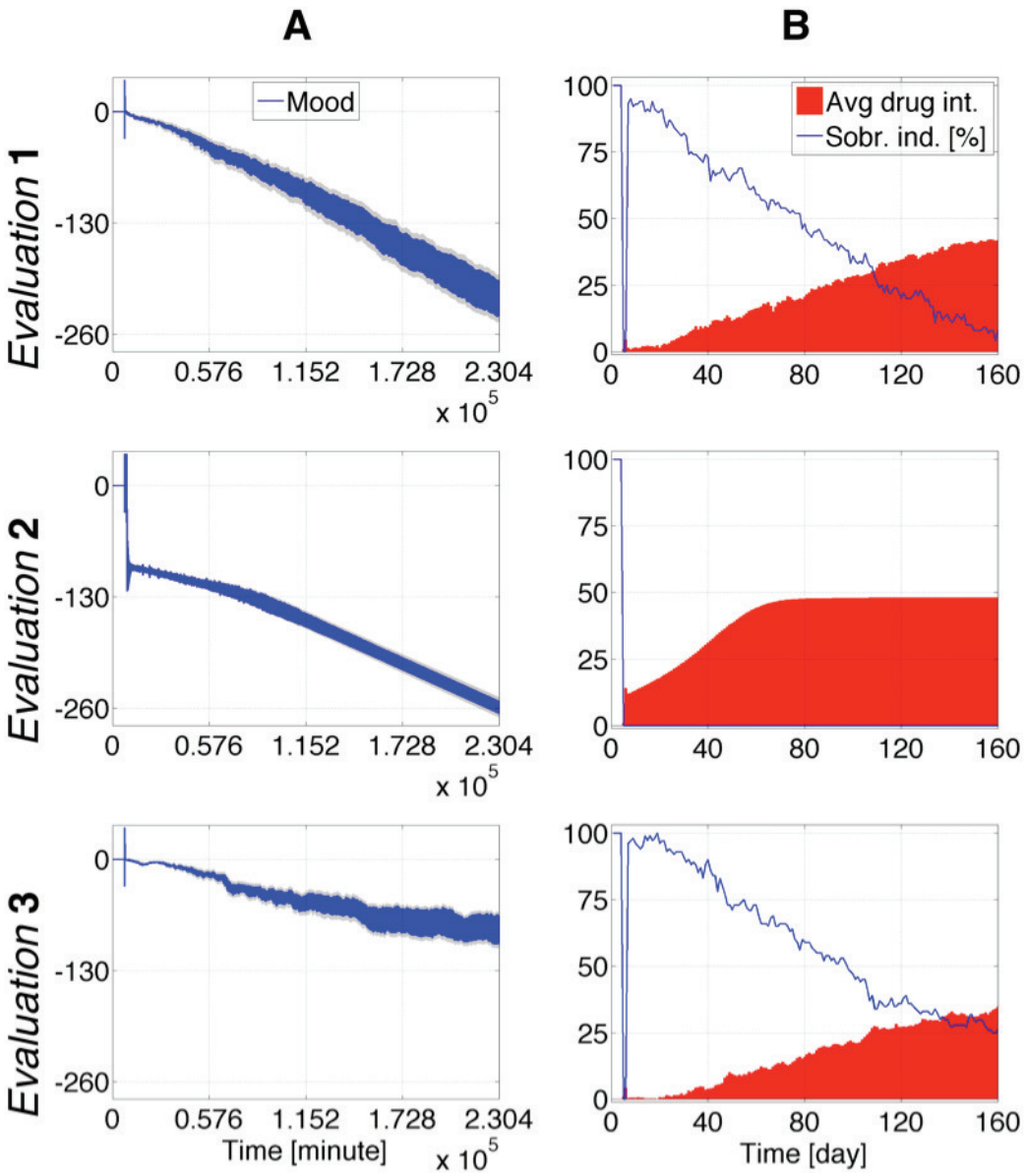

Figure 15: Case Study 1 (mood and health state assessments). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. Column A shows the evolution of the subject's mood M; and column B the average number of drug intakes (red) and the sobriety index (blue). The gray shade in column A corresponds to SEM. The time-scales are minutes for column A, and days for column D. Further details of these simulations are reported in Figure 21.

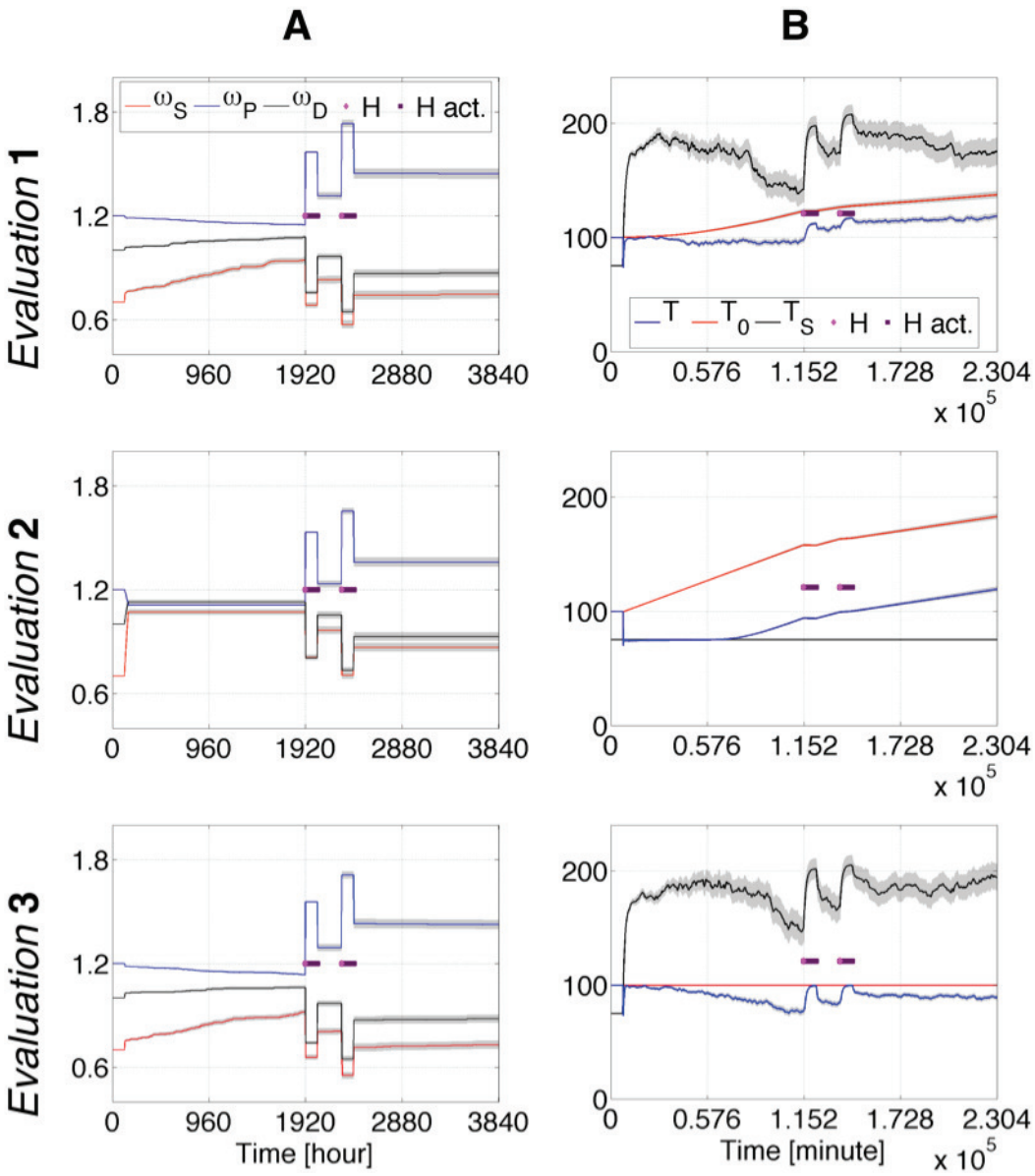

Figure 16: Case Study 2 (cognitive weights and reward components). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. In all evaluations, the recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). Column A shows the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); and column B the progression of T (blue), T_S (black), and T_0 (red). The gray shades correspond to SEM. The time-scales are hours for column A, minutes for column B. Further details of these simulations are reported in Figure 24.

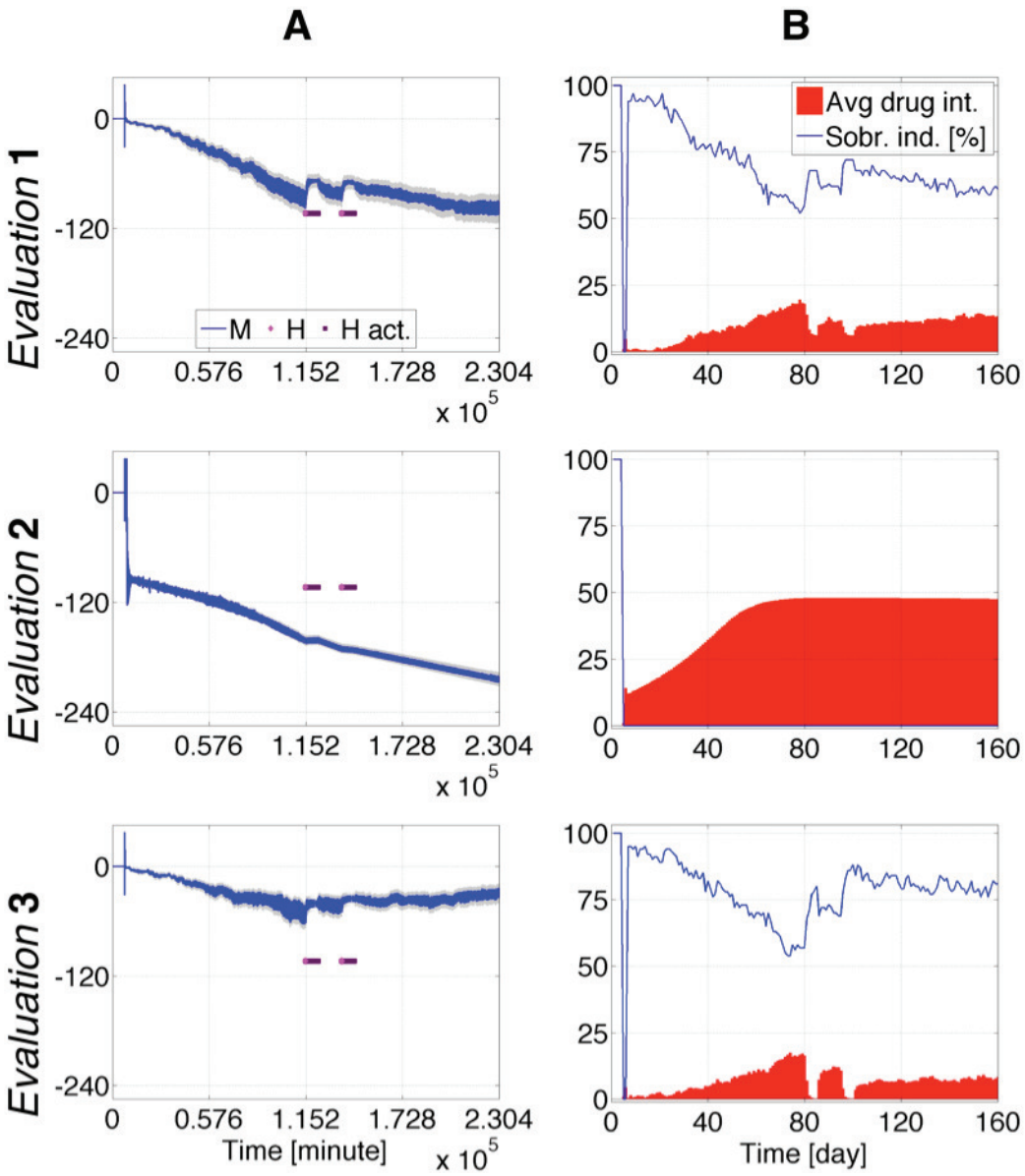

Figure 17: Case Study 2 (mood and health state assessments). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. In all evaluations, the recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). Column A shows the evolution of the subject's mood M; and column D the average number of drug intakes (red) and the sobriety index (blue). The gray shade in column A corresponds to SEM. The time-scales are minutes for column A, and days for column B. Further details of these simulations are reported in Figure 24.

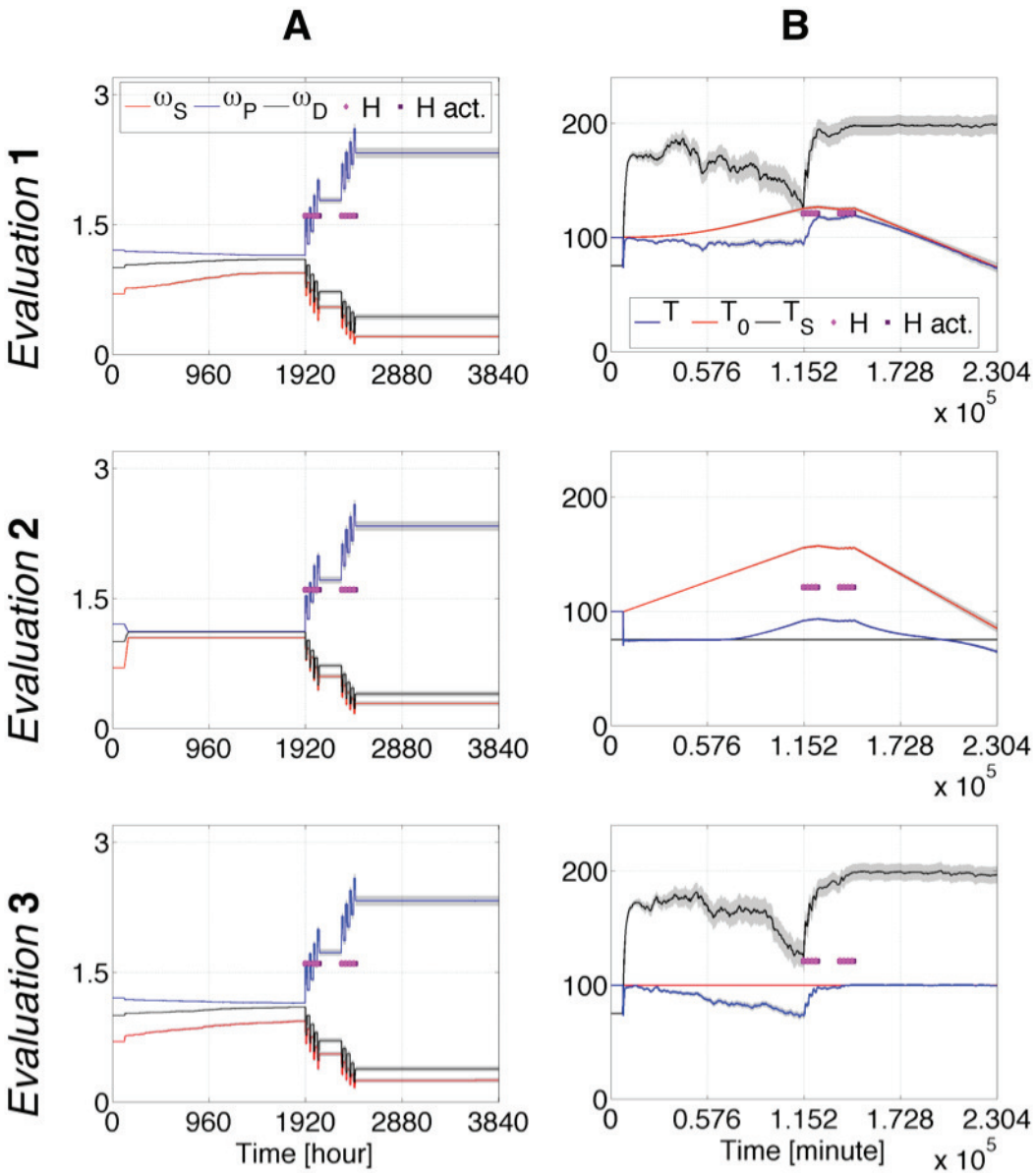

Figure 18: Case Study 3 (cognitive weights and reward components). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. In all evaluations, the recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). Column A shows the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); and column B the progression of T (blue), T_S (black), and T_0 (red). The gray shades correspond to SEM. The time-scales are hours for column A, and minutes for column B. Further details of these simulations are reported in Figure 31.

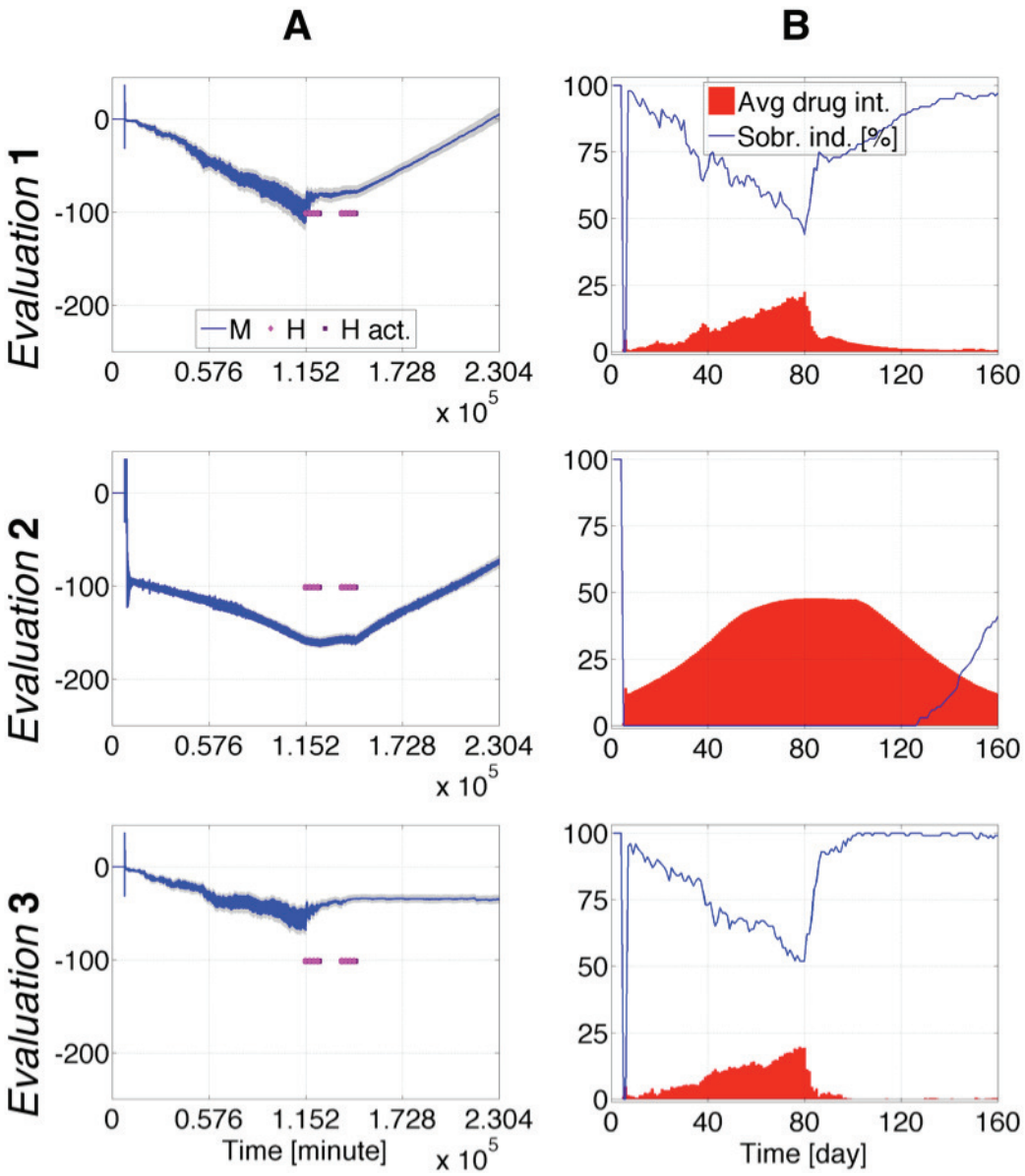

Figure 19: Case Study 3 (mood and health state assessments). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. In all evaluations, the recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). Column A shows the evolution of the subject's mood M; and column B the average number of drug intakes (red) and the sobriety index (blue). The gray shade in columns A corresponds to SEM. The time-scales are minutes for column A, and days for column B. Further details of these simulations are reported in Figure 31.

6.4 Concluding remarks

The computational model presented in this article includes higher-level cognitive elements in addition to behavioral and neural elements. This may raise ethical questions and influence how addicted humans are viewed by society (59). A multi-leveled overlook of addiction that includes biological/psychological/social (35), and even spiritual (15) elements is suggested as a possible compromise to restrain such an undesirable possibility (36). The multiscale standpoint of the framework shown in Figure 12 aims to promote a more comprehensive understanding of addiction and provides prospect for recovery, which seems to occur more often than commonly believed (140). In the present chapter a multiscale computational model is developed to further explore the allostatic theory of addiction (3) in terms of a KR model (101) in line with the exploratory review in (102), which aims to engage hypothesis-driven research (148). Such an approach can facilitate the detection of ambiguous knowledge that requires future biological and computational exploration in order to better understand this disease. The framework presented in this chapter supports the view that integrative medicine can be an effective approach to improve treatment of drug addiction.

CHAPTER 7

DISCUSSION AND CONCLUSION

The computational framework for allostasis presented above unites and elaborates two earlier formal models (37,32). The first relies on a closed-loop representation of the pharmacokinetics, the pharmacodynamics, and a decision-making processes delineating future cocaine consumption in rats (37). The second is a dynamical system model that encompasses neuropsychological and cognitive elements to mimic human occurrences of natural recoveries (32). The allostatic theory of addiction comprises within-system and between-system neuroadaptations that influence the brain's reward system: the former by a direct impact, and the latter by means of antireward system activations. The function of these adaptations is to balance the hedonic state of the addict and to provide the organism with a reasonable operational existence. Manifestations of the allostatic state come through mood alterations (3,51).

The present manuscript is an exploratory instance of knowledge repository (KR) modeling for addiction (101) which investigates cognitive correlates of the allostatic theory. A KR model comprises a collection of empirical observations that are mathematically translated and unified to predict the natural course of an entity (101). This class of models promotes the identification of plausible hypotheses which, if experimentally tested, could provide pertinent knowledge to further improve the computational framework. The repetition of this investigative

process initiates a hypothesis-driven sequence of experiments supporting translational research (148). The present model assembles building blocks of neuropsychology, cognition, and behavior into a multiscale computational framework aiming to facilitate rational entailments of the allostatic theory.

The computational description of a complex phenomenon such as drug use and abuse requires finding a compromise between two desirable but incompatible objectives. On the one hand, the biological components defining the model embrace a simplified ontology of addiction, and on the other hand, the mathematical features of the framework include a sizable number of elements and parameters making the model underconstrained. Moreover, a useful formal system should suggest testable hypotheses to further advance the investigated field. These perspectives are considered herein.

7.1 Biological conjectures and limitations

The simulations discussed in this investigation represent archetypal patterns of drug-seeking including transitions from recreational to heavy use, and rehabilitation. They express the comorbidity between addiction and mood depression for an addict vulnerable to both reward and antireward system neuroadaptations. As drug intake proceeds, the model estimates a steady decrease in the addict's mood that increasingly oscillates until the virtual subject reaches the satiety rate of drug consumption. This computational model also suggests a possible remission to the individual's healthy state as a consequence

of cognitive adjustments induced by conventional or alternative treatments. The model predicts a contraction in the addict's negative mood tendency and fluctuations while solely reward system neuroadaptations influence the hedonic valence of the individual. This rigidity endures during healing interventions as the model predicts stabilization of the subject's mood, rather than its increase. When the unique source of neuroadaptations affecting the subject's mood relies on the antireward system, the model predicts a noteworthy negative deflection of the subject's mood during the first number of drug intakes. The model also predicts that neuroadaptations occurring during healing periods, and that are uniquely induced by the antireward system, empower the individual with the possibility to regain a healthy mood state. These simulations also suggest that the satiety rate of drug consumption is reached more rapidly when the individual expresses only antireward system adaptations.

An important biological limitation of this model resides in the omission of mechanisms responsible for the development of pharmacodynamic tolerance, which arises when receptors or second messengers are blunted by chronic exposure to drugs such as alcohol or opiates (11). One approach to overcome this shortcoming can be found in the expansion and incorporation of a cellular and molecular scale within the model. Such elaboration could also enhance the computational framework with a greater descriptive ability for diverse classes of drugs. For nicotine dependence, a suitable candidate lies in a previously presented KR model which describes how dopaminergic signaling in the VTA

increases through nicotine intake and influences synaptic plasticity in the dorsal striatum, making cigarette smoking compulsive (103). A complementary candidate resides in a model describing how variations of extracellular levels of dopamine and glutamate within the brain's reward system impact the virtual subject's likelihood of drug consumption (149).

The presented model considers that the virtual subject is consuming *some* addictive substance rather than a specific kind. This is a major restriction of the framework which could be addressed by enhancing the pharmacokinetic (PK) module of the model. Previous studies present hypothetical but substance-specific PK units that could be included in the model: e.g., for nicotine and alcohol as reviewed in (150), or cocaine (151).

Furthermore, the model could be elaborated to incorporate elements related to medical conditions that occur frequently together with drug abuse, such as posttraumatic stress disorder, attention deficit hyperactivity disorder, and schizophrenia (152); as well as to include components of genetic regulatory networks pertinent to addiction (153).

7.2 The model's high dimensionality

A KR model is inclined toward a high-dimensionality due to a large number of descriptive variables, since its objective is to describe the studied phenomenon as comprehensively as possible. The predictions presented in this investigation rely on the high-dimensional dynamical model shown in Figure 12 that comprises

twenty-one time-dependent biological processes translated into the same number of mathematical expressions. In addition, there are seventy-one parameters, the setting of which can dramatically affect the model's behavior. Even though a mere approximation of the biological complexity delineating drug addiction in real life, such (computational) high-dimensionality could simulate an assortment of dynamics larger than the ones expressed by living creatures, and consequently limit the model's predictive power. The natural processes included in the presented computational framework are sizable, yet their descriptions are determined conservatively. For instance, the processes comprising the neuropsychological scale of the model have limited domains of definition which facilitate their tractability. These restricted domains reflect biological plausibility and ease the sensitivity analysis, necessary for the model's validation as discussed in (31).

Another attempt of mathematical moderation resides in the definition of healing interventions. The same mathematical definition used with different calibrations to mimic conventional and alternative cures was intentionally deployed as a lower-bound estimation of real-life cleansing episodes. In fact, the minimal duration of nicotine replacement therapies ranges from three weeks to three months (143), and mindfulness meditation requires four weeks of training to effectively influence regions surrounding the ACC of humans (154). Even though broadly delineated and similarly defined, these healing emulations provisionally advocate that for some nicotine addicts short interventions closely spaced in time

(e.g., meditation episodes) have a more beneficial health impact on the brain's cognitive substrate than longer interventions (e.g., nicotine patches). This conjecture is supported by a recent translational study where memories related to drug consumptions are triggered at different times to facilitate their extinction and decrease heroin craving in recovering humans (155,156). The simulated healing processes also corroborate a recent cohort study debating how nicotine replacement therapies may not be the universal solution to attain long-term smoking abstinence (157).

7.3 Conclusion: implications for treatments

The current manuscript provides formal arguments, conditional upon the validity of the hypotheses defining the computational framework, in favor of a stronger consideration of the addict's cognitive state evolution throughout the treatment process. In particular, this investigation suggests that higher rates of rehabilitation from drug addiction in humans can be reached by combining medical therapies that employ pharmaceutical drugs and counseling along with non-conventional treatments.

Several pharmacotherapies are available for smoking cessation, as for example nicotine in various forms (gums, patches, inhalers, tablets) and antidepressant drugs (144). Clinical studies show that these replacement therapies enhance the likelihood of rehabilitation by restraining drug craving during abstinence. The escalation of nicotine craving during smoking cessation is

lower for therapies involving the use of two medications rather than for monotherapies, and results in a higher cessation rate, respectively 54% and 45% in (157). Non-pharmacological interventions included in the therapy, such as behavioral counseling and personal support, aim to further increase smoking cessation rates and are recognized as primary components for the therapy's success (158). Behavioral counseling positively impacts cessation rates (159,160) by providing patients with coping skills effective in the reduction of withdrawal symptoms (161), but is less significant in preventing relapse (162). With respect to rehabilitation, the combination of pharmaceutical drugs is not effective on all occasions. For smokers with low dependence to nicotine and living in high-risk social environments (e.g., with a smoking partner) there is no significant difference in success rates of therapies involving one or the combination of two medications (161).

Behavioral counseling and personal support are instances of behavioral-cognitive therapies: non-pharmacological interventions which flourished from the 1960s for the treatment of depression and anxiety (163,164,165). A complementary category of non-pharmacological interventions resides in mind-body practices, which include mindfulness meditation, guided imagery, and relaxation (166). Both the definitions of behavioral-cognitive (165) and mind-body (166) practices rely on the beneficial impact that healthy cognitive states exert on the person's overall well being. A patient undergoing behavioral-cognitive therapy learns how to recognize and manage real life situations that are negatively

evaluated because of cognitive distortions, whereas mind-body practices provide the patient with a more realistic awareness that decreases irrational thoughts. In both cases the objective is to lead the patient to healthier physical and psychological states.

Behavioral-cognitive practices have demonstrated their positive impact on smoking cessation (162,167), and mind-body techniques related to the treatment of nicotine addiction suffer from a shortage of related investigations (168), even though recent studies demonstrate their great potential. Preliminary experimental support in favor of mindfulness meditation as a practice decreasing relapse rates for post-rehabilitation patients was provided in a study including 168 participants who ceased the use of substances including alcohol, cocaine, and methamphetamines (169).

The rational speculation that arises while considering pharmacological and non-pharmacological healing practices suggests that current therapies deploying one or multiple pharmacological means along with counseling will raise their success rates by uniting with alternative medical practices. The computational framework presented in this investigation provides formal arguments to endorse this conjecture as the allostatic state of an addict, assessed through mood variations, is shown to improve because of cognitive interventions provided by practices comparable to those of conventional and alternative medicine.

If the predictions delivered by the computational model discussed in this investigation constitute a fair approximation to describe how cigarette smoking

influences the allostatic state of a human addicted to nicotine, then it is expected that an integrative medicine approach to drug rehabilitation will provide higher cessation rates and lower relapse rates than current therapies. Given that the allostatic theory of addiction is not limited to the description of a particular substance of abuse, this prediction should apply by extension also to addictive substances including heroin, alcohol, and others.

APPENDIX A

SUPPLEMENTARY METHODS

This Appendix reports the definitions of the computational framework in Figure 12.

Notations

Different time scales are used: t represents time in minutes, and t^* represents time in hours.

When used as a conditional term, the sum $\sum_{s=0}^{t} Z(s)$ is abbreviated with $\sum Z$ and denotes the total number of drug intakes since the beginning of the simulation.

The inequality $t \geq t_{GO}$ indicates that the current time t is equal or grater than the time of the first drug intake t_{GO}. The presented simulations use $t_{GO} = 5$ [day].

The bounding function σ is defined as $\sigma(x) = \begin{cases} 0 & \text{if } x < 0 \\ x & \text{if } x \in [0,1] \\ 1 & \text{if } x > 1 \end{cases}$.

The parameter ν, with $\nu \in [-0.05, 0.05]$, denotes the uniform noise that is different for every process and changes at each time step.

MM1. Expanded PK/PD

(Equation S1) Mood - M

$$M(t) = rc(t) + cd(t),$$

where

$rc(t)$ is the rush/comedown effect of the drug, defined below, and
$cd(t)$ is the cognitive dissonance, defined below.

(Equation S2) Rush/comedown effect of the drug - rc

$$rc(t) = \sum_{s=0}^{t} Z(s) \cdot \left(\alpha - \beta \cdot \left(\frac{t-s}{\Delta} \right)^2 \cdot e^{-\frac{1}{2}\left(\frac{t-s}{\Delta}\right)^2} \right),$$

where

$Z(t)$ is the occurrence of drug intakes, defined below, and
α, β, and Δ are constants $\in \mathbb{R}$ (e.g., $\alpha = 40$, $\beta = 60$, and $\Delta = 10$).

(Equation S3) Cognitive distortion - cd

$$cd(t+1) = \begin{cases} -T(t) + \gamma_M \cdot \Delta TSO(t^*) - \Delta TSO(t^*-1) & \text{if } \sum Z \geq 1 \\ 0 & \text{otherwise,} \end{cases}$$

where

γ_M is a constant $\in \mathbb{R}$ (e.g., $\gamma_M = 0.3$),
$T(t)$ is the lowering effect on reward threshold, defined below,
$\Delta TSO(t^*) = T_S(t^*) - T_0(t^*)$, where $T_S(t^*)$ is the reward set point, and $T_0(t^*)$ is the baseline reward threshold, both defined below, and
$\sum Z$ is defined above.

(Equation S4) Drug intakes - Z

$$Z(t) = \begin{cases} 1 & \text{if } T(t) - T_S(t^*) > 0 \text{ and } \Delta_Z \geq a \text{ and } t \geq t_{GO} \\ 0 & \text{otherwise,} \end{cases}$$

where

$T(t)$ is the lowering effect on reward threshold, defined below,
$T_S(t^*)$ is the reward set point, defined below,
Δ_Z represents the number of minutes elapsed since the last drug intake, and
α is a constant $\in \mathbb{N}$ (e.g., $\alpha = 30$ [minute]).

(Equation S5) Lowering effect on reward threshold - T

$$T(t) = T_0(t^*) - \frac{T_{\max} \cdot C(t)}{T_{50} + C(t)},$$

where

$T_0(t^*)$ is the baseline reward threshold, defined below,
T_{max} is the maximum effect of the drug (e.g., $T_{max} = 120$),
T_{50} is the index of drug potency (e.g., $T_{50} = 588.6$ [nM]), and
$C(t)$ is the drug concentration in the brain, defined below.

(Equation S6) Drug concentration in the brain - C

$$C(t) = D \cdot \frac{k_{12}}{V_b(\alpha - \beta)} \cdot \sum_{s=0}^{t} Z(s) \cdot \left(e^{-\beta \cdot (t-s)} - e^{-\alpha \cdot (t-s)} \right),$$

where

D is the drug unit dose (e.g., $D = 250$ [μg]),
k_{12} is the compartment rate constant (e.g., $k_{12} = 0.0054$),
V_b is the apparent volume of distribution in the brain (e.g., $V_b = 1.67$, from (146)),
α and β are the aggregate rate constants as discussed in (37), and
$Z(t)$ is the occurrence of drug intakes, defined above.

(Equation S7) Reward set point - T_S

$$T_S(t^*+1) = \begin{cases} \lambda \cdot \left(1 - e^{-\beta \cdot d}\right) + T_S(t_c) & \text{if } G(t^*) \geq 0 \text{ and } \sum Z \geq 1 \\ T_S(t_c) \cdot e^{-\gamma \cdot d} & \text{if } G(t^*) < 0 \text{ and } \sum Z \geq 1 \\ T_S(t^*) & \text{otherwise,} \end{cases}$$

where

$T_S(0)$ is a constant (e.g. $T_S(0) = 75$),
β, γ, and λ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.05$, $\gamma = 0.05$, $\lambda = 100$),
d is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes,
t_c is the time t^* of last change of sign of $G(t^*)$,
$G(t^*)$ is the tendency of drug-seeking behavior, defined below, and
$\sum Z$ is defined above.

(Equation S8) Baseline reward threshold - T_0

$$T_0(t^*+1) = \begin{cases} T_0(t^*) + \delta_{T0} \cdot \left(-2 \cdot H(t^*) + 1\right) \cdot \left(\omega_S(t^*) - \omega_P(t^*) + \omega_D(t^*)\right) & \text{if } \sum Z \geq \alpha \\ T_0(t^*) & \text{otherwise,} \end{cases}$$

where

$T_0(0)$ is a constant (e.g. $T_0(0) = 100$),
δ_{T0} is a constant $\in \mathbb{R}^+$ (e.g., $\delta_{T0} = 0.03$),
$H(t^*)$ is the healing intervention process, defined below,
$\omega_S(t^*)$, $\omega_P(t^*)$, and $\omega_D(t^*)$ are the cognitive time-dependent weights, defined below,
α is a constant $\in \mathbb{N}^+$ (e.g., $\alpha = 20$ [intakes]); similar to stage 4 in (147), and
$\sum Z$ is defined above.

MM2. Cognitive scale

(Equation S9) Rationality density - rd

$$\begin{aligned} rd(t^*) = \; & -\omega_S(t^*) \cdot S(t^*) + \omega_P(t^*) \cdot P(t^*) - \omega_D(t^*) \cdot D(t^*) - \\ & -\omega_Q \cdot AQ(t^*) + \omega_A \cdot \left[AS(t^*) + AP(t^*) + AD(t^*)\right] + \omega_H \cdot H(t^*), \end{aligned}$$

where

$\omega_S(t^*)$, $\omega_P(t^*)$, and $\omega_D(t^*)$ are the cognitive time-dependent weights, defined below,
$S(t^*)$, $P(t^*)$, and $D(t^*)$ are the internal processes, defined below,
$A_S(t^*)$, $A_P(t^*)$, $A_D(t^*)$, and $A_Q(t^*)$ are the external processes, defined below, and
$H(t^*)$ is the healing intervention process, defined below.

(Equation S10) Cognitive weights - ω_S, ω_P, ω_D, ω_Q, ω_A, ω_H

• For $i \in \{\mathrm{Q}, \mathrm{A}, \mathrm{H}\}$:

$$\omega = c$$

where

c is a constant $\in \mathbb{R}^+$ (e.g., $\omega_Q = 0.28$, $\omega_A = 0.35$, $\omega_H = 0.8$).

• For $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$:

$$\omega_i(t^*) = \max\left(\alpha_i(t^*-1) + \vartheta_i \cdot H(t^*), 0\right),$$

with

$$\alpha_i(t^*+1) = \begin{cases} \alpha_i(t^*) + \vartheta_i & \text{if } A \\ \alpha_i(t^*) - \eta_i & \text{if } B \\ \alpha_i(t^*) + \vartheta_i - \eta_i & \text{if } A \text{ and } B \\ \alpha_i(t^*) & \text{otherwise,} \end{cases}$$

where

$\alpha_i(0)$ is a constant (e.g., $\alpha_S(0) = 0.7$, $\alpha_P(0) = 1.2$, $\alpha_D(0) = 1$),

Conditions A and B are conditional terms defined as:

A : if $H(\Theta(t^*)) = 1$ and $p_A(t^*) < P(H\eta i)$,

[for some probability, and if H is active, and at last time-step of activation]

where $\Theta(t^*)$ is defined below

$$\mathrm{B}: \text{ if } \sum_{s=t^*-1}^{t^*} Z(s) > 0 \text{ and } p_B(t^*) < P(Z\eta i) \text{ and } \sum Z \leq \beta,$$

[for the first number of drug intakes, and for a certain probability, and if in the past hour there was at least one drug intake]

where β is a constant $\in \mathbb{N}^+$ (e.g., $\beta = 15$ [intakes]), similar to stage 3 in (147)

$p_A(t^*)$ and $p_B(t^*)$ are values sampled from a standard uniform distribution at each time-step t^*,

$P(H\eta i)$ and $P(Z\eta i)$ are constants $\in [0,1]$ which denote, respectively, the probabilities of permanent changes in cognitive weights $\omega_S(t^*)$, $\omega_P(t^*)$, and $\omega_D(t^*)$ after a healing intervention or after a drug intake, with

(e.g.)	S	P	D
$P(H\eta i)$	$P(H\eta S) = 0.7$	$P(H\eta P) = 0.9$	$P(H\eta D) = 0.6$
$P(Z\eta i)$	$P(Z\eta S) = 0.2$	$P(Z\eta P) = 0.1$	$P(Z\eta D) = 0.05$

$H(t^*)$ is the healing intervention process, defined below, and ϑ_i and η_i are constants in the following domains:

	S	P	D
ϑ_i	$\in \mathbb{R}^-$ (e.g., $\vartheta_S = -0.26$)	$\in \mathbb{R}^+$ (e.g., $\vartheta_P = -0.42$)	$\in \mathbb{R}^-$ (e.g., $\vartheta_S = -0.32$)
η_i	$\in \mathbb{R}^-$ (e.g., $\eta_S = -0.1$)	$\in \mathbb{R}^+$ (e.g., $\eta_S = 0.05$)	$\in \mathbb{R}^-$ (e.g., $\eta_S = -0.15$)

(Equation S11) Cognitive state - cs

$$cs(t^*) = \frac{1}{2}\tanh\left(\alpha \cdot cs(t^* - 1) + \beta \cdot rd(t^*) + \gamma\right) + \frac{1}{2}$$

where

α and β are constants $\in \mathbb{R}^+$ (e.g., $\alpha = 0.25$, $\beta = 0.25$)

γ is a constant $\in \mathbb{R}$ (e.g., $\gamma = -0.4052$); this constant can also be computed using the following equation, as described in (31):

$$\gamma = \frac{1}{2}\left[\alpha - \beta \cdot \left(\omega_S(0) - \omega_P(0) + \omega_D(0) + \omega_Q + \omega_A\right)\right], \text{ where}$$

$\omega_S(0)$, $\omega_P(0)$, and $\omega_D(0)$ a are the values of the cognitive time-dependent weights at time $t^* = 0$,

α and β are the same constants used for $cs(t^*)$.

MM3. Healing scale

(Equation S12) Healing intervention - H

$$H(t^*) = \begin{cases} 1 & \text{if } p(t^*) < P(nr) \text{ or if } d \in \left[1, \Theta(t^*)\right] \\ 0 & \text{otherwise,} \end{cases}$$

where

$P(nr)$ is the probability of an healing intervention, $P(nr) \in [0,1]$; this probability can be based on data as in (32),

$p(t^*)$ is a value sampled from a standard uniform distribution at each time-step t^*; in the simulations presented in this article, H processes are triggered at specific times,

d is a time step counter reset at every instance of H, and

$\Theta(t^*)$ is the activation time of H, which increases for consecutive instances:

$$\Theta(t^*) = \begin{cases} \Theta(t^*) + \delta_i & \text{if } p(t^*) < P(nr) \\ \Theta(t^* - 1) & \text{if } d \in \left[1, \Theta(t^* - 1)\right] \\ \max\left(0,\ \Theta(t^*) - \delta_d\right) & \text{otherwise,} \end{cases}$$

where

δ_i and δ_d are constants $\in \mathbb{N}^+$, (e.g., $\delta_i = 15$, $\delta_d = 1$ [hour]).

MM4. Neuropsychological scale

The internal processes are S, P, D, and Q (29). The external triggers are AS, AP, AD, and AQ (29).

(Equation S13) Stress - S

$$S(t^*) = \begin{cases} \sigma\left(1-\left(1-S_0\right)\cdot e^{-\beta\cdot d}+\nu\right) & \text{if } G(t^*)>0 \\ \sigma\left(S(t^*-1)+\nu\right) & \text{if } G(t^*)=0 \\ \sigma\left(S_0\cdot e^{-\gamma\cdot d}+\nu\right) & \text{if } G(t^*)<0, \end{cases}$$

where

S_0 is the value $S(t_c)$, where t_c is the time t^* of last change of sign of $G(t^*)$,

β and γ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.002$, $\gamma = 0.002$),

d is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes,

$G(t^*)$ is the tendency of drug-seeking behavior, defined below, and

ν and $\sigma(x)$ are defined above.

(Equation S14) Pain - P

$$P(t^*) = \begin{cases} \sigma\left(P_0\cdot e^{-\beta\cdot d}+\nu\right) & \text{if } G(t^*)>0 \\ \sigma\left(P(t^*-1)+\nu\right) & \text{if } G(t^*)=0 \\ \sigma\left(1-(1-P_0)\cdot e^{-\gamma\cdot d}+\nu\right) & \text{if } G(t^*)<0, \end{cases}$$

where

P_0 is the value $P(t_c)$, where t_c is the time t^* of last change of sign of $G(t^*)$,

β and γ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.0002$, $\gamma = 0.01$),

d is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes,

$G(t^*)$ is the tendency of drug-seeking behavior, defined below, and

ν and $\sigma(x)$ are defined above.

(Equation S15) Drug craving - D

$$D(t^*) = \begin{cases} \sigma\left(1-\left(1-D_0\right)\cdot e^{-\beta\cdot d}+\nu\right) & \text{if } G(t^*)>0 \text{ and } d\in[1,\tau] \\ \sigma\left(D'_0\cdot e^{-\beta\cdot d}+\nu\right) & \text{if } G(t^*)>0 \text{ and } d>\tau \\ \sigma\left(D(t^*-1)+\nu\right) & \text{if } G(t^*)=0 \\ \sigma\left(1-\left(1-D_0\right)\cdot e^{-\gamma\cdot d}+\nu\right) & \text{if } G(t^*)<0, \end{cases}$$

where

D_0 is the value $D(t_c)$, where t_c is the time t^* of last change of sign of $G(t^*)$,
D'_0 is the value $D(t_c+\tau)$, where t_c is the time t^* of last change of sign of $G(t^*)$, and τ is a constant $\in \mathbb{N}^+$ (e.g., $\tau = 20$ [hour]),
β and γ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.00002$, $\gamma = 0.002$),
d is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes,
$G(t^*)$ is the tendency of drug-seeking behavior, defined below, and
ν and $\sigma(x)$ are defined above.

(Equation S16) Saliency to drug cues - Q

$$Q(t^*) = \begin{cases} \sigma\left(Q(t^*-1)+\nu\right) & \text{if } G(t^*)>0 \text{ and } d\in[1,\tau] \text{ or if } G(t^*)=0 \\ \sigma\left(Q'_0\cdot e^{-\beta\cdot d}+\nu\right) & \text{if } G(t^*)>0 \text{ and } d>\tau \\ \sigma\left(1-\left(1-Q_0\right)\cdot e^{-\gamma\cdot d}+\nu\right) & \text{if } G(t^*)<0, \end{cases}$$

where

Q_0 is the value $Q(t_c)$, where t_c is the time t^* of last change of sign of $G(t^*)$,
Q'_0 is the value $Q(t_c+\tau)$, where t_c is the time t^* of last change of sign of $G(t^*)$, and τ is a constant $\in \mathbb{N}^+$ (e.g., $\tau = 10$ [hour]),
β and γ are constants $\in \mathbb{R}^+$ (e.g., $\beta = 0.002$, $\gamma = 0.0005$),
d is a time-steps counter, reset to 0 when the sign of $G(t^*)$ changes,
$G(t^*)$ is the tendency of drug-seeking behavior, defined below, and
ν and $\sigma(x)$ are defined above.

(Equation S17) Acute shock - AS

$$AS(t^*) = \begin{cases} S_0 & \text{if } G(t^*) > 0 \text{ and } p(t^*) < P(AS) \text{ or if } d \in [1, \tau_1] \\ \rho \cdot AS(t^* - 1) & \text{if } d \in [\tau_1, \tau_2] \\ 0 & \text{otherwise,} \end{cases}$$

where

S_0 and ρ are constants $\in \mathbb{R}^+$ (e.g., $S_0 = 0.75$, $\rho = 0.9$),
$G(t^*)$ is the tendency of drug-seeking behavior, defined below,
$p(t^*)$ is a value sampled from a standard uniform distribution at each time-step t^*,
$P(AS)$ is the probability of an acute shock (e.g., $P(AS) = 0.01$),
d is a time-steps counter, reset to 0 when a new $AS(t^*)$ arises, and
τ_1 and τ_2 are constants $\in \mathbb{N}^+$ with $\tau_2 > \tau_1$ (e.g., $\tau_1 = 20$, $\tau_2 = 60$ [hour]).

(Equation S18) Acute trauma - AP

$$AP(t^*) = \begin{cases} P_0 & \text{if } G(t^*) < 0 \text{ and } p(t^*) < P(AP) \text{ or if } d \in [1, \tau_1] \\ \rho \cdot AP(t^* - 1) & \text{if } d \in [\tau_1, \tau_2] \\ 0 & \text{otherwise,} \end{cases}$$

where

P_0 and ρ are constants $\in \mathbb{R}^+$ (e.g., $P_0 = 0.45$, $\rho = 0.4$),
$G(t^*)$ is the tendency of drug-seeking behavior, defined below,
$p(t^*)$ is a value sampled from a standard uniform distribution at each time-step t^*,
$P(AP)$ is the probability of an acute shock (e.g., $P(AP) = 0.03$),
d is a time-steps counter, reset to 0 when a new $AP(t^*)$ arises, and
τ_1 and τ_2 are constants $\in \mathbb{N}^+$ with $\tau_2 > \tau_1$ (e.g., $\tau_1 = 15$, $\tau_2 = 50$ [hour]).

(Equation S19) Acute drug priming - AD

$$AD(t^*) = \begin{cases} D_0 & \text{if } G(t^*) > 0 \text{ and } p(t^*) < P(AD) \text{ or if } d \in [1, \tau_1] \\ \rho \cdot AD(t^* - 1) & \text{if } d \in [\tau_1, \tau_2] \\ 0 & \text{otherwise,} \end{cases}$$

where

D_0 and ρ are constants $\in \mathbb{R}^+$ (e.g., $D_0 = 0.75$, $\rho = 0.9$),
$G(t^*)$ is the tendency of drug-seeking behavior, defined below,
$p(t^*)$ is a value sampled from a standard uniform distribution at each time-step t^*,
$P(AD)$ is the probability of an acute shock (e.g., $P(AD) = 0.03$),
d is a time-steps counter, reset to 0 when a new $AD(t^*)$ arises, and
τ_1 and τ_2 are constants $\in \mathbb{N}^+$ with $\tau_2 > \tau_1$ (e.g., $\tau_1 = 5$, $\tau_2 = 30$ [hour]).

(Equation S20) Acute drug cue - AQ

$$AQ(t^*) = \begin{cases} Q(t^*) & \text{if } p(t^*) < P(AQ) \\ AQ(t^*-1) & \text{if } d \in [1, \tau_1] \\ \rho \cdot AQ(t^*-1) & \text{if } d \in [\tau_1, \tau_2] \\ 0 & \text{otherwise,} \end{cases}$$

where

$Q(t^*)$ is the saliency to drug cues, defined above,
ρ is a constants $\in \mathbb{R}^+$ (e.g., $\rho = 0.9$),
$p(t^*)$ is a value sampled from a standard uniform distribution at each time-step t^*,
$P(AQ)$ is the probability of an acute shock (e.g., $P(AQ) = 0.02$),
d is a time-steps counter, reset to 0 when a new $AQ(t^*)$ arises, and
τ_1 and τ_2 are constants $\in \mathbb{N}^+$ with $\tau_2 > \tau_1$ (e.g., $\tau_1 = 20$, $\tau_2 = 40$ [hour]).

MM5. Behavioral scale

(Equation S21) Tendency of drug-seeking behavior - G

$$G(t^*) = I \cdot cs(t^*) - C \cdot \left(1 - cs(t^*)\right),$$

where

I and C are a constant (e.g., $I = 1$, $C = 1$),
$cs(t^*)$ is the cognitive state, defined above.

APPENDIX B

SUPPLEMENTARY FIGURES

This Appendix reports the supplementary figures discussed in Chapter 6. The abbreviation *SEM* stands for *standard error of the mean*.

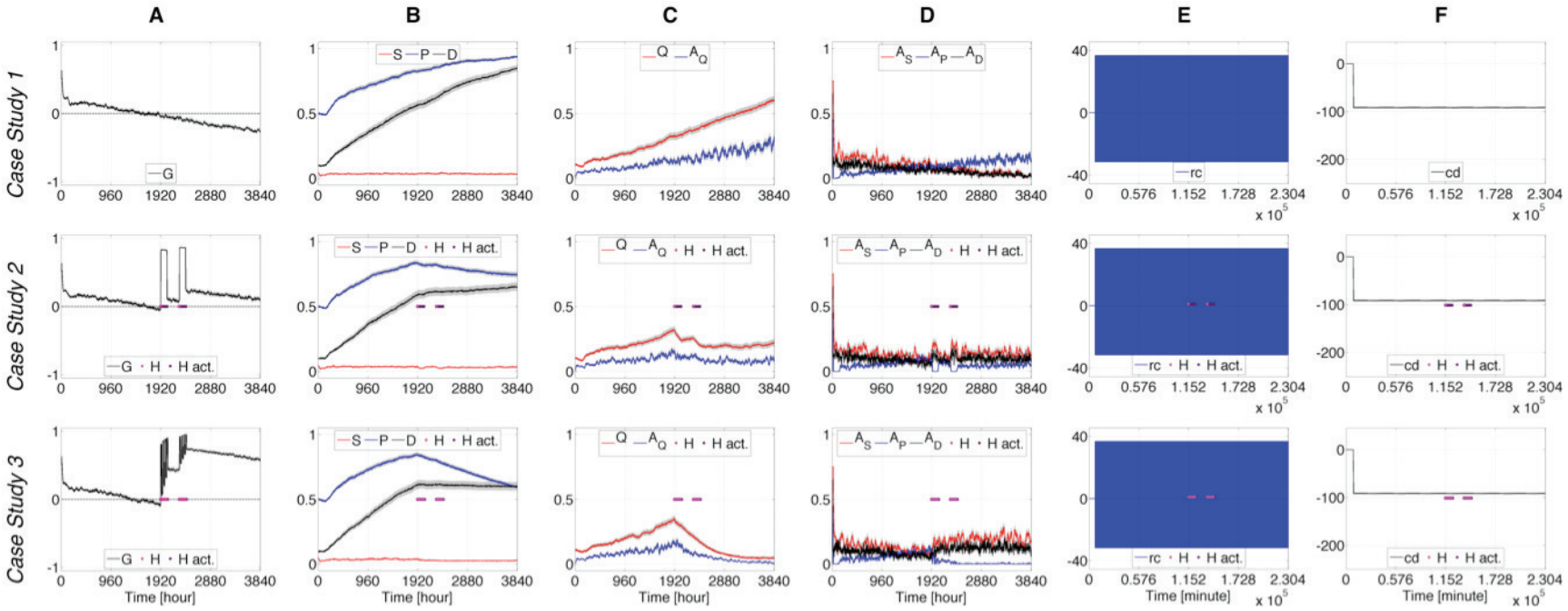

Figure 20: Details of the baseline presented in Figure 13 (T_S and T_0 are constant). Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs when both T_S and T_0 are constant. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The simulation time-scales are multiple: hours for columns A-D, and minutes for columns E-F.

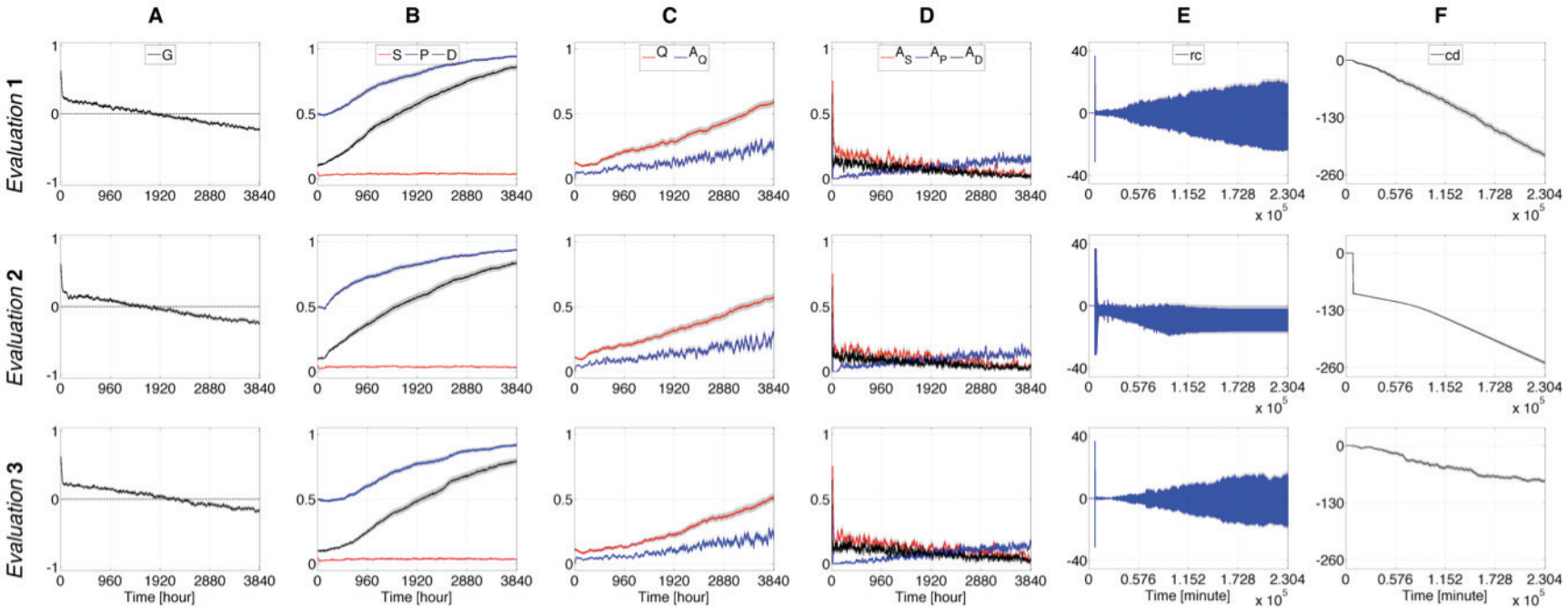

Figure 21: Details of Case Study 1 presented in Figures 14 and 15. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The simulation time-scales are multiple: hours for columns A-D, and minutes for columns E-F.

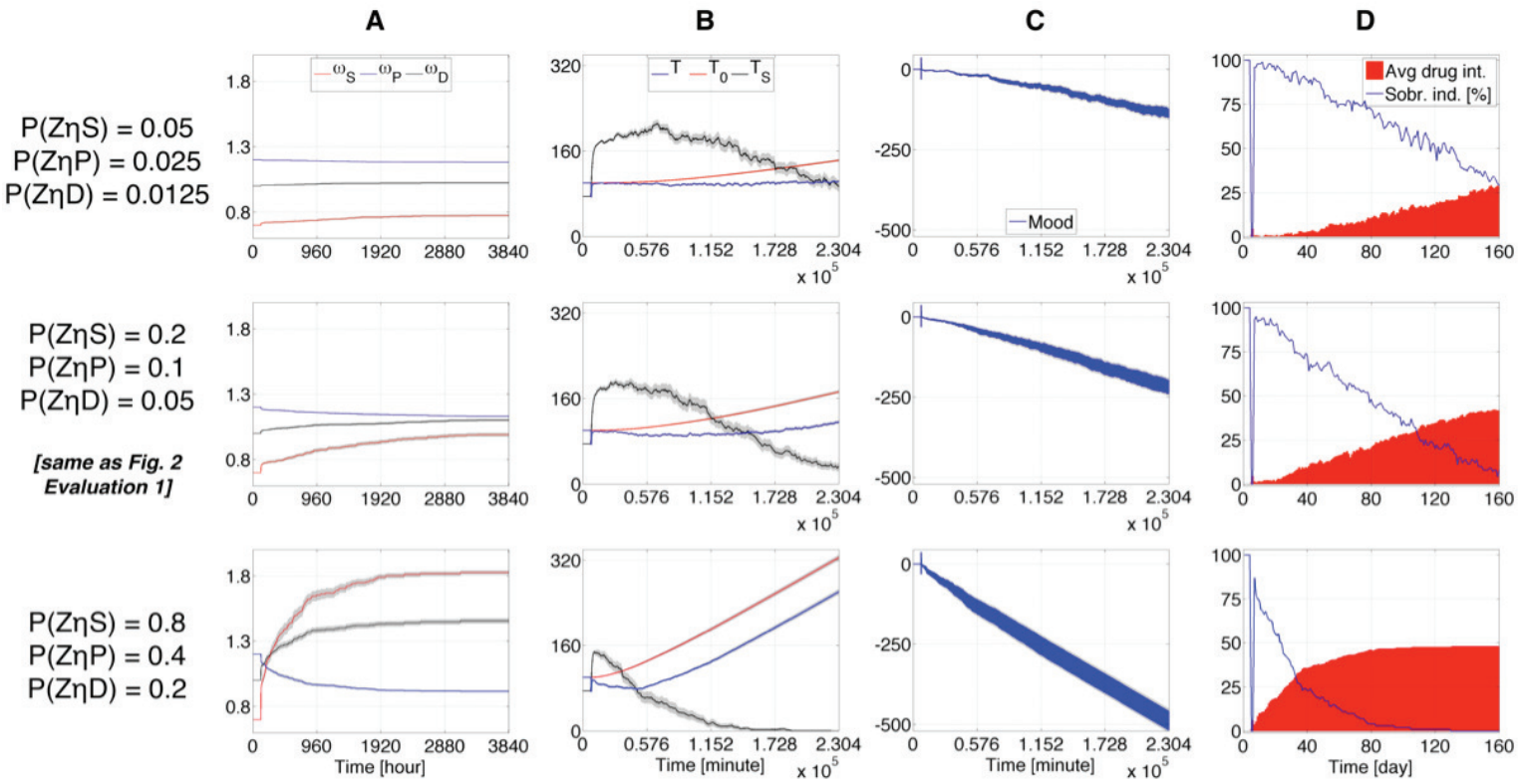

Figure 22: Comparison of different probabilities defining the associative learning between the drug and its pleasurable effect. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. For the first number of consumed cigarettes, alterations of ω_S, ω_P, and ω_D facilitating maladaptive behavior occur with arbitrary probabilities. Three sets of probabilities $P(Z\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$ are tested: $[0.05, 0.025, 0.0125]$, $[0.2, 0.1, 0.05]$, and $[0.8, 0.4, 0.2]$. Column A reports the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); column B the progression of T (blue), T_S (black), and T_0 (red); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the sobriety index (blue) over time. The gray shades in columns A, B, and C corresponds to SEM. The abscissas correspond to the simulation's time-steps: hours in column A; minutes in columns B-C; and days in column D. Maladaptive behavior is facilitated for higher probabilities. Simulations using lower probabilities terminate with the virtual subject exhibiting an average consumption of ~30 intakes/day and a sobriety index of ~30%. Higher probabilities lead these predicted measures to ~45 intakes/day and ~2% sobriety. The downslope of M becomes stronger as the probabilities become larger.

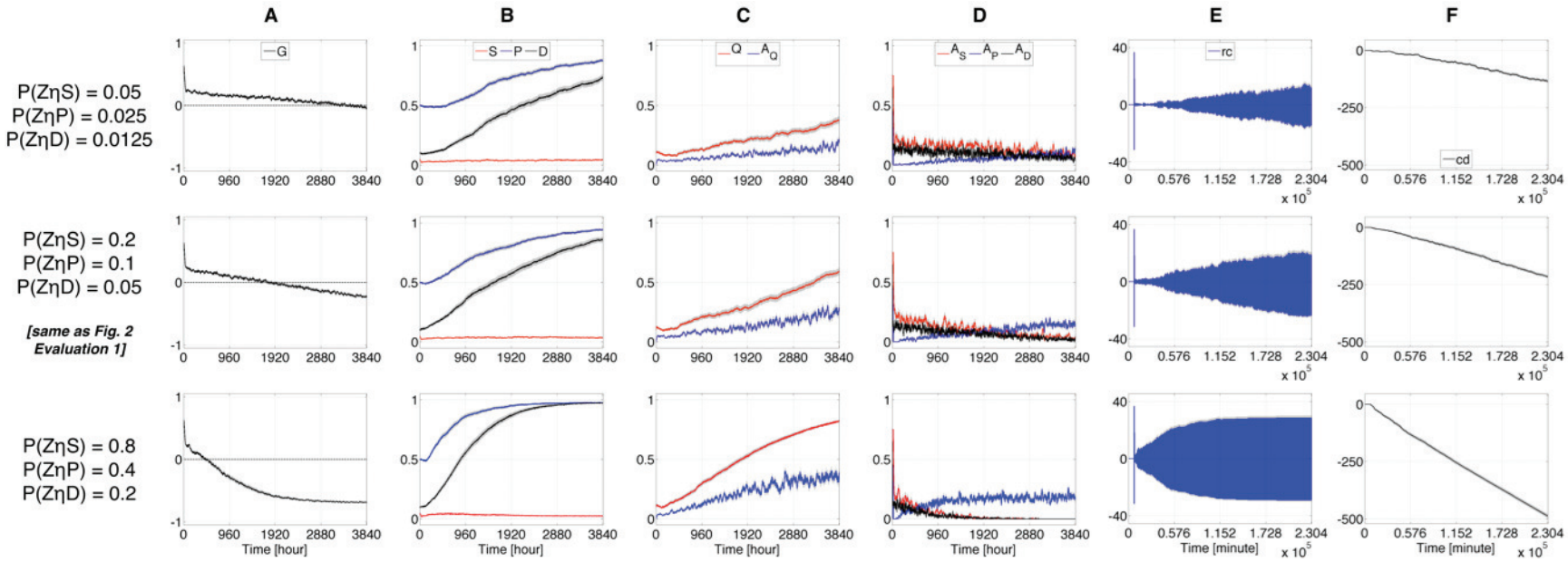

Figure 23: Details of simulations presented in Figure 22. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. For the first number of consumed cigarettes, alterations of ω_S, ω_P, and ω_D facilitating maladaptive behavior occur with arbitrary probabilities. Three sets of probabilities $P(Z\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$ are tested: $[0.05, 0.025, 0.0125]$, $[0.2, 0.1, 0.05]$, and $[0.8, 0.4, 0.2]$. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The abscissas correspond to the simulation's time-steps: hours in columns A-D, and minutes in columns E-F.

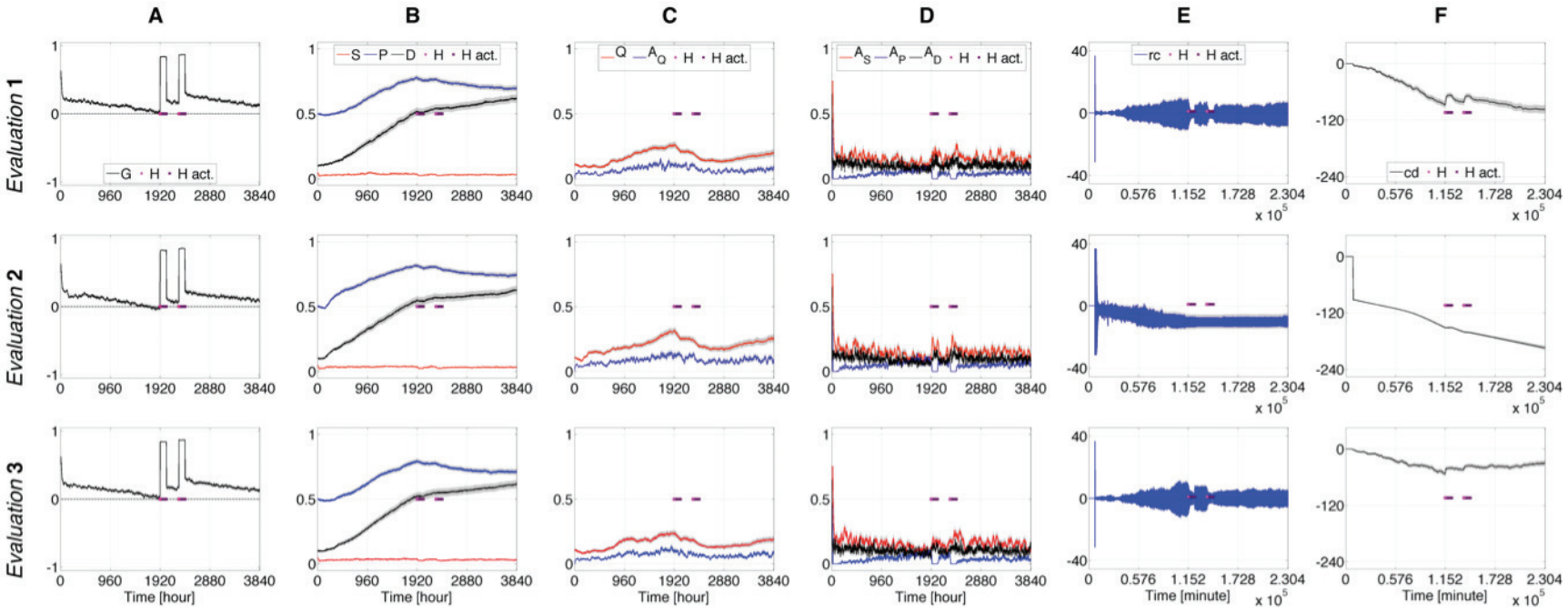

Figure 24: Details of Case Study 2 presented in Figures 16 and 17. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. In all Evaluations, the recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The simulation time-scales are multiple: hours for columns A-D, and minutes for columns E-F.

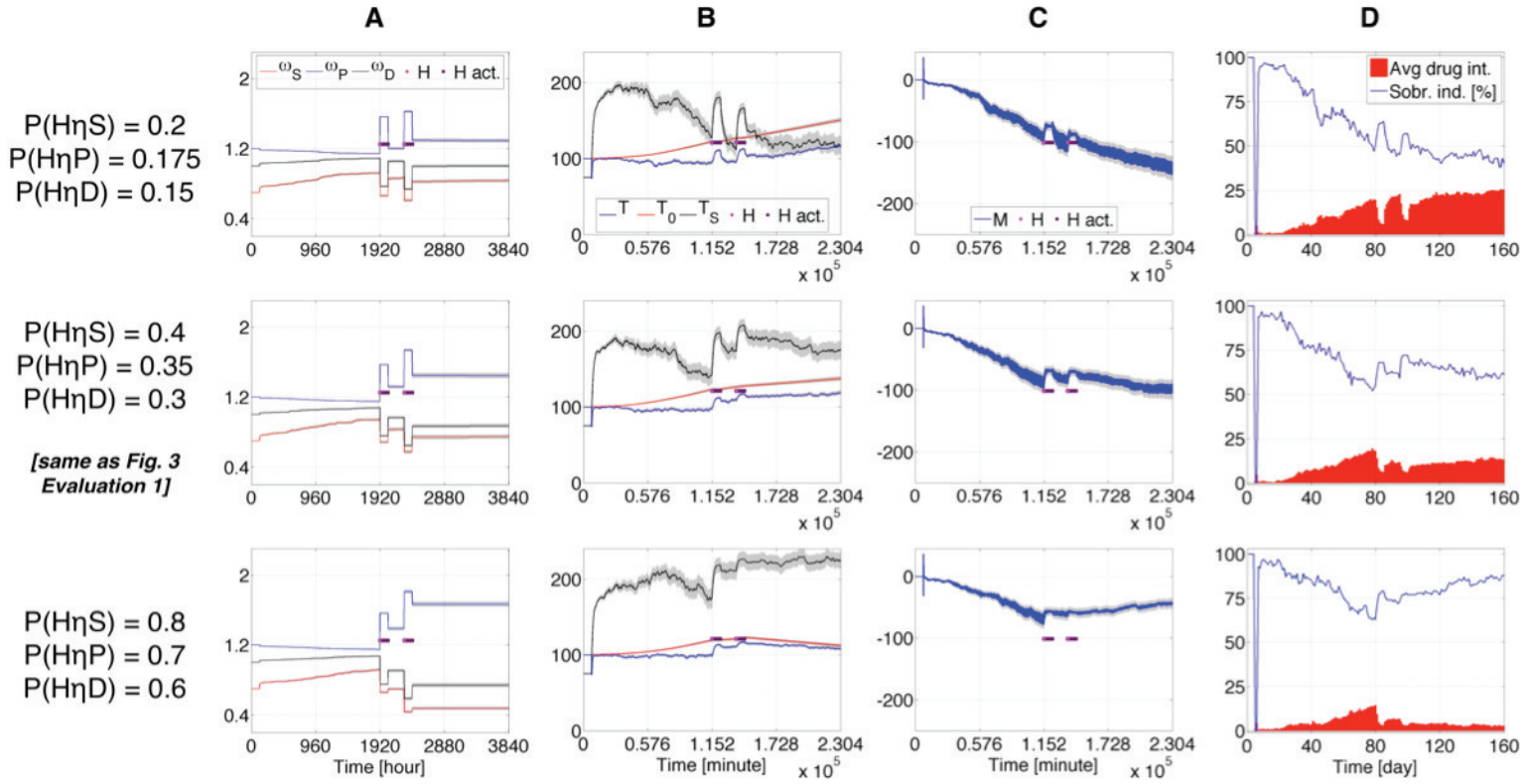

Figure 25: Comparison of different probabilities defining the durability of H for conventional therapies, with both T_S and T_0 time-dependent. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); column B the progression of T (blue), T_S (black), and T_0 (red); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the sobriety index (blue) over time. The gray shades in columns A, B, and C corresponds to SEM. The abscissas correspond to the simulation's time-steps: hours in column A; minutes in columns B-C; and days in column D. The trial employing the lowest probabilities terminates at advanced stage 4 (~25 intakes/day and ~41% sobriety), whereas the highest set of probabilities leads to stage 1 or intermediate stage 2 (~3.5 intakes/day and ~88% sobriety).

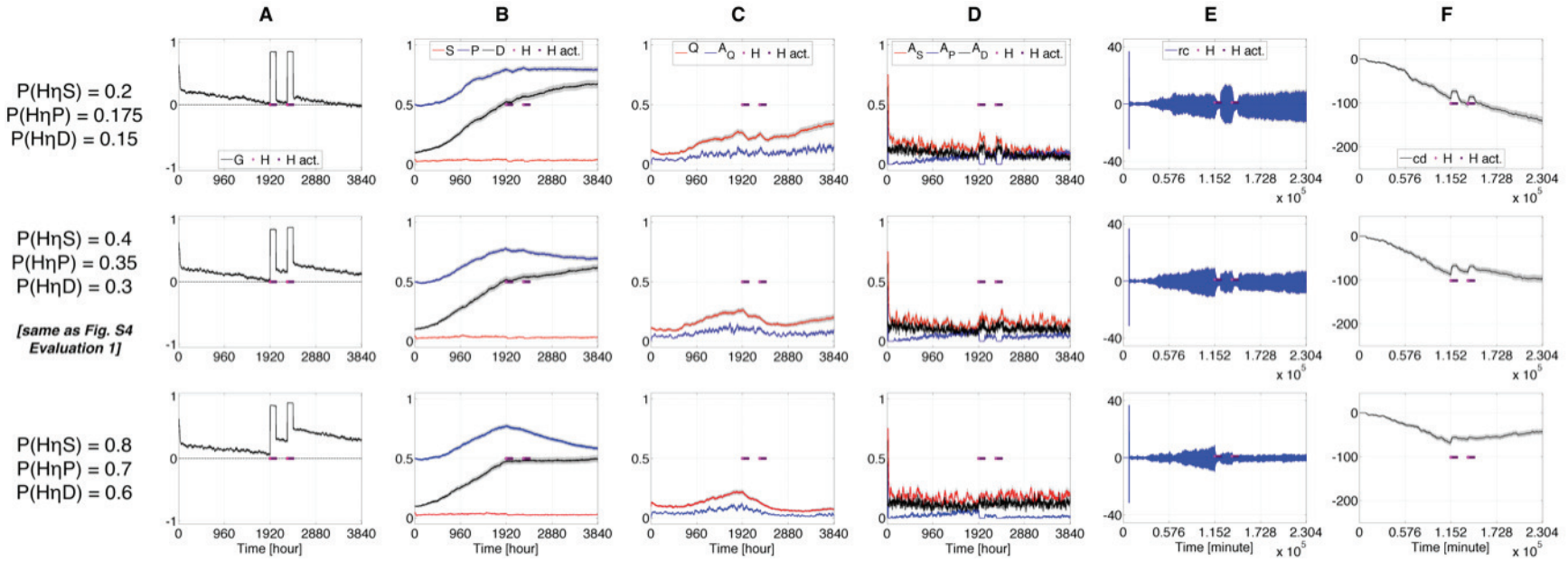

Figure 26: Details of simulations presented in Figure 25. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The abscissas correspond to the simulation's time-steps: hours in columns A-D, and minutes in columns E-F.

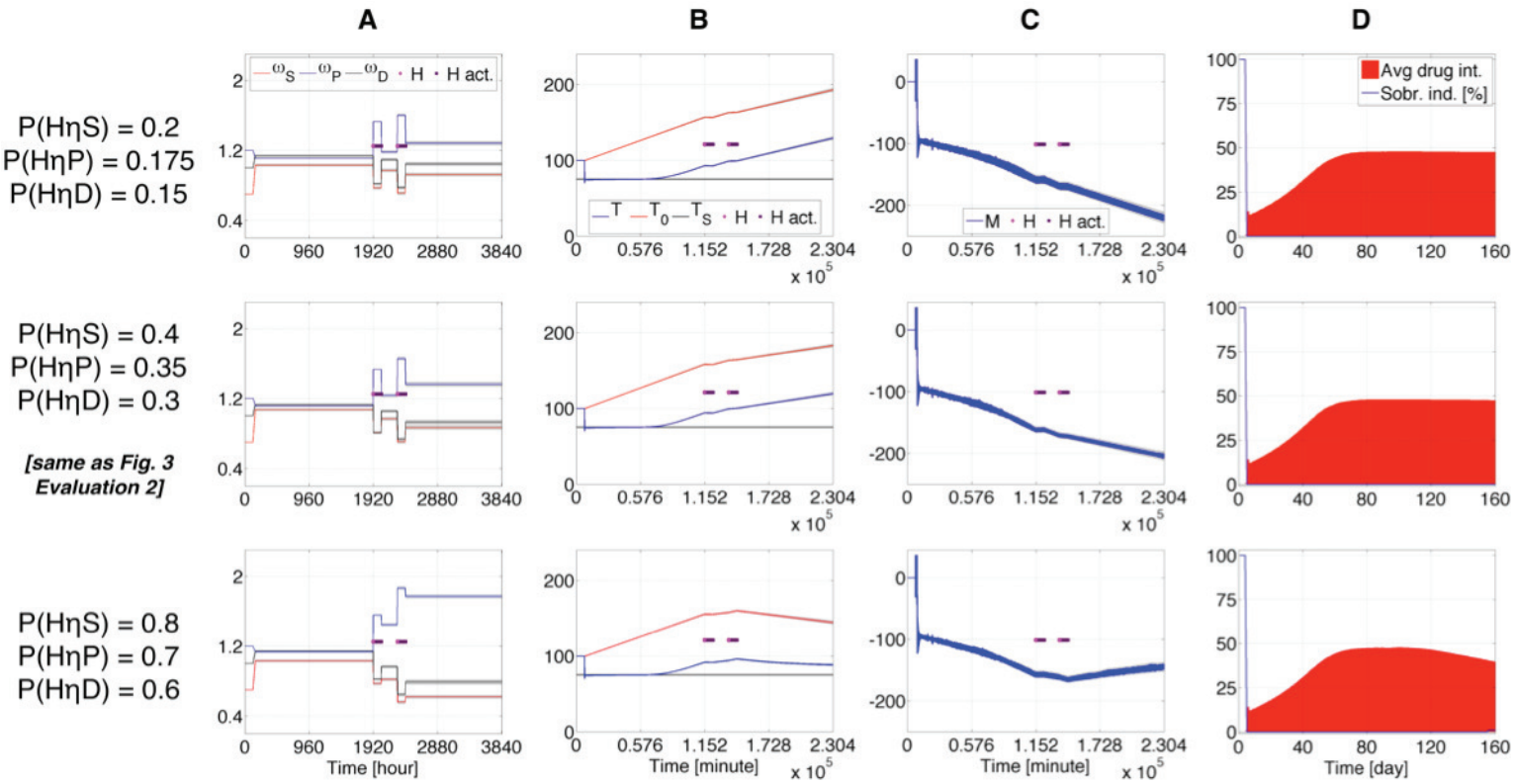

Figure 27: Comparison of different probabilities defining the durability of H for conventional therapies, with T_S constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figure 25 but have constant T_S. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); column B the progression of T (blue), T_S (black), and T_0 (red); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the sobriety index (blue) over time. The gray shades in columns A, B, and C corresponds to SEM. The abscissas correspond to the simulation's time-steps: hours in column A; minutes in columns B-C; and days in column D.

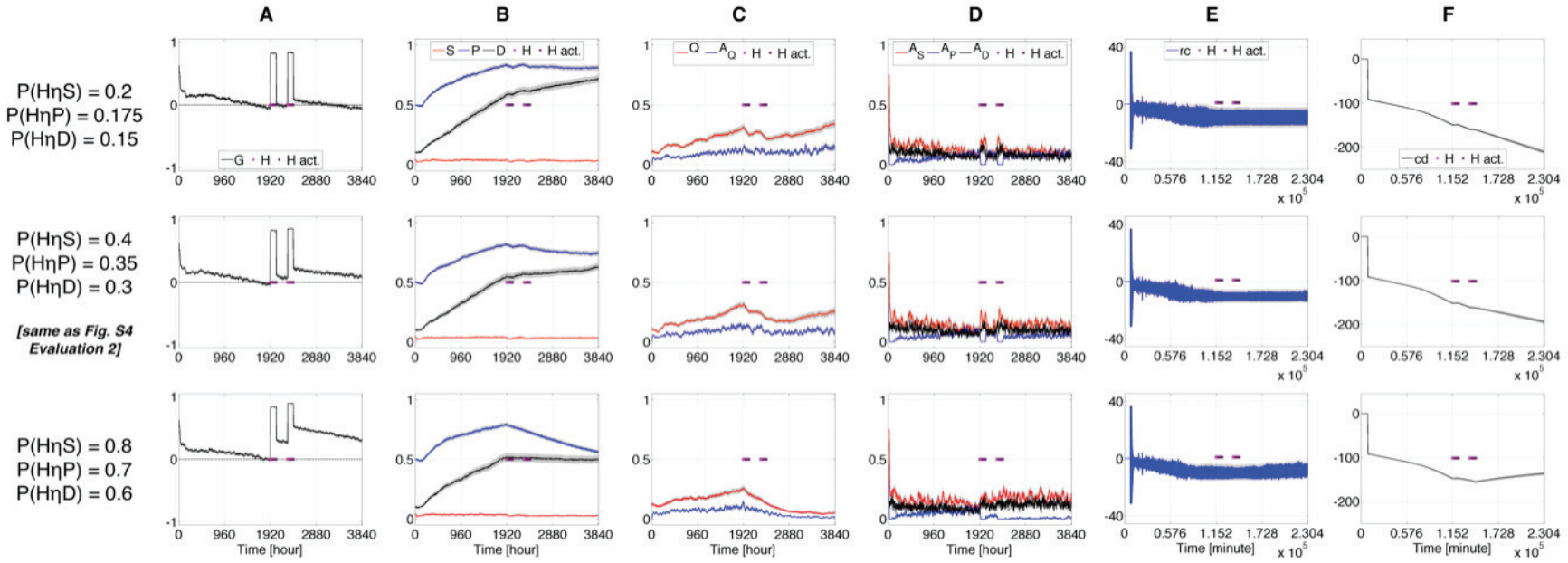

Figure 28: Details of simulations presented in Figure 27. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figure 26 but have constant T_S. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The abscissas correspond to the simulation's time-steps: hours in columns A-D, and minutes in columns E-F.

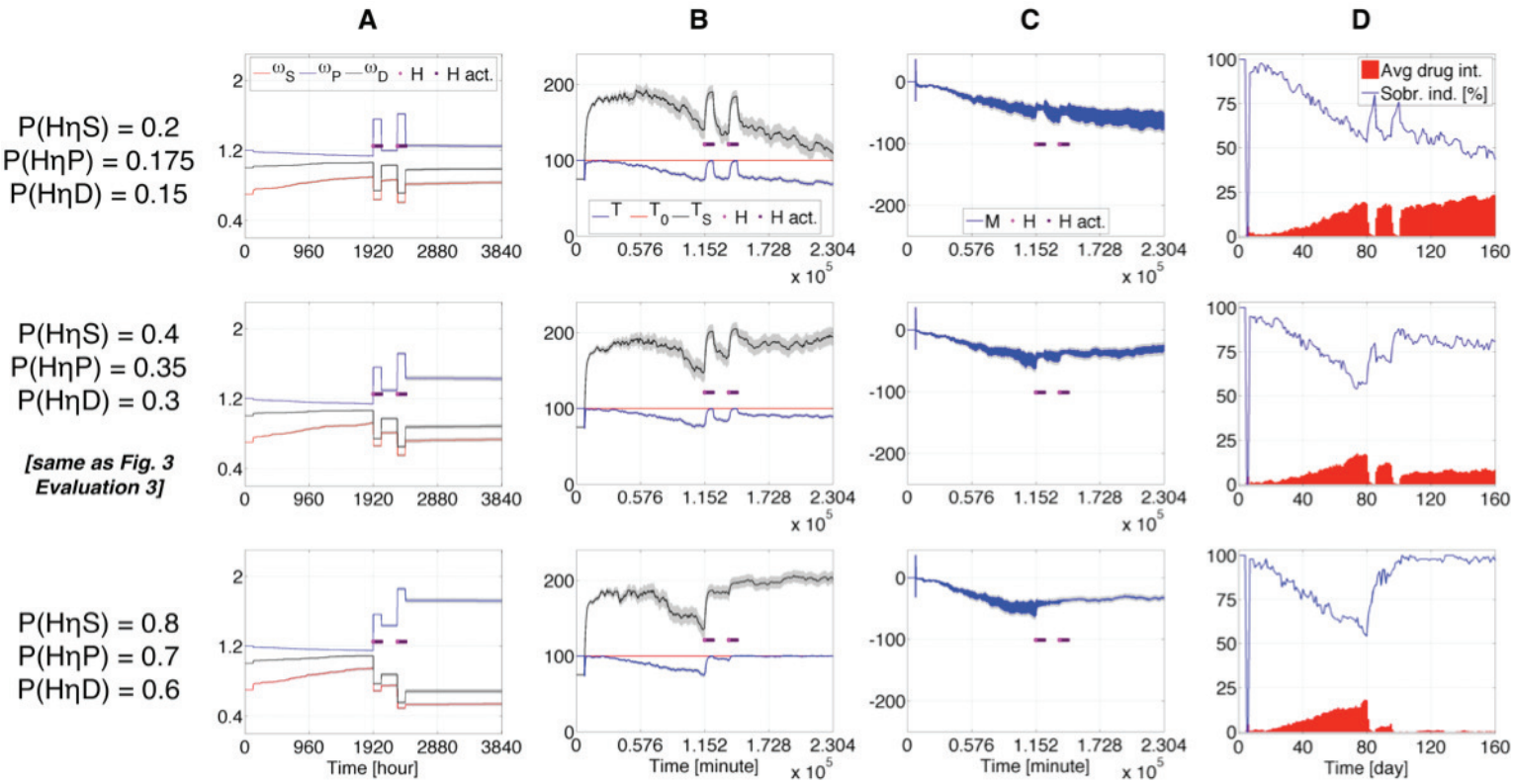

Figure 29: Comparison of different probabilities defining the durability of H for conventional therapies, with T_0 constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figure 25 but have constant T_S. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); column B the progression of T (blue), T_S (black), and T_0 (red); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the sobriety index (blue) over time. The gray shades in columns A, B, and C corresponds to SEM. The abscissas correspond to the simulation's time-steps: hours in column A; minutes in columns B-C; and days in column D.

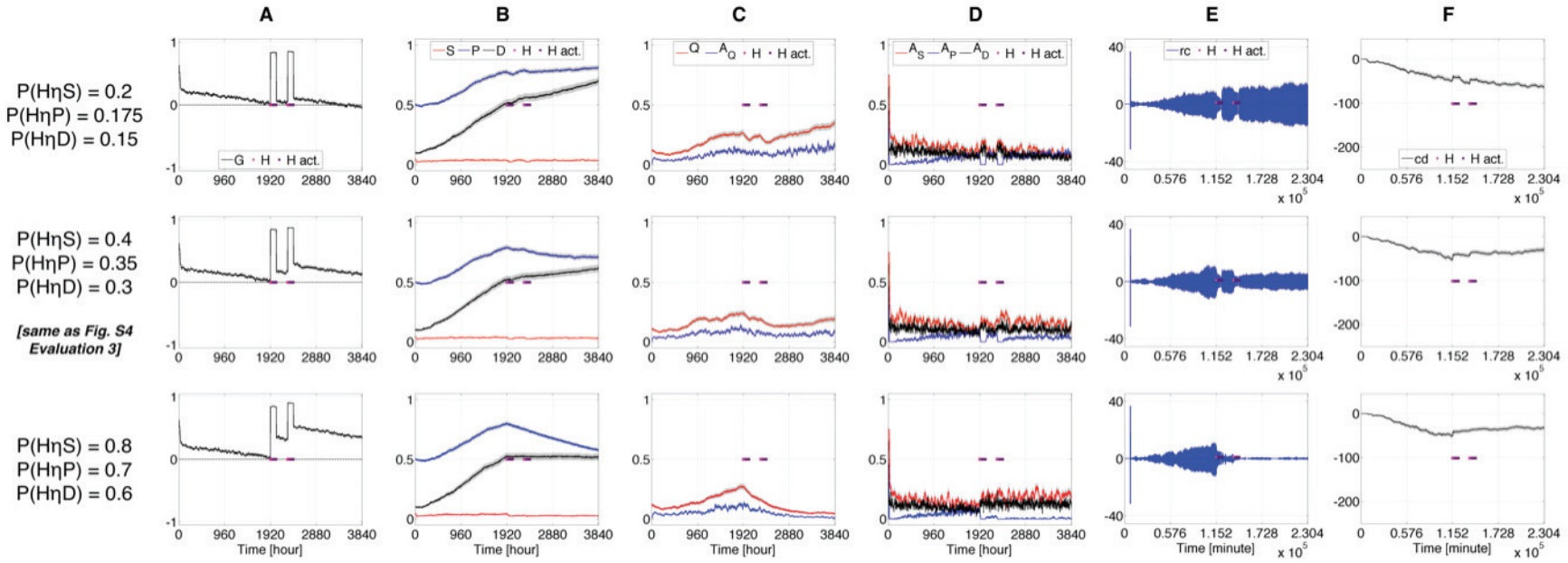

Figure 30: Details of simulations presented in Figure 29. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t = 1920$ and $t = 2280$ [hours] (in light pink) and stays active for 120 hours (dark pink). These simulations use the same experimental setup employed in Figure 26 but have constant T_S. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The abscissas correspond to the simulation's time-steps: hours in columns A-D, and minutes in columns E-F.

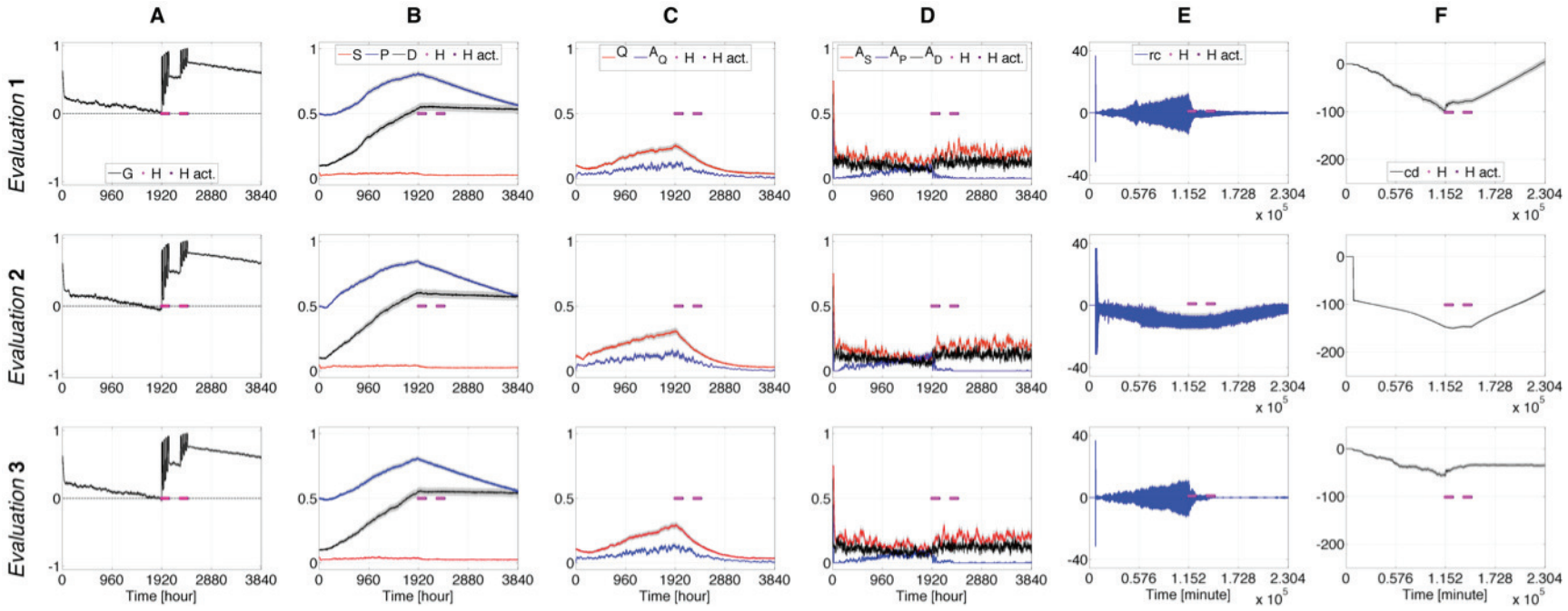

Figure 31: Details of Case Study 3 presented in Figures 18 and 19. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. Evaluation 1 simulates both T_S and T_0 as time-dependent processes. T_S is constant and T_0 time-dependent in Evaluation 2, T_S is time-dependent and T_0 constant in Evaluation 3. In all Evaluations, the recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The simulation time-scales are multiple: hours for columns A-D, and minutes for columns E-F.

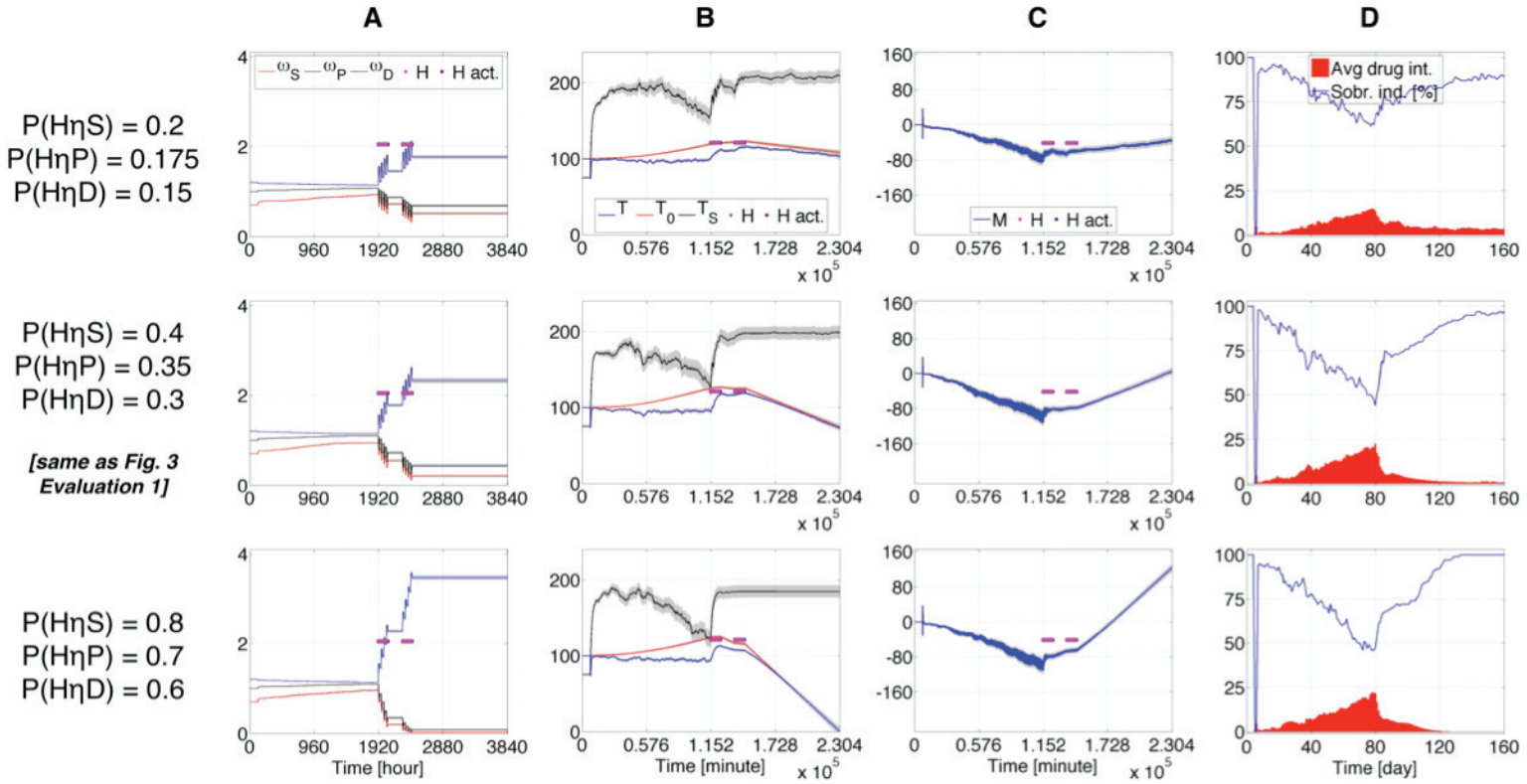

Figure 32: Comparison of different probabilities defining the durability of H for alternative treatments, with both T_S and T_0 time-dependent. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); column B the progression of T (blue), T_S (black), and T_0 (red); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the sobriety index (blue) over time. The gray shades in columns A, B, and C corresponds to SEM. The abscissas correspond to the simulation's time-steps: hours in column A; minutes in columns B-C; and days in column D. Lowest probabilities terminates at advanced stage 1 or intermediate stage 2 (~4 intakes/day and ~85% sobriety), whereas highest probabilities lead the virtual subject to cease using the drug.

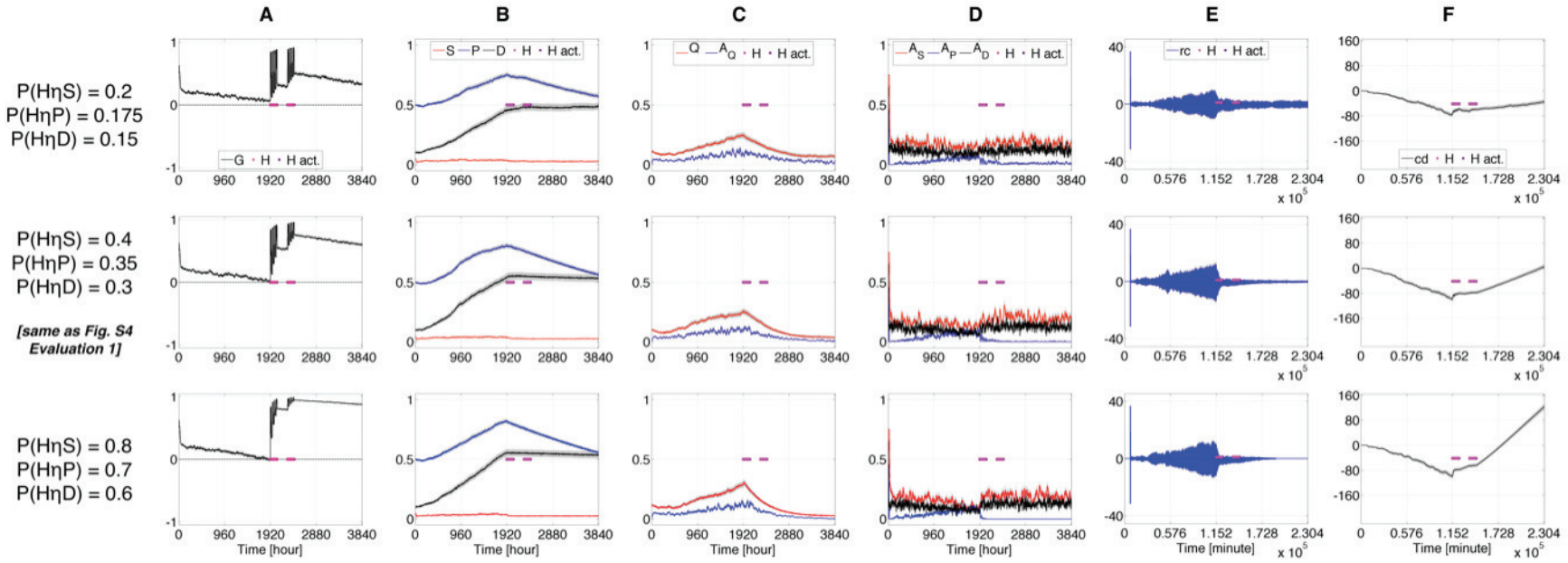

Figure 33: Details of simulations presented in Figure 32. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The abscissas correspond to the simulation's time-steps: hours in columns A-D, and minutes in columns E-F.

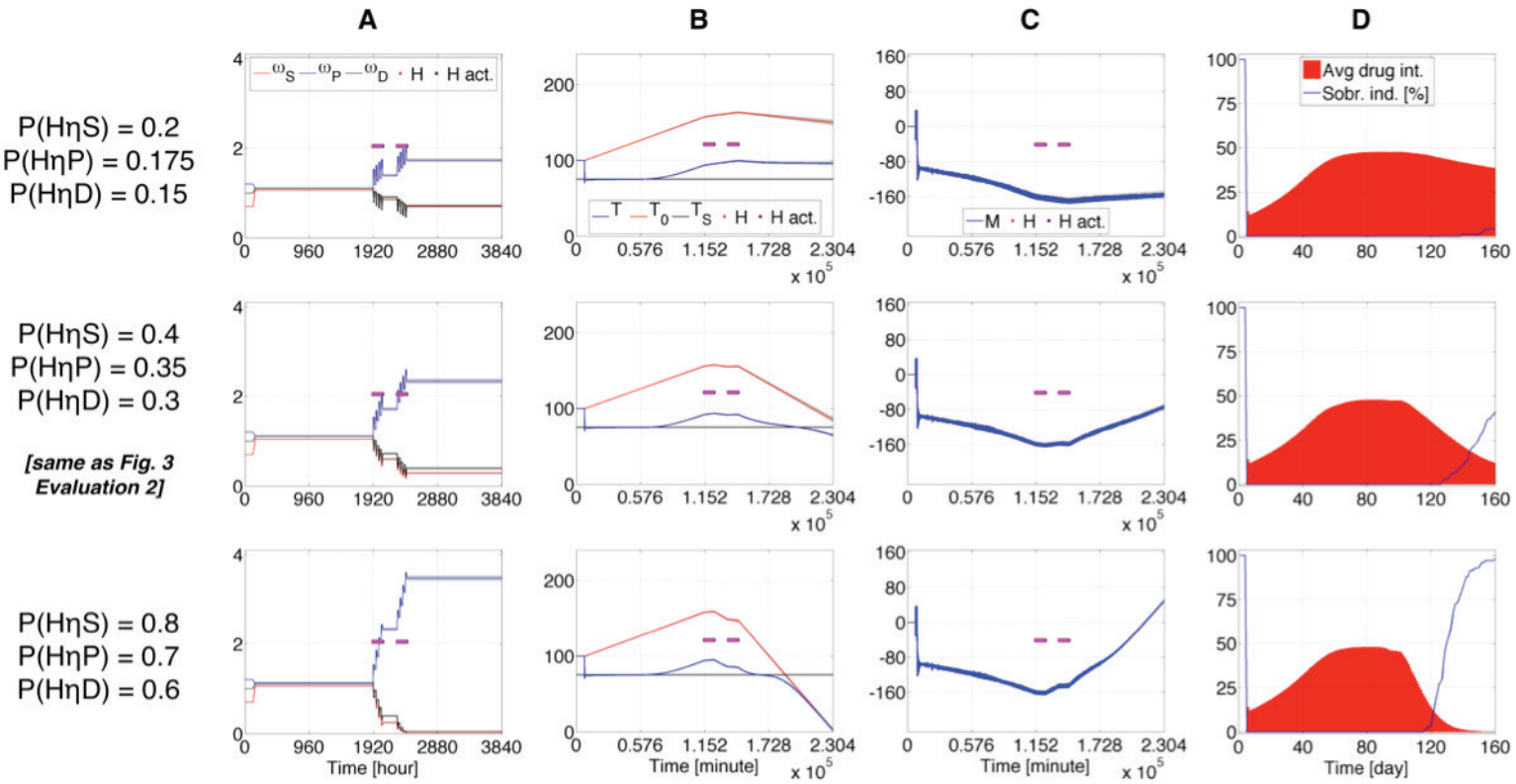

Figure 34: Comparison of different probabilities defining the durability of H for alternative treatments, with T_S constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figure 32 but have constant T_S. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); column B the progression of T (blue), T_S (black), and T_0 (red); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the sobriety index (blue) over time. The gray shades in columns A, B, and C corresponds to SEM. The abscissas correspond to the simulation's time-steps: hours in column A; minutes in columns B-C; and days in column D.

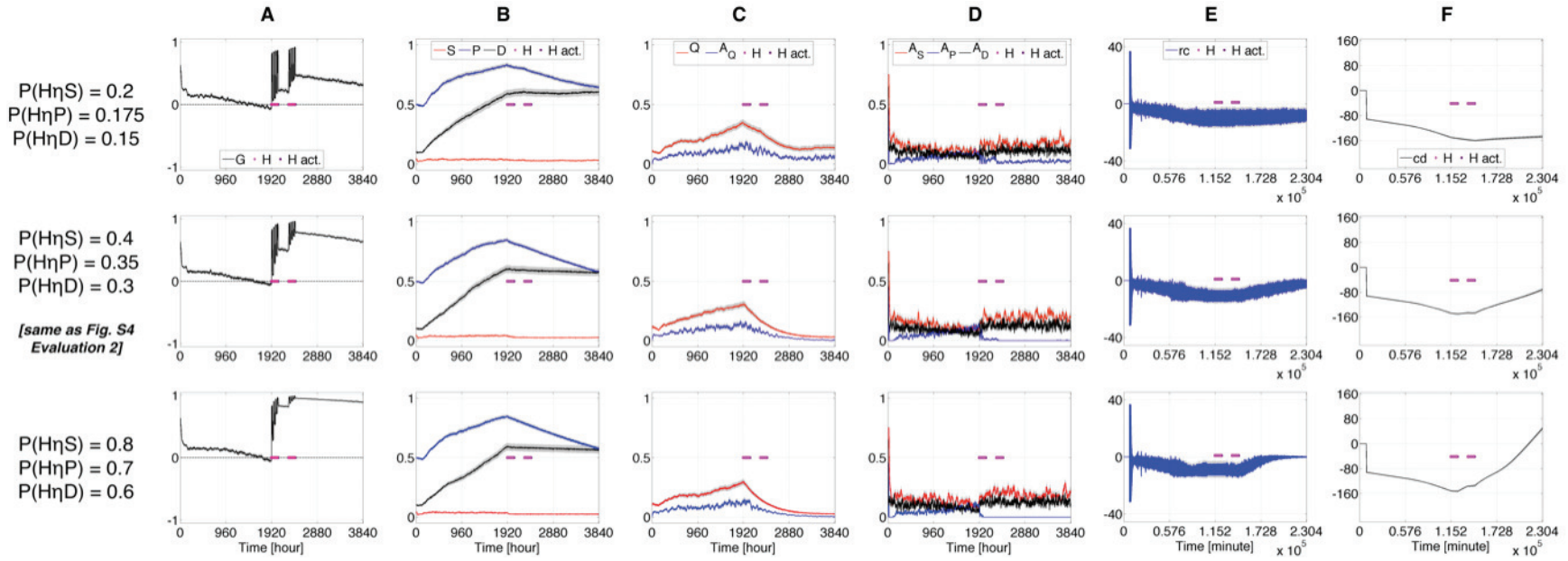

Figure 35: Details of simulations presented in Figure 34. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figure 33 but have constant T_S. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The abscissas correspond to the simulation's time-steps: hours in columns A-D, and minutes in columns E-F.

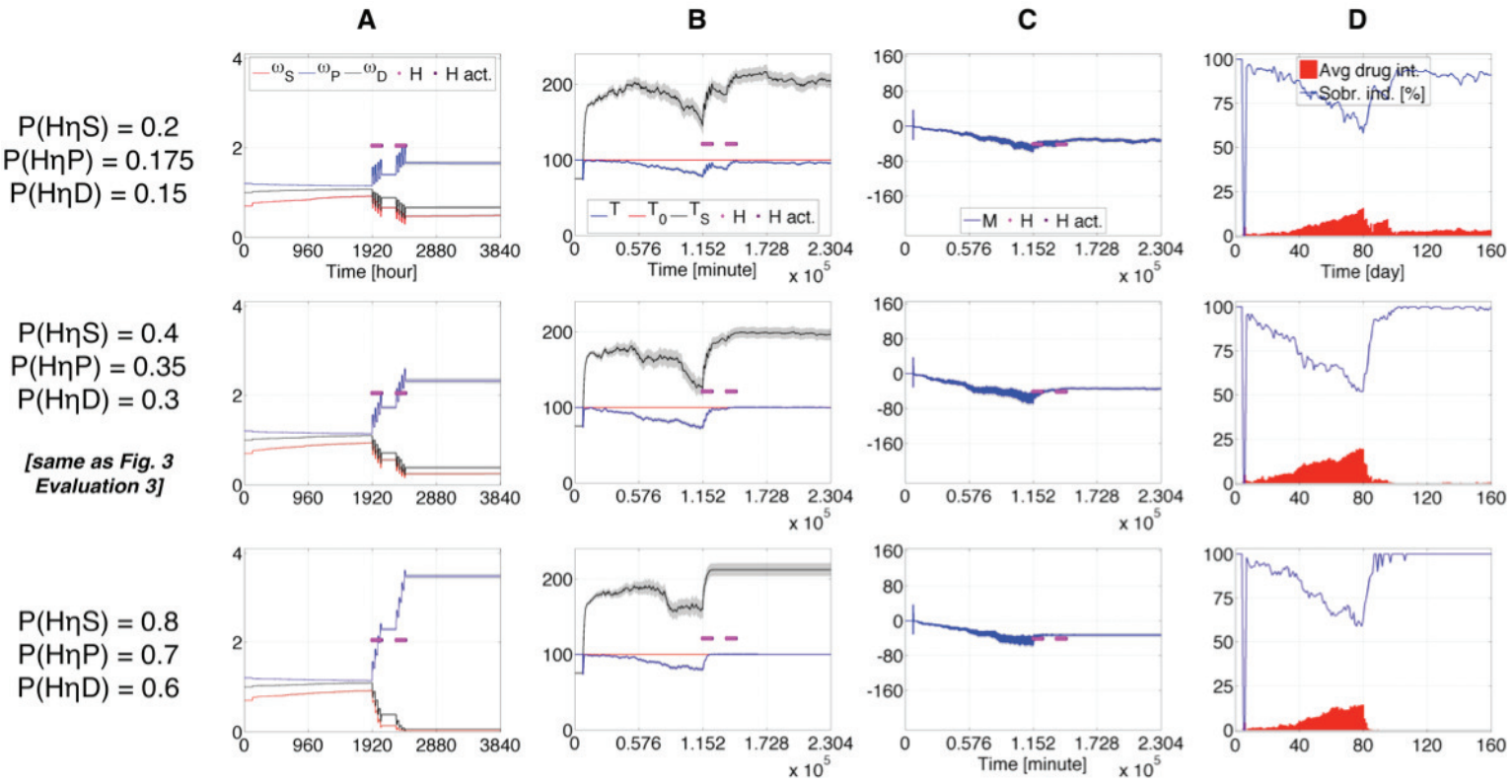

Figure 36: Comparison of different probabilities defining the durability of H for alternative treatments, with T_0 constant. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figure 32 but have constant T_0. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{\mathrm{S}, \mathrm{P}, \mathrm{D}\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of cognitive weights ω_S (red), ω_P (blue), and ω_D (black); column B the progression of T (blue), T_S (black), and T_0 (red); column C the virtual subject's mood; and column D the average number of drug intakes (red), and the sobriety index (blue) over time. The gray shades in columns A, B, and C corresponds to SEM. The abscissas correspond to the simulation's time-steps: hours in column A; minutes in columns B-C; and days in column D.

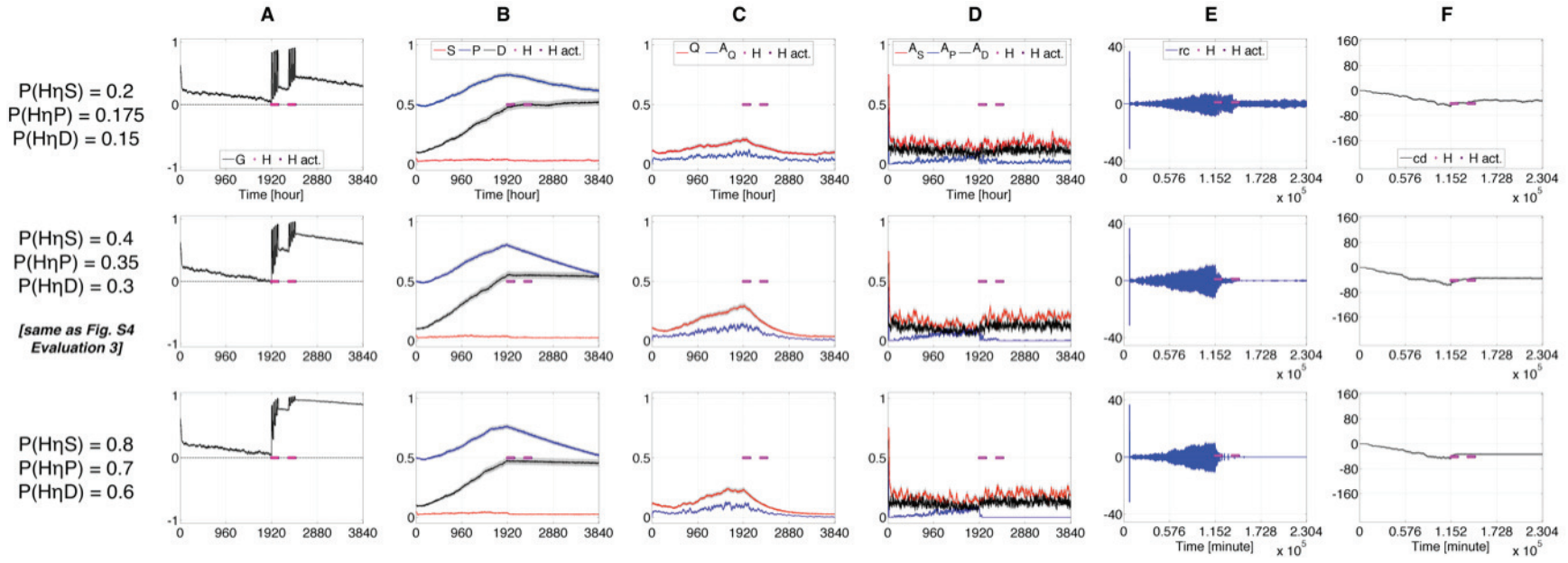

Figure 37: Details of simulations presented in Figure 36. Simulations of virtual behavior for cigarette consumption over a period of 160 days. Cigarettes are available on the fifth day. Results are the average of 100 runs. The recovery process H is activated at $t \in \{1920, 1960, 2000, 2040, 2280, 2320, 2360, 2400\}$ [hours] (in light pink) and stays active for 15 hours (dark pink). These simulations use the same experimental setup employed in Figure 33 but have constant T_0. At the end of each therapeutic session, the positive influence that H exerts on ω_S, ω_P, and ω_D become permanent or disappears, depending on arbitrary probabilities. Three sets of probabilities $P(H\eta i)$, with $i \in \{S, P, D\}$, are tested: $[0.2, 0.175, 0.15]$, $[0.4, 0.35, 0.3]$, and $[0.8, 0.7, 0.6]$. Column A reports the evolution of drug-seeking behavior G; column B the progression of internal processes stress S (red), pain P (blue), and drug craving D (black); column C the internal process of saliency to drug cues Q (red) and external trigger acute drug cue AQ (blue); column D the external triggers of acute shock AS (red), acute trauma AP (blue), and acute drug priming AD (black); column E the rush/comedown effect rc of drug intakes; and column F the cognitive distortion cd. The gray shades correspond to SEM. The abscissas correspond to the simulation's time-steps: hours in columns A-D, and minutes in columns E-F.

APPENDIX C

SUPPLEMENTARY TABLE

Table 2: Values of the parameters as used in Figures 13 to 37.

Eq.	Parameter	Value
S1,S9	N/A	N/A
S2	α	40
	β	60
	Δ	10
S3	γ	0.3
S4	α	30
S5	T_{max}	120
	T_{50}	588.6
S6	D	250
	k_{12}	0.0054
	V_b	1.67
S7	$T_S(0)$	75
	β	0.05
	γ	0.05
	λ	100
S8	$T_0(0)$	100
	δ_{T0}	0.03
	α	20
S10	ω_O	0.28
	ω_A	0.35
	ω_H	0.8
	$\alpha_S(0)$	0.7
	$\alpha_P(0)$	1.2
	$\alpha_D(0)$	1
	$P(H\eta S)$	0.2, 0.4, 0.8
	$P(H\eta P)$	0.175, 0.35, 0.7
	$P(H\eta D)$	0.8, 0.7, 0.6
	$P(Z\eta S)$	0.05, 0.1, 0.2, 0.4, 0.8
	$P(Z\eta P)$	0.025, 0.05, 0.1, 0.2, 0.4
	$P(Z\eta D)$	0.0125, 0.025, 0.05, 0.1, 0.2
	υ_S	–0.26
	υ_P	0.42
	υ_D	–0.32
	η_S	–0.1
	η_P	0.05
	η_D	–0.15
S11	α	0.25
	β	0.85
	γ	–0.4052
S12	δ_i	15
	δ_d	1
S13	β	0.002
	γ	0.002
S14	β	0.0002
	γ	0.01
S15	τ	20
	β	0.00002
	γ	0.002
S16	τ	10
	β	0.002
	γ	0.0005
S17	S_0	0.75
	ρ	0.9
	$P(AS)$	0.01
	τ_1	20
	τ_2	60
S18	P_0	0.45
	ρ	0.4
	$P(AP)$	0.03
	τ_1	15
	τ_2	50
S19	D_0	0.65
	ρ	0.55
	$P(AD)$	0.03
	τ_1	5
	τ_2	30
S20	ρ	0.9
	$P(AQ)$	0.02
	τ_1	20
	τ_2	40
S21	I	1
	C	1

BIBLIOGRAPHY

1. Leshner AI. Addiction is a brain disease, and it matters. Science. 1997; 278(5335): p. 45-47.
2. Interlandi J. What Addicts Need. Newsweek. 2008: p. 36-42.
3. Koob G, Le Moal M. Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 2001; 24(2): p. 97-129.
4. Schiff PLJ. Opium and its alkaloids. Am J Pharm Educ. 2002 January; 66: p. 186-194.
5. Szasz TS. Ceremonial chemistry: the ritual persecution of drugs, addicts, and pushers. Syracuse: Syracuse University Press; 2003.
6. Kramer I. Tea Drinking and Its Culture. In Dingbo W, Murphy PD. Handbook of Chinese Popular Culture. Santa Barbara: Greenwood Publishing Group; 1994. p. 55-76.
7. Hillman DCA. The Chemical Muse: Drug Use and the Roots of Western Civilization New York: Thomas Dunne Books, St. Martin's Press; 2008.
8. De Quincey T. Confessions of an English Opium-Eater (Part I). The London Magazine. 1821 Sept; 4(21).
9. De Quincey T. Confessions of an English Opium-Eater (Part II). The London Magazine. 1821 Oct; 4(22).
10. Berridge V, Mars S. History of addictions. J Epidemiol Community Health. 2004 Apr 22; 58(9): p. 747-750.
11. Meyer JS, Quenzer LF. Psychopharmacology: Drugs, the Brain and Behavior Sunderland: Sinauer Associates, Inc.; 2005.
12. The Columbia Encyclopedia. Drug addiction and drug abuse: Encyclopedia.com; 2008.
13. Edwards G. The trouble with drink: why ideas matter. Addiction. 2010; 105(5): p. 797-804.
14. Department of Mental Health and Substance Abuse. Neuroscience of Psychoactive Substance Use and Dependence Saraceno B, editor. Geneva: World Health Organization; 2004.
15. Leukefeld CG, Leukefeld S. Primary socialization theory and a bio/psycho/social/spiritual practice model for substance use. Subst Use Misuse. 1999; 34(7): p. 983-991.
16. Office of National Drug Control Policy (ONDCP). The Economic Costs of Drug Abuse in the United States: 1992-2002. Washington, DC; 2004.

17. Centers for Disease Control and Prevention. Annual Smoking-Attributable Mortality, Years of Potential Life Lost, and Productivity Losses -United States, 1997-2001. Morbidity and Mortality Weekly Report. 2005 July: p. 625-628.
18. Harwood HJ. Updating Estimates of the Economic Costs of Alcohol Abuse in the United States: Estimates, Update Methods, and Data Report. National Institute on Alcohol Abuse and Alcoholism (prepared by The Lewin Group). 2000.
19. National Institute on Drug Abuse (NIDA). Understanding Drug Abuse and Addiction. NIDA InfoFacts. 2011; March: p. 1-4.
20. Waldorf D. Natural recovery from opiate addiction: Some social-psychological processes of untreated recovery. J Drug Issues. 1983; 13(2): p. 237-280.
21. Carter-Sobell L, Ellingstad TSM. Natural recovery from alcohol and drug problems: methodological review of the research with suggestions for future directions. Addiction. 2000; 95(5): p. 749-764.
22. Winick C. Maturing out of narcotic addiction. United Nations Office On Drugs and Crime (UNODC) Bulletin on Narcotics. 1962; 14(1): p. 1-7.
23. Carballo JL, Fernandez-Hermida JR, Secades-Villa R, Carter-Sobell L, Dum M, Garcia-Rodriguez O. Natural Recovery from Alcohol and Drug Problems: A Methodological Review of the Literature from 1999 through 2005. In Klingemann H, Carter-Sobell L. In Promoting Self-Change From Addictive Behaviors: Practical Implications for Policy, Prevention, and Treatment, Behavioral Science. New York: Springer; 2007. p. 87-101.
24. Maddux JF, Desmond DP. New light on the maturing out hypothesis in opioid dependence. United Nations Office On Drugs and Crime (UNODC) Bulletin on Narcotics. 1980; 32(2): p. 15-25.
25. Anglin MD, Brecht ML, Woodward JA, Bonett DG. An empirical study of maturing out: conditional factors. Int J Addict. 1986; 21(2): p. 233-246.
26. National Institutes of Health (NIH). NIH Working Definition of Bioinformatics and Computational Biology. Biomedical Information Science and Technology Initiative Committee (BISTIC). 2000; July: p. 1.
27. Levy D, Siegelmann HT. Addiction and Rehabilitation: A Non-monotonic Computational Process. Unpublished working document. 2006.
28. Siegelmann HT, Levy D, Levy YZ. Addiction and Rehabilitation: A Non-monotonic Computational Process. Tech Report. UMass Amherst, Computer Science; 2009. Report No.: UM-CS-2009-002.

29. Levy YZ, Levy D, Meyer JS, Siegelmann HT. Drug Addiction: a Computational Multiscale Model Combining Neuropsychology, Cognition, and Behavior. In Proceedings of the International Conference on Bio-inspired Systems and Signal Processing (BIOSIGNALS 2009); 2009; Porto, Portugal. p. 87-94.
30. Levy YZ, Levy D, Meyer JS, Siegelmann HT. Drug Addiction as a Non-monotonic Process: a Multiscale Computational Model. In Lim C, Goh J, editors. 13th International Conference on Biomedical Engineering. Singapore: Springer; 2008. p. 1688-1691.
31. Levy YZ, Levy D, Meyer JS, Siegelmann HT. Identification and Control of Intrinsic Bias in a Multiscale Computational Model of Drug Addiction. In Proceedings of the 2010 Symposium on Applied Computing (ACM SAC); 2010; Sierre, Switzerland. p. 2389-2393.
32. Levy YZ, Levy D, Meyer JS. Computational Hypothesis for Maturing Out of Addiction and Mindfulness-Based Cognitive Techniques. Proceedings of the Second Annual Meeting of the Biologically Inspired Cognitive Architectures Society (BICA 2011). 2011;: p. 222-231.
33. Zeigler BP, Praehofer H, Kim TG. Theory of Modelling and Simulation: Integrating Discrete Event and Continuous Complex Dynamic Systems. 2nd ed. San Diego: Academic Press; 2000.
34. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. Am J Psychiatry. 2002; 159(10): p. 1642–1652.
35. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977; 196(4286): p. 129-36.
36. Buchman DZ, Skinner W, Illes J. Negotiating the relationship between addiction, ethics, and brain science. AJOB Neurosci. 2010; 1(1): p. 36-45.
37. Ahmed SH, Koob GF. Transition to drug addiction: a negative reinforcement model based on an allostatic decrease in reward function. Psychopharmacology (Berl). 2005; 180(3): p. 473-490.
38. Levy YZ, Levy DJ, Barto AG, Meyer JS. A computational hypothesis for allostasis: delineation of substance dependence, conventional therapies, and alternative treatments. (in preparation). 2012.
39. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV Arlington: Amer Psychiatric Pub; 1994.
40. Siegler M, Osmond H. Models of Drug Addiction. Int J Addict. 1968; 3(1): p. 3-24.
41. National Institute on Drug Abuse (NIDA). Theories on Drug Abuse: Selected Contemporary Perspectives Letieri DJ, Sayers M, Wallenstein-Pearson H, editors. Bethesda: NIDA Research Monograph; 1980.

42. Robinson T, Berridge K. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev. 1993; 18(3): p. 247-291.
43. Robinson T, Berridge K. The psychology and neurobiology of addiction: an incentive-sensitization view. Addiction. 2000; 95(Suppl 2).
44. Robinson T, Berridge K. Addiction. Annu Rev Psychol. 2003; 54: p. 25–53.
45. Solomon R, Corbit J. An opponent-process theory of motivation. I. Temporal dynamics of affect. Psychol Rev. 1974; 81(2): p. 119-145.
46. Sterling P, Eyer J. Allostasis: A new paradigm to explain arousal pathology. In Fisher S, Reason J, editors. Handbook of Life Stress Cognition and Health. Oxford: Wiley & Sons; 1998. p. 629-649.
47. Koob G, Le Moal M. Drug abuse: hedonic homeostatic dysregulation. Science. 1997; 278(5335): p. 52-58.
48. Koob G, Bloom F. Cellular and molecular mechanisms of drug dependence. Science. 1998; 242(4879): p. 715-723.
49. Ahmed S, Kenny P, Koob G, Markou A. Neurobiological evidence for hedonic allostasis associated with escalating cocaine use. Nat Neurosci. 2002; 5(7): p. 625-626.
50. Camí J, Farré M. Mechanisms of Disease: Drug Addiction. N Engl J Med. 2003; 349(10): p. 975-986.
51. Koob G, Le Moal M. Addiction and the brain antireward system. Annu Rev Psychol. 2008; 59: p. 29-53.
52. Koob G. A role for brain stress systems in addiction. Neuron. 2008; 59(1): p. 11-34.
53. George O, Le Moal M, Koob G. Allostasis and addiction: Role of the dopamine and corticotropin-releasing factor systems. Physiol Behav. 2012; 106(1): p. 58-64.
54. Koob G, Le Moal M. Plasticity of reward neurocircuitry and the 'dark side' of drug addiction. Nat Neurosci. 2005; 8(11): p. 1442-1444.
55. Jellinek EM. Alcoholism, a genus and some of its species. Can Med Assoc J. 1960; 83(26): p. 1341-1345.
56. Jellinek EM. The disease concept of alcoholism. New Haven: Millhouse Press; 1960.
57. Dackis C, O'Brien C. Neurobiology of addiction: treatment and public policy ramifications. Nat Neurosci. 2005; 8(11): p. 1431-1436.
58. Satel S, Lilienfeld SO. Singing the brain disease blues. AJOB Neuroscience. 2010; 1(1): p. 46-47.
59. Buchman D, Illes J, Reiner P. The Paradox of Addiction Neuroscience. Neuroethics. 2010 June; online first.

60. Ahmed SH, Bobashev G, Gutkin BS. The simulation of addiction: pharmacological and neurocomputational models of drug self-administration. Drug Alcohol Depend. 2007; 90(2-3): p. 304-311.
61. Tretter F, Albus M. Systems biology and psychiatry - modeling molecular and cellular networks of mental disorders. Pharmacopsychiatry. 2008; 41(Suppl.1): p. S2-S18.
62. Tegnér J, Compte A, Auffray C, An G, Cedersund G, Clermont G, et al. Computational disease modeling - fact or fiction? BMC Syst Biol. 2009; 3: p. 56.
63. Ahmed SH, Graupner M, Gutkin B. Computational approaches to the neurobiology of drug addiction. Pharmacopsychiatry. 2009; 42(Suppl. 1): p. S144-S152.
64. Diekmann O, Heesterbeek JAP. Mathematical Epidemiology of Infectious Diseases: Model Building, Analysis and Interpretation NY: Wiley; 2000.
65. Castillo-Chavez G, Jordan SG, Rodriguez AH. Mathematical models for the dynamics of tobacco use, recovery and relapse. Technical Report Series BU-1505-M. Cornell University, Department of Biometrics; 2000.
66. Brauer F, Castillo-Chavez C. Mathematical Models in Population Biology and Epidemiology: Text in Applied Mathematics, Springer; 2000.
67. Sharomi O, Gumel AB. Curtailing smoking dynamics: A mathematical modeling approach. Appl Math Comput. 2008; 195: p. 475-499.
68. Zaman G. Qualitative behavior of giving up smoking model. Bulletin of the Malaysian Mathematical Sciences Society. 2009.
69. White E, Comiskey C. Heroin epidemics, treatment and ODE modelling. Mathematical Biosciences. 2007; 208: p. 312-324.
70. Mulone G, Straughan B. A note on heroin epidemics. Mathematical Biosciences. 2009; 218: p. 138–141.
71. Sanchez F, Wang X, Castillo-Cahvez C, Gorman DM, Gruenwald PJ. Drinking as an epidemic: a simple mathematical model with recovery and relapse. In Witkiewitz KA, Marlat GA. Therapist's Guide to Evidence-Based Relapse Prevention (Practical Resources for the Mental Health Professional).: Elsevier; 2007. p. 353-368.
72. Benedict B. Modeling Alcoholism as a Contagious Disease: How “Infected” Drinking Buddies Spread Problem Drinking. SIAM News. 2007.
73. Newman P. Modelling Alcoholism as an Epidemic: The Wrath of Grapes. Durham University, Department of Mathematical Sciences; 2008.
74. Liang L, Chaloupka FJ, Nichter M, Clayton R. Prices, policies and youth smoking, May 2001. Addiction. 2003; 98(Suppl 1): p. 105-122.

75. Bickel WK, Miller ML, Yi R, Kowal BP, Lindquist DM, Pitcock JA. Behavioral and neuroeconomics of drug addiction: Competing neural systems and temporal discounting processes. Drug Alcohol Depend. 2007; 90(Suppl 1): p. S85-S91.

76. Sloan FA, Wang Y. Economic theory and evidence on smoking behavior of adults. Addiction. 2008; 103(11): p. 1777-1785.

77. Chaloupka FJ, Warner KE. The economics of smoking. In Culyer AJ, Newhouse JP. Handbook of Health Economics.: Elsevier; 2000. p. 1539-1627.

78. Becker G, Murphy K. A Theory of Rational Addiction. The Journal of Political Economy. 1988; 96(4): p. 675-700.

79. Bickel WK, Odum AL, Madden GJ. Impulsivity and cigarette smoking: Delay discounting in current, never, and ex-smokers. Psychopharmacology. 1999; 146(4): p. 447-454.

80. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nature Neuroscience. 2005; 8(11): p. 1458-1463.

81. Holford NHG, Sheiner LB. Kinetics of pharmacologic response. Pharmacol. Ther. 1982; 16(2): p. 143-166.

82. Derendorf H, Meibohm B. Modeling of pharmacokinetic/pharmacodynamic (PK/PD) relationships: concepts and perspectives. Pharm Res. 1999; 19(2): p. 176-185.

83. Welling PG. Pharmacokinetics: Processes, Mathematics, and Applications Washington, DC: An American Chemical Society Publication; 1986.

84. Meibohm B, Derendorf H. Basic concepts of pharmacokinetic/pharmacodynamic (PK/PD) modelling. Int J Clin Pharmacol Ther. 1997; 35(10): p. 401-413.

85. Tsibulsky VL, Norman AB. Satiety threshold: a quantitative model of maintained cocaine self-administration. Brain Res. 1999; 839(1): p. 85-93.

86. Wise RA, Newton P, Leeb K, Burnette B, Pocock D, Justice JB. Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats. Psychopharmacology. 1995; 120(1).

87. Rang HP. The receptor concept: pharmacology's big idea. Br J Pharmacol. 2006; 147(Suppl. 1): p. S9-16.

88. Sizemore GM, Martin TJ. Toward a mathematical description of dose-effect functions for self-administered drugs in laboratory animal models. Psychopharmacology (Berl). 2000; 153(1): p. 57-66.

89. Sutton RS, Barto AG. Reinforcement learning: an introduction Cambridge: MIT Press; 1998.

90. Sutton RS. Learning to predict by the methods of temporal differences. Machine learning. 1988; 3: p. 9-44.
91. Schultz W. Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey. J Neurophysiol. 1986; 56(5): p. 1439-1461.
92. Barto AG. Adaptive critics and the basal ganglia. In Houk J, Davis J, Beiser D, editors. Models of information processing in the basal ganglia. Cambridge: MIT Press; 1995. p. 215-232.
93. Houk JC, Adams JL, Barto AG. A model of how the basal ganglia generate and use neural signals that predict reinforcement. In Houk J, Davis J, Beiser D, editors. Models of information processing in the basal ganglia. Cambridge: MIT Press; 1995. p. 249-270.
94. Montague P, Dayan P, Sejnowski T. A framework for mesencephalic dopamine systems based on predictive Hebbian learning. J Neurosci. 1996; 16(5): p. 1936-1947.
95. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. Science. 1997; 275(5306): p. 1593-1599.
96. Schultz W. Predictive reward signal of dopamine neurons. J Neurophysiol. 1998; 80(1): p. 1-27.
97. Redish AD. Addiction as a computational process gone awry. Science. 2004; 306(5703): p. 1944-1947.
98. Panlilio LV, Thorndike EB, Schindler CW. Blocking of conditioning to a cocaine-paired stimulus: testing the hypothesis that cocaine perpetually produces a signal of larger-than-expected reward. Pharmacol Biochem Behav. 2007; 86(4): p. 774-777.
99. Dezfouli A, Piray P, Keramati MM, Ekhtiari H, Lucas C, Mokri A. A neurocomputational model for cocaine addiction. Neural Comput. 2009; 21(10): p. 2869-2893.
100. Mahadevan S. Average reward reinforcement learning: Foundations, algorithms, and empirical results. Mach Learn. 1996; 22(1): p. 159-195.
101. Bobashev G, Costenbader E, Gutkin B. Comprehensive mathematical modeling in drug addiction sciences. Drug Alcohol Depend. 2007; 89(1): p. 102-106.
102. Tretter F, Gebicke-Haerter PJ, Albus M, an der Heiden U, Schwegler H. Systems biology and addiction. Pharmacopsychiatry. 2009; 42(Suppl.1): p. S11-S31.
103. Gutkin BS, Dehaene S, Changeux JP. A neurocomputational hypothesis for nicotine addiction. Proc Natl Acad Sci USA. 2006; 103(4): p. 1106-1111.

104. Graupner M, Gutkin BS. Modeling nicotinic neuromodulation from global functional and network levels to nAChR based mechanisms. Acta Pharmacol Sin. 2009; 30(6): p. 681-693.

105. Waldorf D, Biernacki P. Natural recovery from heroin addiction: A review of the incidence literature. J Drug Issues. 1979; 9(2): p. 282–289.

106. Levy YZ, Levy D, Meyer JS, Siegelmann HT. Neuropsychology, cognition, and behavior of drug addiction: A non-monotonic multiscale computational model. In 13th International Conference on Cognitive and Neural Systems (ICCNS 2009); 2009; Boston, MA.

107. Levy YZ, Levy D, Meyer JS, Siegelmann HT. Ceasing the use of narcotics without treatments in the context of a multiscale computational model of addiction. In 6th Annual Meeting of the Society for Autonomous Neurodynamics: Principles of Autonomous Neurodynamics (SAND VI); 2009; La Jolla, CA. p. 8.

108. Saltelli A, Ratto M, Andres T, Campolongo F, Cariboni J, Gatelli D, et al. Global Sensitivity Analysis: The Primer West Sussex: Wiley-Interscience; 2008.

109. Bourgine P, Stewart J. Autopoiesis and Cognition. Artif Life. 2004; 10(2): p. 327-345.

110. Shaw L. The National Drug Abuse Conference. Br Med J. 1977; 2(6092): p. 943-944.

111. Marcus M, Zgierska A. Mindfulness-based therapies for substance use disorders: part 1 (Eds). Subst Abus. 2009; 30(4): p. 263-265.

112. Zgierska A, Marcus M. Mindfulness-based therapies for substance use disorders: part 2 (Eds). Subst Abus. 2010; 31(2): p. 77-78.

113. Grant S, London ED, Newlin DB, Villemagne VL, Liu X, Contoreggi C, et al. Activation of memory circuits during cue-elicited cocaine craving. Proc Natl Acad Sci USA. 1996; 93(21): p. 12040-12045.

114. George O, Koob G. Individual Differences in Prefrontal Cortex Function and the Transition from Drug Use to Drug Dependence. Neurosci Biobehav Rev. 2010; [Epub ahead of print].

115. O'Reilly RC, Munakata Y. Computational Explorations in Cognitive Neuroscience: Understanding the Mind by Simulating the Brain Cambridge: MIT Press; 2000.

116. Sun R, Slusarz P, Terry C. The interaction of the explicit and the implicit in skill learning: a dual-process approach. Psychol Rev. 2005; 112(1): p. 159-192.

117. Samsonovich A, De Jong K. Designing a self-aware neuromorphic hybrid. In Thorisson K, Vilhjalmsson H, Marsela S, editors. AAAI-05 Workshop on Modular Construction of Human-Like Intelligence: AAAI Technical Report. Menlo Park: AAAI Press; 2005. p. 71-78.

118. Washington B. Rumination and distraction in pathological gamblers: A cognitive model of addiction and implications for treatment. The 20th Annual Conference on Prevention, Research and Treatment of Problem Gambling. 2006.
119. Ahmed SH, Koob GF. Transition from moderate to excessive drug intake: change in hedonic set point. Science. 1998; 282(5387): p. 298-300.
120. Yurica CL, DiTomasso RA. Cognitive Distortions. In Freeman A, Felgoise SH, Nezu CM, M NA, Reinecke MA, editors. Encyclopedia of Cognitive Behavior Therapy. New York: Springer; 2005. p. 117-122.
121. Morgenstern J, McCrady BS. Curative factors in alcohol and drug treatment: behavioral and disease model perspectives. Br J Addict. 1992; 87(6): p. 901-912.
122. Chase HW, Clark L. Gambling severity predicts midbrain response to near-miss outcomes. J Neurosci. 2010; 30(18): p. 6180-6187.
123. Fortune EE, Goodie AS. Cognitive distortions as a component and treatment focus of pathological gambling: a review. Psychol Addict Behav. 2012; 26(2): p. 298-310.
124. Powers PS, Perez A, Boyd F, Rosemurgy A. Eating pathology before and after bariatric surgery: a prospective study. Int J Eat Disord. 1999; 25(3): p. 293-300.
125. Davis RA. A cognitive-behavioral model of pathological Internet use. Comput Hum Behav. 2001; 17(2): p. 187-195.
126. Wise RA. Addictive drugs and brain stimulation reward. Annu Rev Neurosci. 1996; 19: p. 319-340.
127. Hodgins DC, El-Guebaly N, Armstrong S. Prospective and retrospective reports of mood states before relapse to substance use. J Consult Clin Psych. 1995; 63(3): p. 400-407.
128. Aston-Jones G, and Harris GC. Brain substrates for increased drug seeking during protracted withdrawal. Neuropharmacology. 2004; 47(Suppl. 1): p. 167-179.
129. De Alba I, Samet JH, Saitz R. Burden of medical illness in drug- and alcohol-dependent persons without primary care. Am J Addict. 2004; 13(1): p. 33-45.
130. Kalivas PW, Duffy P. Effect of acute and daily cocaine treatment on extracellular dopamine in the nucleus accumbens. Synapse. 1990; 5(1): p. 48-58.
131. Heidbreder CA, Thompson AC, Shippenberg TS. Role of extracellular dopamine in the initiation and long-term expression of behavioral sensitization to cocaine. J Pharmacol Exp Ther. 1996; 278(2): p. 490-502.

132. Volkow ND, Wang GJ, Fowler JS, Hitzemann R, Angrist B, Gatley SJ, et al. Association of methylphenidate-induced craving with changes in right striato-orbitofrontal metabolism in cocaine abusers: implications in addiction. Am J Psychiatry. 1999; 156(1): p. 19-26.

133. Erb S, Shaham Y, Stewart J. Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. Psychopharmacology (Berl). 1996; 128(4): p. 408-412.

134. Sinha R, Fuse T, Aubin LR, O'Malley SS. Psychological stress, drug-related cues and cocaine craving. Psychopharmacology (Berl). 2000; 152(2): p. 140-148.

135. Pollini RA, McCall L, Mehta SH, Vlahov D, Strathdee SA. Non-fatal overdose and subsequent drug treatment among injection drug users. Drug Alcohol Depend. 2006; 83(2): p. 104-110.

136. Barth J, Critchley J, Bengel J. Efficacy of psychosocial interventions for smoking cessation in patients with coronary heart disease: a systematic review and meta-analysis. Ann Behav Med. 2006; 32(1): p. 10-20.

137. de Wit H, Stewart J. Drug reinstatement of heroin-reinforced responding in the rat. Psychopharmacology (Berl). 1983; 79(1): p. 29–31.

138. Spealman RD, Barrett-Larimore RL, Rowlett JK, Platt DM, Khroyan TV. Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. Pharmacol Biochem Behav. 1999; 64(2): p. 327–336.

139. See RE. Neural substrates of conditioned-cued relapse to drug-seeking behavior. Pharmacol Biochem Behav. 2002; 71(3): p. 517-529.

140. Heyman GM. Addiction: a disorder of choice Cambridge: Harvard UP; 2010.

141. Goldstein RZ, Volkow ND. Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. 2011; 12(11): p. 652-669.

142. Volkow ND, Wang GJ, Fowler JS, Tomasi D. Addiction circuitry in the human brain. Annu Rev Pharmacol Toxicol. 2012; 52: p. 321-336.

143. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2008; CD000146.

144. Brewer JA, Mallik S, Babuscio TA, Nich C, Johnson HE, Deleone CM, et al. Mindfulness training for smoking cessation: results from a randomized controlled trial. Drug Alcohol Depend. 2011; 119(1-2): p. 72-80.

145. Barlas Y. Formal aspects of model validity and validation in system dynamics. Syst Dynam Rev. 1996; 12(3): p. 183-210.

146. Muzic RF, Berridge MS, Friedland RP, Zhu N, Nelson AD. PET quantification of specific binding of carbon-11-nicotine in human brain. J Nucl Med. 1998; 39(12): p. 2048-2054.

147. Difranza JR, Wellman RJ, Savageau JA. Does progression through the stages of physical addiction indicate increasing overall addiction to tobacco? Psychopharmacology. 2012; 219(3): p. 815-822.

148. Kitano H. Systems Biology: a Brief Overview. Science. 2002; 295(1662): p. 1662-1664.

149. Levy D, Levy YZ, Siegelmann HT. Modeling Addiction in Terms of Fluctuating Neurotransmitters within the Reward System. Tech Report. UMass Amherst, Computer Science; 2011. Report No.: UM-CS-2011-033.

150. Liu J, Derendorf H. Clinical Pharmacology of Addicting Drugs. In Miller NS, Gold MS, editors. Addictive Disorders in Medical Populations. Chichester: Wiley-Blackwell; 2010. p. 107-124.

151. Cone EJ. Pharmacokinetics and pharmacodynamics of cocaine. J Anal Toxicol. 1995; 19(6): p. 459-478.

152. Brady KT, Sinha R. Co-occurring mental and substance use disorders: the neurobiological effects of chronic stress. Am J Psychiatry. 2005; 162(8): p. 1483-1493.

153. Agrawal A, Verweij KJH, Gillespie NA, Heath AC, Lessov-Schlaggar CN, Martin NG, et al. The genetics of addiction-a translational perspective. Transl Psychiatry. 2012; 2: p. e140.

154. Tang YY, Lu Q, Fan M, Yang Y, Posner M. Mechanisms of white matter changes induced by meditation. Proc Natl Acad Sci USA. 2012;: p. In press.

155. Xue YX, Luo YX, Wu P, Shi HS, Xue LF, Chen C, et al. A memory retrieval-extinction procedure to prevent drug craving and relapse. Science. 2012; 336(6078): p. 241-245.

156. Milton AL, Everitt BJ. Wiping drug memories. Science. 2012; 336(6078): p. 167-168.

157. Bolt DM, Piper ME, Theobald WE, Baker TB. Why two smoking cessation agents work better than one: role of craving suppression. J Consult Clin Psychol. 2012; 80(1): p. 54-65.

158. Thompson GH, Hunter DA. Nicotine replacement therapy. Ann Pharmacother. 1998; 32(10): p. 1067-1075.

159. Fiore MC, Smith SS, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation. a meta-analysis. JAMA. 1994; 271(24): p. 1940-1947.

160. U.S. Department of Health and Human Services; Public Health Service. Treating Tobacco Use and Dependence: 2008 Update - Clinical Practice Guideline. [Online]; 2008 [cited 2012 08 01]. Available from: http://www.ahrq.gov/clinic/tobacco/treating_tobacco_use08.pdf.

161. Loh WY, Piper ME, Schlam TR, Fiore MC, Smith SS, Jorenby DE, et al. Should all smokers use combination smoking cessation pharmacotherapy? Using novel analytic methods to detect differential treatment effects over 8 weeks of pharmacotherapy. Nicotine Tob Res. 2012; 14(2): p. 131-141.

162. McCarthy DE, Piasecki TM, Jorenby DE, Lawrence DL, Shiffman S, Baker TB. A multi-level analysis of non-significant counseling effects in a randomized smoking cessation trial. Addiction. 2010; 105(12): p. 2195-2208.

163. Beck AT. Cognitive therapy. A 30-year retrospective. Am Psychol. 1991; 46(4): p. 368-375.

164. Childress A, Burns D. The basics of cognitive therapy. Psychosomatics. 1981; 22(12): p. 1017-1027.

165. Kendall PC, Hollon SD. Cognitive-behavioral interventions: overview and current status. In Kendall PC, Hollon SD, editors. Cognitive-behavioral interventions: theory, research and procedures. New York: Academic Press; 1979. p. 1-13.

166. U.S. Department of Health and Human Services; National Institutes of Health; National Center for Complementary and Alternative Medicine. What is Complementary and Alternative Medicine? [Online]; 2008 [cited 2012 08 01]. Available from: http://nccam.nih.gov/sites/nccam.nih.gov/files/D347_05-25-2012.pdf.

167. Hendricks PS, Delucchi KL, Hall SM. Mechanisms of change in extended cognitive behavioral treatment for tobacco dependence. Drug Alcohol Depend. 2010; 109(1-3): p. 114-119.

168. Hathaway KM, Erasmus Y. Integrative Therapies for Tobacco Cessation. In Chlan L, Hertz MI, editors. Integrative Therapies in Lung Health and Sleep. New York: Springer; 2012. p. 223-246.

169. Bowen S, Chawla N, Collins SE, Witkiewitz K, Hsu S, Grow J, et al. Mindfulness-based relapse prevention for substance use disorders: a pilot efficacy trial. Subst Abus. 2009; 30(4): p. 295-305.