



Published in final edited form as:

Methods Rep RTI Press. 2017 June ; 2017: .

A Control Theory Model of Smoking

Georgiy Bobashev, PhD,

Fellow in RTI International's Center for Data Science

John Holloway, BFA,

Multimedia design specialist in RTI International's Center for Forensic Sciences

Eric Solano, PhD, and

Senior data scientist at Maana

Boris Gutkin, PhD

Professor in the Group for Neural Theory in the Institut d'Etudes de la Cognition at the École Normale Supérieure in Paris

Abstract

We present a heuristic control theory model that describes smoking under restricted and unrestricted access to cigarettes. The model is based on the allostasis theory and uses a formal representation of a multiscale opponent process. The model simulates smoking behavior of an individual and produces both short-term ("loading up" after not smoking for a while) and long-term smoking patterns (e.g., gradual transition from a few cigarettes to one pack a day). By introducing a formal representation of withdrawal- and craving-like processes, the model produces gradual increases over time in withdrawal- and craving-like signals associated with abstinence and shows that after 3 months of abstinence, craving disappears. The model was programmed as a computer application allowing users to select simulation scenarios. The application links images of brain regions that are activated during the binge/intoxication, withdrawal, or craving with corresponding simulated states. The model was calibrated to represent smoking patterns described in peer-reviewed literature; however, it is generic enough to be adapted to other drugs, including cocaine and opioids. Although the model does not mechanistically describe specific neurobiological processes, it can be useful in prevention and treatment practices as an illustration of drug-using behaviors and expected dynamics of withdrawal and craving during abstinence.

Introduction

This paper presents a working prototype of a control-theoretic model that simulates realistic daily smoking patterns governed by a multiscale opponent process representing neurobiology of addictive behaviors. Until recently, many people considered drug addiction to be a moral failure, a lack of willpower. Only in the last few decades have scientific developments in neurobiology, especially functional magnetic resonance imaging (MRI), convincingly proven that addiction is a brain disease (Koob & Volkow, 2010). Prolonged use of certain drugs like nicotine or heroin can change brain functioning and, consequently,

decision-making processes. How much of addictive behavior is the result of mechanistic brain function and how much is it influenced by the environment? Modern science's attempt to explain and reproduce the complexity of human behavior is challenged by bridging human behavioral science with laboratory-based neurobiology, areas that traditionally were disconnected from each other. Computational models facilitate such bridging. For some chronic diseases (cardiovascular, cancer, diabetes, and obesity) models connecting behavior and physiology have already been developed, e.g., a proprietary Archimedes model simulates a virtual patient in the context of daily routine activities (Eddy et al., 2013). No analog of such a model yet exists for substance use. In this paper, we present a first step toward creating such a model where processes in the brain drive behavior and the environment impacts brain processes.

We start with a simpler model that serves the educational purpose of illustrating pathways from occasional smoking to dependence and examining how different periods of abstinence impact withdrawal and craving. General public and drug-treatment counselors can use this model to provide a science-based explanation of daily smoking behavior. As more validated models of neurobiological processes become available, they can be incorporated into our model to expand the variety of explained behaviors.

Control-Theoretic Models of Substance Use Are Complementary to Biological Models

A large body of knowledge has been collected in neurobiology, genetics, behavior, treatment, and epidemiology of substance use (Ahmed et al., 2007; Bobashev et al., 2007; Gutkin et al., 2006; Koob & Volkow, 2010; Redish, 2004). A recent book on computational neurobiology (Gutkin & Ahmed, 2012) covered the spectrum of models in each area. At least two models combine positive drug-induced learning and neural meta-plasticity mechanisms for the onset of drug-seeking and the opponent process as the origin of the transition to addictive behavior (Gutkin et al., 2006; Graupner, M., & Gutkin, 2012; Keramati & Gutkin, 2014). For example, according to Gutkin et al. (2006), nicotine seeking is initiated by drug-induced dopamine-dependent plasticity and upregulation in nicotinic receptor function; on the other hand, the addictive state depends on an opponent down-regulation of nicotinic receptor function and a subsequent disconnect between the motivation brain circuits and cortico-striatal action selection loops. Comprehending a cascade of feedback loops between a variety of biologic, neurocognitive, behavioral, social, and environmental factors is one of the main challenges in substance use research. A few models exist that describe various feedback loops (Lamy et al., 2011; Levy et al., 2013; O'Reilly & Munakata, 2000). However, most of these models are quite complex, and their practical utility for prevention and treatment is low.

In our study, we considered a different approach. Rather than combining many complex biological components, we started with a simple model based on control theory principles. The model describes multiscale behavior of an individual in its entirety and aims to achieve qualitative behavioral rather than biological accuracy. In control theory, "understanding" of substance-using behavior brings a utilitarian perspective where the scientific narrative is translated into mathematical models (Newlin et al., 2012; Bobashev, 2014). For example, when an individual is walking, several complex processes happen simultaneously in the

brain, but from the control theory perspective, maintaining balance is just a coordination of feedback loops that can be formally modeled and realized in self-stabilizing devices such as a walking robot. Although the real stabilizing mechanisms in a human brain and a robot are different, the stabilizing feedback principles remain the same. The model presented in this paper can be considered as a drug-using robot whose behavior mimics smoking patterns of a human under certain conditions. The feedback mechanisms modeled in this robot are based on the regulating principal of opponent process described below. Unlike a biological model that aims to uniquely describe “the truth,” a number of control process models can lead to the same phenomenological description. In this sense, we present *a* model rather than *the* model. A proposed control theoretic model has a module structure allowing one to replace individual components with specific neurobiological models.

Homeostasis, Opponent Process, and Allostasis

Scientists and researchers historically conceptualized the brain as designed to maintain a steady emotional state (homeostasis). Specifically, there exists a certain homeostatic set point, and when deviations from it occur (e.g., because of an external stimulus), the neurobiological processes bring the system back to the set point, thus maintaining a steady state. Homeostasis in the reward circuits means that when a strong reward creates a lasting effect, it must be countered by the opposite counter effect (i.e., “opponent process”), thus limiting the reward and returning brain neurocircuitry to the steady state. Similar to a thermostat in cold weather that responds to a door left open, the response is not immediate and cannot immediately change the state, but it works its way to establish the steady state. Solomon and Corbit (1973, 1974) formally introduced the concept of the opponent process with respect to emotional states in 1973 and further developed it in 1974; however, anecdotal mentions of an opponent process can be spotted in Plato (Fowler, 1966, p. 209):

What a strange thing, my friends, that seems to be which men call pleasure! How wonderfully it is related to that which seems to be its opposite, pain, in that they will not both come to a man at the same time, and yet if he pursues the one and captures it he is generally obliged to take the other also, as if the two were joined together in one head.

Solomon (1980) described drug addiction as the result of an emotional pairing of pleasure and the delayed emotional symptoms associated with withdrawal. According to this theory, during recreational drug use pleasure levels are high and withdrawal levels are low. After long use, levels of pleasure from using the drug decrease and withdrawal increases. Thus, eventually a switch in motivation occurs: rather than using the drug for pleasure, the subject is using to alleviate withdrawal. Such a long-term shift cannot be explained by the homeostasis theory because the optimization objective changes from optimizing pleasure to minimizing withdrawal (Ahmed & Koob, 2005). Interestingly, the hedonic theory of addiction, as Solomon phrased it, was modified in recent years to focus more on motivation rather than emotional impact. Ample evidence has shown that liking a drug and wanting a drug are dissociable and that the latter actually drives the addiction process. In this way, the initial drive to seek a drug is based on its motivation-reinforcing properties, whereas the opponent process is linked to motivational withdrawal states. In the negative reinforcement theory of addiction (Koob & LeMoal, 2006; Koob & Volkow, 2010), the drug addict finds

him- or herself in a motivationally suboptimal state when the drug is absent and is therefore motivated to seek and take the drug to redress the imbalance. Most clearly one can observe the dissociation between the motivation and hedonic impact for nicotine. It is a highly addictive substance, yet it has virtually no euphorogenic properties and produces rather mild hedonic withdrawal symptoms.

The concept of allostasis (Sterling & Eyer, 1988) expands the homeostasis theory by allowing adaptation through slow long-term changes in the set point. It suggests that long-term (chronic) adaptive change occurs to the reward set point. For example, after prolonged use of a drug, achieving the satiated state requires increasingly larger drug doses, which in turn can lead to loss of control over the drug taking, eventually leading to dependence (Koob & LeMoal, 2006).

We developed and applied the model to describe self-administration of cocaine among rats; we then showed that the control-theoretic model fitted to the data from one experiment would accurately predict multiscale patterns in another experiment with a different group of rats and different setting (Bobashev et al., 2015). Encouraged by these results, we attempted to develop a similar model for a cigarette smoker, because smoking remains a major public health problem. Additionally, there is large public health interest in understanding the use of electronic cigarettes because the rates of use are rising among middle and high school youth (CDC, 2016). Cigarettes are legal (at least for adults), and before the wide adoption of public health policy banning smoking in public places, an individual could smoke a cigarette almost whenever he or she wanted. Many studies have addressed smoking habits, quitting attempts, and the development of tolerance, which provides data and parameterization for control theory models. Our approach is to start with a simpler model (a smoking robot) and eventually increase model complexity to incorporate more complex behavior that the simple model does not describe. Our initial model focuses on the period when an individual has been introduced to smoking and is transitioning toward dependence.

Control process models that describe the phenomenology of allostasis implemented in a practical software application/tool can be used in both prevention and treatment of drug dependence. As summarized in Koob and Volkow (2010) the drug-dependent brain moves through three states (binge/intoxication, withdrawal, and craving) that are distinctly characterized by activations in specific parts of the brain. Interactive visualization of brain regions activated when a drug user moves through these stages can illustrate the biological addiction for patients.

The rest of the paper describes the working prototype of a control-theoretic model that simulates daily smoking patterns governed by the opponent process; presents the results of several experiments producing realistic patterns of smoking; and links the processes with visualizations of the brain areas that are activated during each of the drug use phases: binge, withdrawal, and craving. Potential extensions and future work are described in the discussion.

The Model

We considered a mathematical model of cascading feedback loops aimed to represent the following scientific narrative of allostasis and opponent process. Following Koob and LeMoal (2006) we considered a set point corresponding to a satiated state. If the actual state is lower than the set point, a signal is sent to use the drug (i.e., smoke a cigarette). If the drug is available, it is immediately consumed producing a hedonistic stimulus in the brain, which in turn excites a cascade of stabilizing processes. Each next process in a sequence is slower than the predecessor, producing a delay between the peak values of these processes. The set point is a function of the combined effect of the slower processes reflecting the accumulation of the deviation from the satiated state because of prolonged use. Thus, the set point slowly moves toward increased consumption (when consumption is intense) and toward less consumption (when consumption is slower). Intermediate time scale processes that could be interpreted as accumulated toxicity affect the infinite drift of the set point to guard against unlimited drug consumption. Relapse after long abstinence is controlled by a very slow process that can be vaguely interpreted as long-term memory. This process quickly resets use to the preabstinence level.

Main Model

Many biological processes are related to a concentration of some substance. We thus chose a family of continuous functions to represent cascading processes. We considered linear accumulation (i.e., increase in concentration) and first-order extraction. The mathematical model of such a process is sometimes called a running weighted mean or “leaky” integration in analogy with a leaky bucket in which water pours in with constant speed and leaks out with speed depending on the amount of water in the bucket (Newlin et al., 2012). Each process is characterized by a temporal scale associated with the accumulation and extraction rates. Because the next process is constructed as a weighted integration of the previous process, the characteristic scale of the next one is longer than the scale of the previous process. Although the equations are not designed to represent any real biological process, they are developed with a phenomenological interpretation in mind. The first process, Y_1 , corresponds to the effect of the drug, which is modeled with a pharmacokinetic equation. We assume that hedonistic effect depends on drug concentration and for smoking is defined on the scale of hours. The second process, Y_2 , vaguely corresponds to toxicity and describes the accumulation of the drug and the body’s processing of it. This process is modeled as a running weighted mean of Y_1 . The third process, Y_3 , characterizes how much drug an individual consumes over a long period, and is sensitive to the consumption mode (e.g., constant vs. binge) even if the amount consumed is the same. This process can thus resemble a “habit” and is defined on the scale of days. It was modeled as a running weighted mean of Y_2 . Process Y_4 is again a running weighted mean of Y_3 . We did not interpret this process, which represents an even longer period. We keep process Y_4 primarily for mathematical consistency to identify process Y_5 as a long-term hedonistic memory defined on the scale of years. After a long period of abstinence, when processes Y_1 through Y_3 are quite low or virtually zero, Y_5 process holds its slow-changing values. A diagram of the model is presented in Figure 1.

The corresponding system of equations becomes the following:

$$\begin{aligned}
 \text{Process A: } dY_1/dt &= e^{-\alpha t} - b_1 Y_1 \\
 \text{Process B: } dY_2/dt &= a_1 Y_1 - b_2 Y_2 \\
 \text{Process C: } dY_3/dt &= a_2 Y_2 - b_3 Y_3 \\
 \text{Process D: } dY_4/dt &= a_3 Y_3 - b_4 Y_4 \\
 \text{Process E: } dY_5/dt &= a_4 Y_4 - b_5 Y_5, \quad (1)
 \end{aligned}$$

where a , b , and α are the scaling coefficients, and the initial conditions of all Y_i are equal to zero.

To sustain recurrent drug-using behavior, we introduced a trigger that prompts self-administration. If the drug is available at that point, it is immediately used. We thus defined a dynamic threshold T such that when the effect Y_1 drops below T , drug self-administration is prompted. The higher the threshold, the faster the drug effect drops below it and, therefore, the shorter the time intervals are between self-administrations. If the decision to use a drug after reaching a threshold is not deterministic but probabilistic, the intervals between the consequent uses vary (i.e., the drug could be occasionally used either before or after the effect crosses the threshold).

We modeled the threshold after the following narrative: Process Y_3 reflects the level of use over a long period (e.g., habit); thus, the threshold should be positively correlated with this process. A long-term memory process, Y_5 , allows resumption of use after long abstinence when process Y_3 is close to zero; thus, the threshold should be positively associated with Y_5 . Process Y_2 reflects toxicity and should prevent unlimited loading with the drug (e.g., smoking 100 cigarettes in a row) so the threshold should be negatively balanced by toxicity Y_2 . We modeled such relationships as multiplicative effects.

$$T = (\beta_3 Y_3 + \beta_5 Y_5) / (1 + \beta_2 Y_2), \quad (2)$$

where parameters β_2 , β_3 , and β_5 are calibrating coefficients. Because process Y_2 can be zero, we added a stabilizing unit “1” in the denominator.

External pressures and stressors can prompt use even when a person is in a satiated state. This is modeled through lifting the threshold by adding a “stressor” factor:

$$T = T + T_{stress} \quad (3)$$

These stressors could be internal (mood, stress) or external (environmental) cues such as peer pressure, places that are associated with smoking, smell of tobacco smoke, etc. (Weirs et al. 2007, 2013).

Finally, the availability of cigarettes was modeled as a binary (0,1) indicator at each time point. If use is prompted but the availability indicator is zero, then no smoking occurs. Such

formulation of the threshold concludes the model, which is then calibrated to specific patterns of smoking. The model was implemented in Java as a virtual smoker tool and in R as a developer tool.

Representations of Withdrawal and Craving States

As a person continues regular use of the drug and moves into addiction, he or she can experience emotional states of withdrawal and craving. The mechanisms of withdrawal and craving have been intensely discussed in scientific and popular literature (Goldstein & Volkow, 2002; Koob & Volkow, 2010; Nicotine and tobacco, 2015). Although we do not model the biology of these states, we do use existing narrative to define withdrawal- and craving-like states as functions of prolonged use without access to cigarettes. We conceptualize that these states are continuous functions of the underlying control processes; the manifestation of withdrawal or craving occurs when a certain threshold is crossed. Under this conceptualization, the withdrawal- and craving-like processes start immediately with use, but their manifestation is negligible. As the person uses more, these processes evolve and, after crossing their respective thresholds, define withdrawal- and craving-like states. Several studies and reviews (Benowitz, 2010; Shadel et al., 2000) show that the signs and symptoms of nicotine withdrawal syndrome can appear within 2 hours of the last use of tobacco, usually peak between 24 and 48 hours after cessation, and last from a few days to a week. This timing is supported by discussions in smoking cessation online forums. In our control-theoretic model we introduced a W -process aimed to represent withdrawal as a function of how far the current drug effect Y_1 is from the satiation threshold T . This difference is modified by representative use level Y_3 , and attenuated by the drug effect:

$$W = d_3 Y_3 (T - Y_1) / (Y_{0w} + Y_1), \quad (3)$$

Similarly, we defined a craving-like process Cr as a function of the difference between the threshold and the effect but modified by the long-term processes Y_5 .

$$Cr = d_5 Y_5 (T - Y_1) / (Y_{0c} + Y_1), \quad (4)$$

where d_5 and Y_{0c} are the calibrating coefficients. Two thresholds T_w and T_c are defined to indicate when each of the states manifests itself. Once again, we emphasize that these formulations are mathematical representations of narratives, not necessarily biological processes.

Although binge/intoxication is not common for many regular smokers even with unrestricted access to cigarettes, sometimes external stimuli such as extreme stress, social environment associated with heavy drinking, and chain smoking create situations for nicotine binge/intoxication. In our model, such events are possible when external factors artificially lift the trigger threshold T . A smaller amount of bingeing can be also observed after a period of abstinence when an individual is “loading up.” We thus introduce a notion of binge/intoxication, which is quantified in terms of effect Y_1 exceeding a binge threshold T_b . We

define the threshold as the multiple of the maximum effect during regular smoking. The value of the multiplier is somewhat arbitrary (e.g., 10 cigarettes in a row). The problem with a practical definition of intoxication for cigarettes is that the dose for nicotine poisoning might be higher than the dose usually received when the user reports intoxication because of the role of numerous additives to tobacco. This topic, however, becomes of increased importance with electronic cigarettes when users can manipulate the dose they self-administer.

Simulation Scenarios

The model was calibrated to the following typical scenario: A subject started smoking with seven cigarettes a day and in 9 months progressed to smoking a pack a day. Such scenarios were described, for example, in <http://www.smokingfeelsgood.com>, Benowitz (2010), and Stolerman and Jarvis (1995). The subject had unrestricted access to cigarettes during the day except for 8 hours at night for sleep.

Model parameters were then fixed and used to simulate the following scenarios where cigarettes were not available for short and long periods. Such scenarios can occur, for example, when an individual attempts to quit and restricts smoking. In this simple model, we do not describe tobacco-seeking behavior leading to relapse but rather restrict or not restrict access to cigarettes without modeling the reasons. Both an R model and the JAVA-based application allow one to select any restriction schedule. Here we present two scenarios that illustrate the consequences of short- and long-term abstinence.

- **Short-term restrictions.** We restricted access to cigarettes for two 5-day periods mimicking an individual who attempts to quit but relapses after 5 days.
- **Long-term restrictions.** Following results in peer-reviewed literature (Cosgrove et al., 2009; Ward et al., 2001) that abstaining from smoking for a period longer than a month (90 days is recommended) is critical for long-term abstinence, we restricted access to cigarettes for more than 30 days but allowed for relapse.

Results

The actual simulation model is available upon request from the lead author. In this section, we present the results of the simulated scenarios and show a few model screenshots.

Model Calibration by Describing Regular Daily Use

We calibrated model parameters to produce a long-term steady state of smoking about a pack of cigarettes a day.

The model shows a gradual increase in the number of cigarettes per day, low levels of withdrawal- or craving-like functions (both under the respective thresholds), and a low level of the long-term process Y_5 . After repeated use of the drug, W gradually increases in value; this, combined with an increase in the number of cigarettes per day, leads to crossing the T_w threshold and manifestation of withdrawal. Craving function Cr slowly increases, too, but does not reach the threshold point. These effects signal the pathway to dependence when both W and Cr cross their respective thresholds. The times when increase in use by one

cigarette per day occurs is noticeable by a slight dip in withdrawal (e.g., on day 29). Starting with 10 cigarettes per day, the individual in month 6 stabilizes consumption at around 24 cigarettes per day, the rate identified by the American Cancer Society as heavy smoking. This rate of increase in consumption corresponds to the average rate (11 months for women and 16 months for men) at which individuals who start smoking reach the level of a pack a day (Thorner et al., 2007). In our model, such stabilization is achieved because of the inherent slow-changing negative feedback loops that eventually restrict unlimited use.

When an individual stops smoking for a short time, there is little effect on craving, which is illustrated in the example of a smoking break during sleep. When cigarettes are available any time, both W and Cr functions are virtually zero and the pattern of self-administration repeats almost perfectly. Some scientists view this process as a biological clock resulting in regular self-administration (Al-Delaimy et al., 2007, Tsibulsky & Norman, 2012). After a period of forced abstinence (8 hours of sleep), the levels of both Cr and W functions increase, but the increase in W is much faster. Because both function W and the trigger threshold T are influenced by the growing function Y_3 , the increase in W is associated with a slight rise in the second nicotine dose and shortening of the interval between the first and the second dose compared to the rest of the doses (Figure 2).

After we calibrated the model to represent this pathway, we used the model without modifying its parameters to represent scenarios that reflect life events.

Scenario 1. Stop Smoking for a Short Time (5 Days), Relapse, and Then Stop Again

We turned off cigarette availability for 5 days, turned it back on for a week, and turned it off again for 5 days. The resulting plot with overlaid drug effect, Cr , and W functions is presented in Figure 3.

This plot illustrates the difficulty in quitting and the high likelihood of relapse after a few days. W grows quickly and peaks around a day or two after quitting. Then, while W declines over the a few days, the Cr process builds up slowly. Figure 4 presents the same simulation as Figure 3 without overlaying the drug effect to emphasize the increased dynamics of Cr and W functions.

Scenario 2. Stop Using for a Long Time

We restricted drug availability for a long time to illustrate how long-term effects of abstinence impact withdrawal- and craving-like processes. Although process W can be strong at the beginning of the abstinence period, it wanes over the next few days. The Cr process continuously builds up over a longer time and peaks sometimes over a month after stopping use (Figure 5). Although the Cr process stays high for quite a while, it eventually declines to low levels. This observation reveals an important message: the feeling of craving will eventually subside if the subject stays abstinent for a long enough time.

Discussion

We developed a multiscale simulation model and a visualization tool to illustrate how theoretical narratives can be modeled through a control process model. The model

incorporates an opponent process theory and reproduces allostatic behavior. In addition, the model illustrates how drug self-administration is governed by a dynamically changing threshold with a number of processes governing slow and fast changes. Our model illustrates smoking behaviors of a heavy smoker and introduces withdrawal- and craving-like functions to link controlled processes. The model was calibrated to mimic an increase in smoking consumption from 10 to 24 cigarettes a day. When use is disturbed by a lack of drug availability, the model illustrates why most individuals relapse within a day or two because of withdrawal and why repeated quitting and relapsing leads to the buildup of withdrawal. In terms of long-term effects, the model illustrates how craving builds up over a long period, but after a longer time, generally 2 to 3 months, craving mostly disappears. Finally, our model shows that even after a long period of abstinence, a small priming of use (e.g., smoking a single cigarette) can lead to a return to the use pattern before abrupt quitting.

By manipulating model parameters in Equations (1) and (2), one can control the rate at which an individual increases the daily rate of consumption, reaches the steady consumption, and responds to abstinence. Parameters in Equations (3) and (4) allow one to manipulate the time period when withdrawal and craving reach their peaks and how fast they disappear. Thus, the model provides the means to describe heterogeneity of behaviors.

For prevention, the visualization of possible behaviors and underlying mechanisms provides a powerful message to teenagers and young adults about the short- and long-term effects of smoking. For treatment, the tool provides a potential explanation of the recovery process and the short- and long-term emotional effects of drug use reduction and abstinence. As discussed in Weirs et al. (2013), cognitive biases among drug users could be at least partially attenuated by self-awareness and understanding of neurobiological processes. Tools are needed to bring underlying, implicit, dynamics of craving to the explicit attention of substance abusers. After calibrating the model to typical behaviors, the users can further explore “what if” scenarios through simulations and develop additional awareness of potential outcomes.

Visualizations of Brain Regions

Intoxication, withdrawal, and craving are characterized by the activation of certain brain regions that Koob and Volkow (2010) clearly defined. We developed an interactive 3D visualization tool that highlights each of the regions as described in Koob and Volkow (2010) (Figure 6).

We also created still 2D slice images of the 3D brain that correspond to each stage using three different angles. Our withdrawal- and craving-like functions offer a link between the use and manifestation of these states and visualizations of active areas in the brain. These images were incorporated in the simulation application such that when processes C or W reach their corresponding threshold, the brain images corresponding to craving and withdrawal appear on the screen. For example, in Figure 5, on day 40 process C is above the threshold T_c while process W is below its threshold, indicating that the person is at the craving stage. Figure 7 is a snapshot of the part of the screen that highlights regions activated during the craving stage.

Limitations and Future Work

The results of the simulations are as good as the model assumptions, and there are plenty of them. Two key assumptions are that the drug is always available and that it is the only behavioral reinforcer. These assumptions are practical for laboratory experiments and allow translation of such experiments to real life. For smoking, these assumptions are somewhat justifiable: before restrictions on public smoking, cigarettes were broadly available and there were no adequate substitutions for the effects of having a cigarette. Other assumptions simplify parameter variation, an impact of environmental stressors, and ignore potential drug-seeking behaviors during withdrawal and craving. Although several complex models (Lamy, 2011; Levy, 2013) simultaneously include many aspects of measurable and unmeasurable human behavior, we started with a relatively simple model that was recently validated on data from animal experiments (Bobashev et al., 2015) and developed a representation of a specific substance use theory.

Future work on the model will expand it in two directions. One is the inclusion of factors that changed the dynamics of use, such as restrictions on smoking in public spaces, social acceptance of smoking, the availability of nicotine replacement therapies such as Nicorette, and environmental cues. Data collected from Ecological Momentary Assessment (EMA), wearable sensors and laboratory experiments (Shiffman et al., 2009, 2014; Stevenson et al., 2017) could be used for calibration and validation of the enhanced behavioral model. Another direction is the replacement of specific individual components of the control theory model with corresponding neurobiological models as in Keramati & Gutkin, (2013). Many neurobiological theories are developed from animal experiments that are infeasible or unethical for use on humans. How applicable are these theories to realistic human life? Simulation modeling using virtual patients (in our case smokers) allows one to test the limits of theories developed from a controlled laboratory experiment, and thus to provide a translational link to behavioral science.

Acknowledgments

This study was funded in part by RTI's Internal Research and Development funds and an R01 grant from the National Institute on Drug Abuse (R01DA025163). Boris Gutkin acknowledges support from Russian Federation Excellence Program 5–100. We would like to thank Michelle Myers for her careful editing of the manuscript.

References

- Ahmed SH, Bobashev G, Gutkin BS. The simulation of addiction: Pharmacological and neurocomputational models of drug self-administration. *Drug and Alcohol Dependence*. 2007; 90(2–3):304–311. <https://doi.org/10.1016/j.drugalcdep.2007.01.008>. [PubMed: 17944023]
- Ahmed SH, Koob GF. Transition to drug addiction: A negative reinforcement model based on an allostatic decrease in reward function. *Psychopharmacology*. 2005; 180(3):473–490. <https://doi.org/10.1007/s00213-005-2180-z>. [PubMed: 15731896]
- Al-Delaimy WK, Pierce JP, Messer K, White MM, Trinidad DR, Gilpin EA. The California Tobacco Control Program's effect on adult smokers: (2) Daily cigarette consumption levels. *Tobacco Control*. 2007; 16(2):91–95. <https://doi.org/10.1136/tc.2006.017061>. [PubMed: 17400945]
- Benowitz NL. Nicotine addiction. *The New England Journal of Medicine*. 2010; 362(24):2295–2303. <https://doi.org/10.1056/NEJMra0809890>. [PubMed: 20554984]

- Bobashev G, Costenbader E, Gutkin B. Comprehensive mathematical modeling in drug addiction sciences. *Drug and Alcohol Dependence*. 2007; 89(1):102–106. <https://doi.org/10.1016/j.drugalcdep.2006.12.029>. [PubMed: 17549822]
- Bobashev G. myEpi. *Epidemiology of one*. *Frontiers in Public Health*. 2014; 2:97. <https://doi.org/10.3389/fpubh.2014.00097>. [PubMed: 25161995]
- Bobashev, GV., Seider, N., Ahmed, S. A computation opponent process model describes and predicts cocaine self-administration among naïve rats. Poster presented at CPDD; 2015; 2015. <https://doi.org/10.1016/j.drugalcdep.2015.07.977>
- Centers for Disease Control and Prevention (CDC). Tobacco use among middle and high school students — United States, 2011–2015. 2016. Retrieved from <http://www.cdc.gov/mmwr/volumes/65/wr/mm6514a1.htm>
- Cosgrove KP, Batis J, Bois F, Maciejewski PK, Esterlis I, Kloczynski T, ... Staley JK. β 2-Nicotinic acetylcholine receptor availability during acute and prolonged abstinence from tobacco smoking. *Archives of General Psychiatry*. 2009; 66(6):666–676. <https://doi.org/10.1001/archgenpsychiatry.2009.41>. [PubMed: 19487632]
- Eddy, D., Cohen, M., Shum, K., Dziuba, J. Validation methodology and results. ARChES Simulator 2.5. Archimedes. Retrieved from <http://http.archimedesmodel.com/sites/default/files/Archimedes-Validation-ARChESimulator-2.5.pdf>
- Fowler, HN. *Phaedo, Plato in twelve volumes*. Vol. 1. Cambridge, MA: Harvard University Press. London: William Heinemann Ltd; 1966.
- Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *The American Journal of Psychiatry*. 2002; 159(10):1642–1652. <https://doi.org/10.1176/appi.ajp.159.10.1642>. [PubMed: 12359667]
- Graupner, M., Gutkin, B. Modelling local circuit mechanisms for nicotine control of dopamine activity. In: Gutkin, B., Ahmed, S., editors. *Computational neuroscience of drug addiction*. Vol. 10. New York, NY: Springer; 2012. Springer Series in Computational Neuroscience https://doi.org/10.1007/978-1-4614-0751-5_4
- Gutkin, BS., Ahmed, SH., editors. *Computational neuroscience of drug addiction*. Vol. 10. New York, NY: Springer; 2012. Springer Series in Computational Neuroscience <https://doi.org/10.1007/978-1-4614-0751-5>
- Gutkin BS, Dehaene S, Changeux JP. A neurocomputational hypothesis for nicotine addiction. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103(4):1106–1111. <https://doi.org/10.1073/pnas.0510220103>. [PubMed: 16415156]
- Keramati M, Gutkin B. Collecting reward to defend homeostasis: A homeostatic reinforcement learning theory. *eLife*. 2014; 3:e04811. <https://doi.org/10.7554/eLife.04811.001>.
- Keramati M, Gutkin BS. Drug dominated dopamine circuits spiral addicts into a cognitive behavioral conflict. *PLoS One*. 2013; 8(4):e61489. <https://publications.hse.ru/en/articles/145094118>. [PubMed: 23637842]
- Koob, GF., Le Moal, M. *Neurobiology of addiction*. San Diego, CA: Academic Press; 2006.
- Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology*. 2010; 35(1):217–238. <https://doi.org/10.1038/npp.2009.110>. [PubMed: 19710631]
- Lamy, F., Bossomaier, T., Perez, P. SimUse: Simulation of recreational poly-drug use. 2011. Retrieved from <https://ccl.northwestern.edu/papers/2011/lamy.pdf>
- Levy YZ, Levy DJ, Barto AG, Meyer JS. A computational hypothesis for allostasis: Delineation of substance dependence, conventional therapies, and alternative treatments. *Frontiers in Psychiatry*. 2013; 4:167. <https://doi.org/10.3389/fpsy.2013.00167>. [PubMed: 24391601]
- Newlin, DB., Regalia, PA., Seidman, TI., Bobashev, GV. Control theory and drug addiction. In: Gutkin, B., Ahmed, S., editors. *Computational neuroscience of drug addiction*. New York, NY: Springer; 2012. p. 57-108. https://doi.org/10.1007/978-1-4614-0751-5_3
- Nicotine and tobacco: Symptoms of withdrawal. *New York Times Health*. 2015 Mar 27. Retrieved from <http://www.nytimes.com/health/guides/disease/nicotine-withdrawal/symptoms-of-withdrawal.html>
- O'Reilly, RC., Munakata, Y. *Computational explorations in cognitive neuroscience: Understanding the mind by simulating the brain*. Cambridge, MA: The MIT Press; 2000.

- Redish AD. Addiction as a computational process gone awry. *Science*. 2004; 306(5703):1944–1947. <https://doi.org/10.1126/science.1102384>. [PubMed: 15591205]
- Shadel WG, Shiffman S, Niaura R, Nichter M, Abrams DB. Current models of nicotine dependence: What is known and what is needed to advance understanding of tobacco etiology among youth. *Drug and Alcohol Dependence*. 2000; 59(Suppl 1):9–S22. [https://doi.org/10.1016/S0376-8716\(99\)00162-3](https://doi.org/10.1016/S0376-8716(99)00162-3).
- Shiffman S. Ecological momentary assessment (EMA) in studies of substance use. *Psychological Assessment*. 2009; 21(4):486–497. <https://doi.org/10.1037/a0017074>. [PubMed: 19947783]
- Shiffman S, Dunbar MS, Li X, Scholl SM, Tindle HA, Anderson SJ, Ferguson SG. Smoking patterns and stimulus control in intermittent and daily smokers. *PLoS One*. 2014; 9(3):e89911. <https://doi.org/10.1371/journal.pone.0089911>. [PubMed: 24599056]
- Solomon RL, Corbit JD. An opponent-process theory of motivation. II. Cigarette addiction. *Journal of Abnormal Psychology*. 1973; 81(2):158–171. <https://doi.org/10.1037/h0034534>. [PubMed: 4697797]
- Solomon RL, Corbit JD. An opponent-process theory of motivation. I. Temporal dynamics of affect. *Psychological Review*. 1974; 81(2):119–145. <https://doi.org/10.1037/h0036128>. [PubMed: 4817611]
- Solomon RL. The opponent-process theory of acquired motivation: The costs of pleasure and the benefits of pain. *American Psychologist*. 1980; 35(8):691–712. [PubMed: 7416563]
- Sterling, P., Eyer, J. Allostasis: A new paradigm to explain arousal pathology. In: Fisher, S., Reason, JT., editors. *Handbook of life stress, cognition, and health*. Chichester, NY: Wiley; 1988.
- Stevenson JG, Oliver JA, Hallyburton MB, Sweitzer MM, Conklin CA, McClernon FJ. Smoking environment cues reduce ability to resist smoking as measured by a delay to smoking task. *Addictive Behaviors*. 2017; 67:49–52. <https://doi.org/10.1016/j.addbeh.2016.12.007>. [PubMed: 28012965]
- Stolerman IP, Jarvis MJ. The scientific case that nicotine is addictive. *Psychopharmacology*. 1995; 117(1):2–10. <https://doi.org/10.1007/BF02245088>. [PubMed: 7724697]
- Thorner ED, Jaszyna-Gasior M, Epstein DH, Moolchan ET. Progression to daily smoking: Is there a gender difference among cessation treatment seekers? *Substance Use & Misuse*. 2007; 42(5):829–835. <https://doi.org/10.1080/10826080701202486>. [PubMed: 17613947]
- Tsibulsky, VL., Norman, AB. Simple deterministic model of maintained drug self-administration behavior and its pharmacological applications. In: Gutkin, B., Ahmed, S., editors. *Computational neuroscience of drug addiction*. New York, NY: Springer; 2012. p. 3-18. https://doi.org/10.1007/978-1-4614-0751-5_1
- Ward MM, Swan GE, Jack LM. Self-reported abstinence effects in the first month after smoking cessation. *Addictive Behaviors*. 2001; 26(3):311–327. [https://doi.org/10.1016/S0306-4603\(00\)00107-6](https://doi.org/10.1016/S0306-4603(00)00107-6). [PubMed: 11436924]
- Wiers RW, Bartholow BD, van den Wildenberg E, Thush C, Engels RC, Sher KJ, ... Stacy AW. Automatic and controlled processes and the development of addictive behaviors in adolescents: A review and a model. *Pharmacology, Biochemistry, and Behavior*. 2007; 86(2):263–283. <https://doi.org/10.1016/j.pbb.2006.09.021>.
- Wiers RW, Gladwin TE, Hofmann W, Salemink E, Ridderinkhof KR. Cognitive bias modification and cognitive control training in addiction and related psychopathology: Mechanisms, clinical perspectives, and ways forward. *Clinical Psychological Science*. 2013; 1(2):192–212. <https://doi.org/10.1177/2167702612466547>.

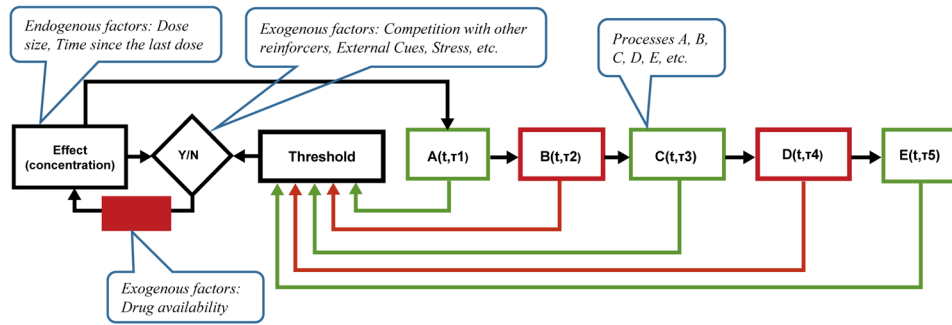


Figure 1.
A schematic diagram of the model

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

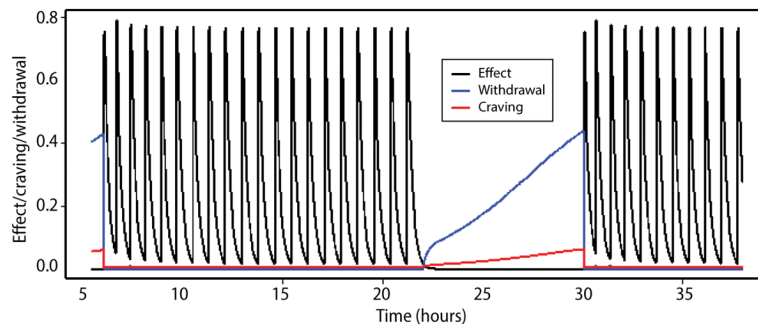


Figure 2. A plot of the drug effect, with overlaid withdrawal-like (W) and craving-like (Cr) functions

Note: Each peak of the effect plot corresponds to smoking a cigarette when nicotine concentration quickly rises, and then drops. Withdrawal-like function builds up overnight but disappears after the first smoked cigarette. Craving-like function slowly builds up overnight but is quite weak to manifest craving.

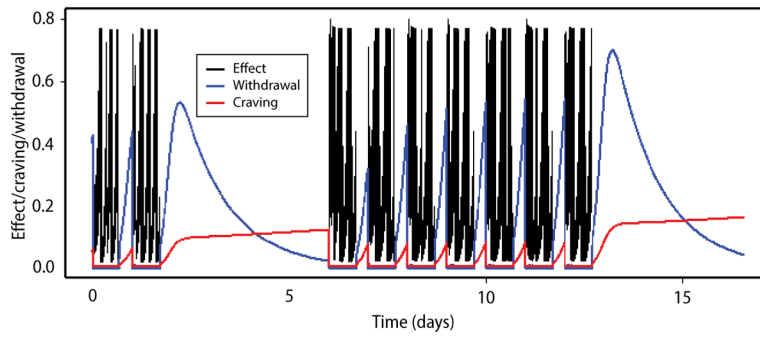


Figure 3. Plots of drug effect, Cr and W functions for multiple short-term abstinence

Note: After stopping use for a few days, withdrawal-like function W is high at the beginning but quickly diminishes. Craving-like function increases slowly and disappears immediately after smoking is resumed. At the second abstinence after a few days, both withdrawal-like and craving-like functions reach higher levels than during the first abstinence period.

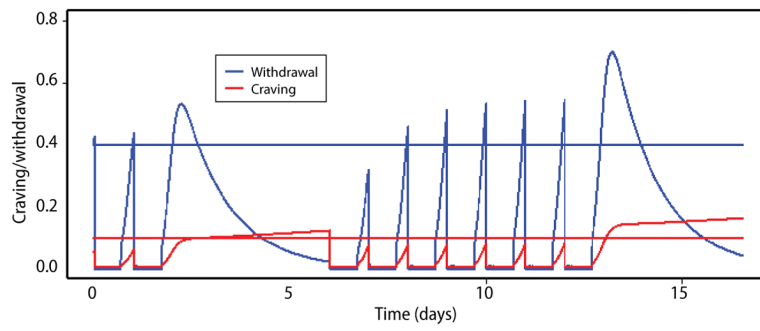


Figure 4. W and Cr processes reaching their thresholds after short-term break in smoking

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

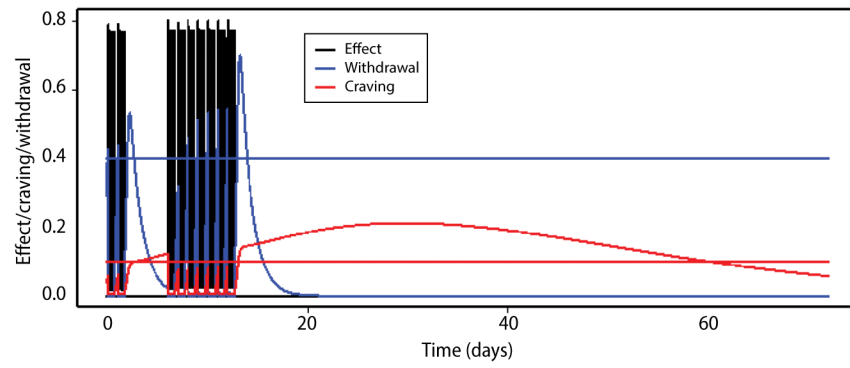


Figure 5. Illustration of the long-term dynamics of W and Cr functions

Note: After abstinence for several months, both withdrawal- and craving-like functions drop below their respective threshold levels.

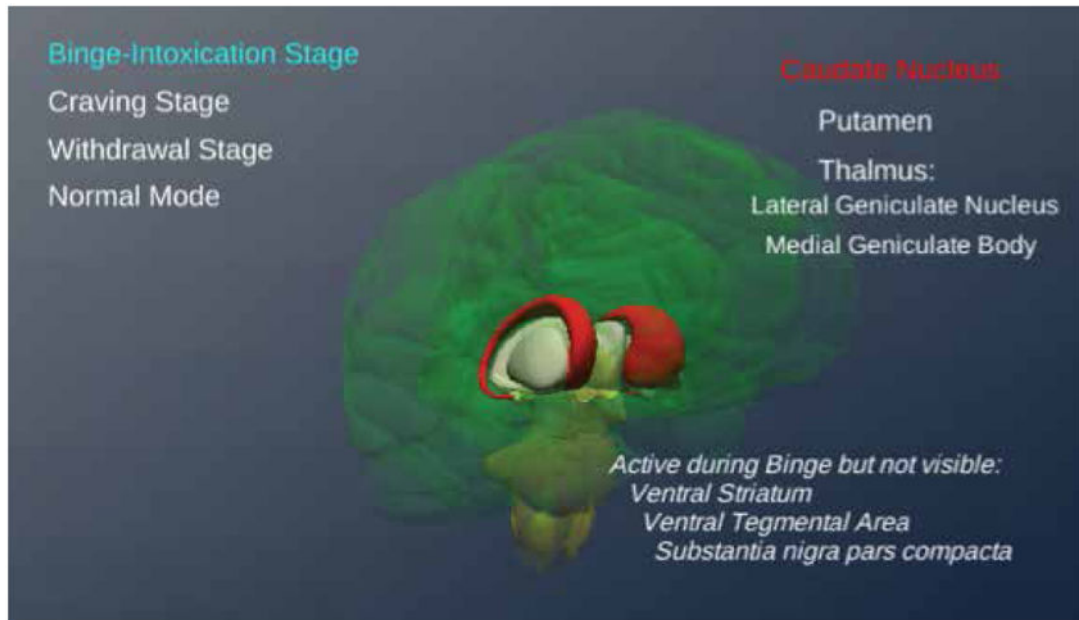


Figure 6. Screenshot of the interactive 3D model visualizing affected brain areas

Source: Model developed at RTI International by Georgiy Bobashev and John Holloway. Special thanks to Nicole Seider.

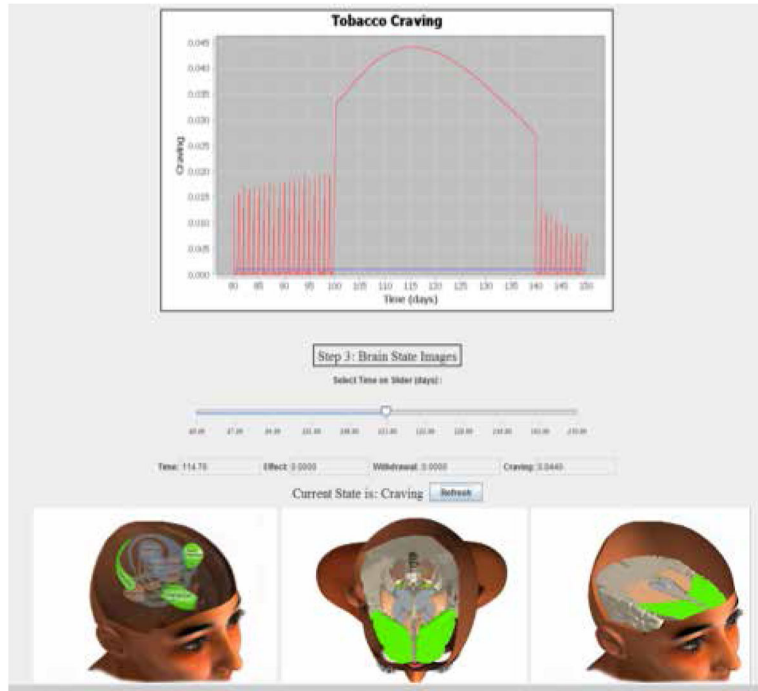


Figure 7. Application screenshot illustrating activated brain components during craving stage after no smoking for 12 days