Drug Addiction : A Computational Multiscale Model Combining Neuropsychology, Cognition, and Behavior.

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Abstract

According to the United Nations, approximately 24.7 million people used amphetamines, 16 million used cocaine, and 12 million used heroin in 2006/07 [Costa, 2008]. Full recovery from drug addiction by chemical treatment and/or social and psychological support is uncertain. The present investigation was undertaken to expand our understanding of the factors that drive the dynamics of addiction. A new multiscale computational model is presented which integrates current theories of addiction, unlike previous models, considers addiction as a reversible process [Siegelmann, 2008]. Explicit time dependency is added to the inhibition and the compulsion processes. Preliminary computational predictions of drug-seeking behavior are presented and potential correlation with experimental data is discussed. Validation of the model appears promising, however additional investigation is required.

1 INTRODUCTION

Drug addiction is a global problem. Historically, addicted people have been simply considered to be lacking the willpower to quit. But the prevailing view has changed in response to scientific studies which show that addiction correlates with social, psychological, and physiological factors. Addiction is now classified as a disease, a "bio-psycho-social-spiritual disorder" [Interlandi, 2008], but the underling causes and prospects for full recovery remain uncertain. Computational models for addictive behavior could assist in this quest for understanding.

Many computational models of addiction have been proposed and applied in order to provide a better understanding of factors which affect the nature of the addictive process. The relevant literature includes two types of models: one deals with either behavior acquisition or behavior maintenance of drug self-administration, and the other integrates both acquisition and maintenance based on machine learning or neuronal network dynamical approaches [Ahmed et al., 2007]. Both model types share the common assumption that addiction is a non-reversible process, and hence can not describe experimental observations which support possible recovery [Winick, 1962, Sobell et al., 2000]. A new model of addiction, the"dynamical addict", takes into account both relapse and rehabilitation processes [Siegelmann, 2008]. This approach considers addiction as a dynamical system where actual addiction behavior and processes of inhibition and compulsion are separated. Unlike other computational and mathematical models, it does not condemn the addict to a monotonic worsening

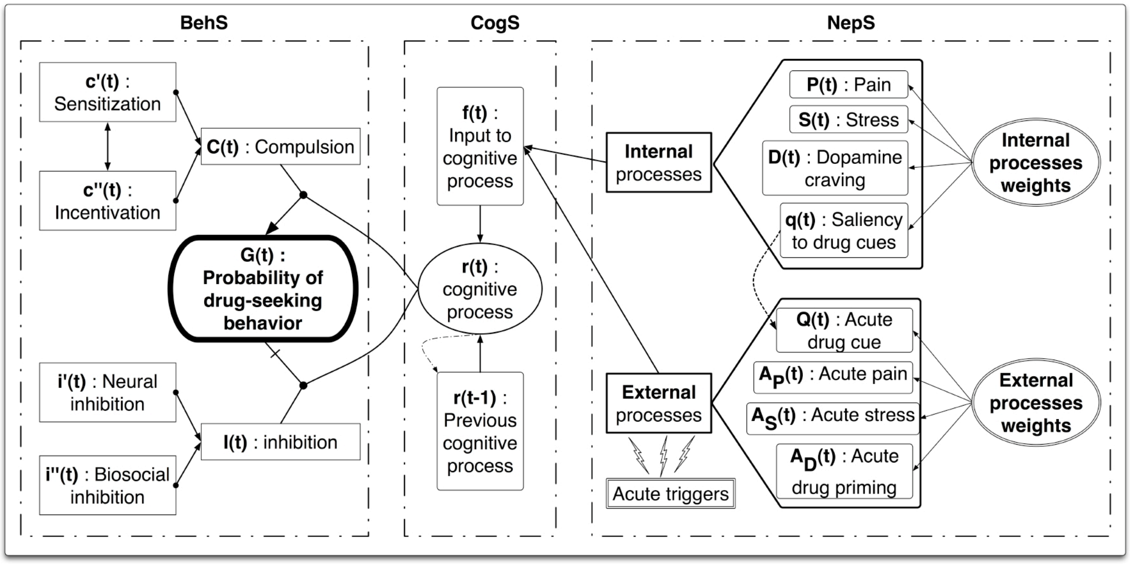

Figure 1: Addiction model combining neuropsychological (NepS), cognitive (CogS), and behavioral (BehS) scales. The output $G(t)$ is the likelihood of drug-seeking behavior.

of the addictive condition. Moreover, temporal parameters are introduced to quantify the virtual subject's level of cognitive rationality and levels of feedback parameters that make addiction so difficult to defeat.

The present investigation was undertaken to describe this new model in terms of *neuropsychological, cognitive, and behavioral* observations, to incorporate the temporal dimension within the processes of inhibition and compulsion, and to present a preliminary correlation between synthetic data presented in this work and empirical data found in the literature.

2 DESCRIPTION OF THE MODEL

This section describes the multiscale framework for formulating this new addiction model [Siegelmann, 2008]. The model can be considered to comprise three resolution scales: neuropsychological (NepS), cognitive (CogS), and behavioral (BehS) scales as shown in Figure 1. The original formulation of the model's output is the likelihood of drug-seeking behavior $G(t)$:

$$G(t) = (1 - r(t)) \cdot (-C) + r(t) \cdot I \tag{1}$$

where $r(t)$ is a cognitive parameter defined below in Section 2.2, and C and I are behavioral processes with longer time scales than r which are approximated by constants. The output of the model, $G(t)$, is generated at the BehS. The BehS is composed of inhibition I and compulsion C signals that respectively prevent and encourage drug-seeking behavior. The balance between I and C is modulated by the CogS, which is mainly intended to integrate the information coming from the NepS where internal and

external processes are computed and weighted.
The remainder of this section presents further details of the model parameters. The following two sub-sections 2.1 and 2.2 present a brief review of the original model from a multi-scale viewpoint. This is followed by a sub-section 2.3 which introduces inhibition and compulsion as dynamical time-dependent processes.

2.1 Neuropsychological Scale (NepS)

The NepS consists of effects which are dependent on the internal state of the virtual subject as well as acute external effects. How these internal and external processes behave is summarized in Table 1 with corresponding mathematical details in the Appendix.

Internal processes are considered to include $P(t)$, $S(t)$, $D(t)$ and $q(t)$. $P(t)$ denotes the level of pain or negative consequences, in areas such as health or social relations; which are increased by drug intake [De Alba et al., 2004]. $S(t)$ denotes the level of stress or the negative emotional state of the virtual subject. $S(t)$ increases during withdrawal periods [Hodgins et al., 1995, Koob and Le Moal, 2001, Aston-Jones and Harris, 2004] and may trigger craving [Stewart, 2000]. $D(t)$ denotes the level of current craving which depends on dopamine transmission in the nucleus accumbens (NAc). Finally, $q(t)$ denotes the saliency of drug-associated cues that increase with repeated drug consumption. When considering drug addiction as a disease of the learning and memory mechanism [Hyman, 2005], repeated learning results in a stronger association between the stimuli and the rewards, causing a sensitized saliency for drug associated cues [Robinson and Berridge, 2003]. The signal $q(t)$ defines the initial value of the drug-associated cue $Q(t)$ when it is encountered, as described below.

External processes are considered to include $A_P(t)$, $A_S(t)$, $A_D(t)$ and $Q(t)$. $A_P(t)$ denotes a painful trauma that may cause an addict to stop taking drugs immediately [Bradby and Williams, 2006, Barth et al., 2006]; $A_S(t)$ denotes a stressful episode that leads to immediate drug use [Erb et al., 1996, Sinha et al., 2000]; $A_D(t)$ denotes drug priming that could reinstate drug use again [de Wit and Stewart, 1983, Spealman et al., 1999]; and $Q(t)$ denotes a drug-associated cue that may be triggered, for example, by visiting a particular friend who uses that drug [See, 2002]. If an event $Q(t)$ is encountered, the saliency of this signal is defined by the value of $q(t)$. When any of these external processes is triggered, its value jumps to a fixed value, stays constant for a number of time steps, and then decreases exponentially. If this external process is triggered again before its previous effect disappears, it reverts to its initial value, stays constant for a number of time steps and then decreases exponentially.

2.2 Cognitive Scale (CogS)

The CogS mediates between low and high level controls of behavior. As such, it computes the cognitive rationality factor $r(t)$ and the input to the cognitive rationality $f(t)$ [Siegelmann, 2008]. The parameter $r(t)$ characterizes the activity of the addiction-related neuronal patterns: low levels cause compulsion to dominate and the value of $G(t)$ to decrease, and high levels cause inhibition to dominate and $G(t)$ to increase. The value of $r(t)$ at any instant is a combination of the previous value of the cognitive process $r(t-1)$ and the input to the cognitive process $f(t)$:

Table 1: Effects of $G(t)$, the likelihood of drug-seeking behavior, on internal and external processes for NepS.

Processes		***behavior when*** $G(t) > 0$	***behavior when*** $G(t) < 0$
Internals	$S(t)$	exponentially increases	exponentially decreases
	$P(t)$	exponentially decreases	exponentially increases
	$D(t)$	starting from the change in the sign of $G(t)$, from negative to positive, $D(t)$ exponentially increases for a fixed number of time steps, then exponentially decreases	exponentially increases
	$q(t)$	starting from the change in the sign of $G(t)$, from negative to positive, $q(t)$ stays constant for a fixed number of time steps, then exponentially decreases	exponentially increases
Externals	$A_S(t)$	can be triggered	can NOT be triggered
	$A_P(t)$	can NOT be triggered	can be triggered
	$A_D(t)$	can be triggered	can NOT be triggered
	$Q(t)$	can be triggered - its initial value depends on $q(t)$	

$$r(t) = \frac{1}{2}\tanh\Big(\alpha \cdot r(t-1) + \beta \cdot f(t) + \gamma\Big) + \frac{1}{2} \tag{2}$$

where $r \in [0, 1]$, and α, β, and γ are constants.

The input to the cognitive process $f(t)$ can be expressed as a weighted sum of the internal processes, that make addiction so difficult to overcome, and the external processes that have a strong but temporary effect:

$$\begin{aligned} f(t) = & \\ & \Big[\omega_P P(t) - \omega_S S(t) - \omega_D D(t)\Big] + \\ & \Big[\omega_A \Big(A_P(t) - A_S(t) - A_D(t) \Big) - \omega_Q Q(t)\Big] \end{aligned} \tag{3}$$

where ω_S, ω_P, and ω_D are the constants weighting factors for $S(t)$, $P(t)$, and $D(t)$, respectively; ω_A is the constant weighting factor for $A_P(t)$, $A_S(t)$, and $A_D(t)$; and ω_Q is the constants weighting factor for $Q(t)$.

2.3 Behavioral Scale (BehS)

The global output from the model $G(t)$ computed in the BehS is the likelihood of drug-seeking behavior. $G(t)$ indicates whether the virtual subject is more or less likely to manifest behavior inducing drug intake at time t according to Equation 1, which can be readily modified to include time dependence:

$$G(t) = (1 - r(t)) \cdot (-C(t)) + r(t) \cdot I(t) \tag{4}$$

Here $G(t) \in [-1, 1]$, $I(t)$ represents the time-dependant inhibition, and $C(t)$ the time-dependant compulsion as defined below. For $G(t) > 0$ the virtual subject is less likely to have an episode of drug-seeking behavior (healthy behavior), whereas for $G(t) < 0$ the virtual subject is more likely to exhibit drug-seeking behavior (maladaptive behavior).

The overall inhibition $I(t)$ is the arithmetical mean of inhibitions $i'(t)$ and $i''(t)$. Inhibition $i'(t)$ is related to the virtual subject's neural development of the frontal lobes of the cortex [Durston et al., 2002, Leon-Carrion et al., 2004, Blakemore and Choudhury, 2006], given by:

$$i'(t) = \begin{cases} 1 - e^{\beta_1 d} \cdot i'_{max,s_1} & \text{if } t < s_1 \\ i'(t-1) + (2d - 1)\delta_{s_2} & \text{if } t < s_2 \\ i'_{max} - (i'_{max} - i'_0)e^{-\beta_2 d} & \text{if } t < s_3 \\ i'(t-1) & \text{else} \end{cases} \tag{5}$$

where s_1, s_2 and s_3 correspond to developmental changes age from birth to childhood (s_1), to puberty (s_2), to adulthood (s_3); β_1 and β_2 are constants; i'_{max,s_1} is the maximum value of $i'(t)$ for age stage s_1; i'_{max} is the maximal value of $i'(t)$; δ_{s_2} is the maximal increase of $i'(t)$ during age stage s_2; d is the number of time steps after a change in the age stage s_1, s_2 and s_3; and i'_0 is the value $i'(d)$.
The inhibition $i''(t)$ is ascribable to social rules governing the society in which the virtual subject is living. We assume $i'(t)$ a sinusoidal function bounded by two exponential functions:

$$i''(t) = \frac{1 - e^{-\chi_e t}}{2}[(\chi_h - \chi_l)\sin(\chi_s t) + \chi_h + \chi_l] \tag{6}$$

where χ_e is a constant, χ_h is the asymptote of the higher exponential function that bounds $i''(t)$, χ_l is the asymptote of the lower exponential function that bounds $i''(t)$ and χ_s is the angular frequency whose value is changed randomly. Random noise is added to $i'(t)$ and $i''(t)$.

The compulsion $C(t)$ is the arithmetical mean of $c'(t)$ and $c''(t)$ which are computed according to the "incentive-sensitization theory of addiction" [Robinson and Berridge, 1993]. This theory assumes that the neural substrate of the subject using drugs for the first few times becomes more sensitive to the drug by assigning high saliency to drug-related inputs, and this saliency alteration is then the instigator to the compulsive behavior to repetitive drug intakes. According to this theory, the first step is the pleasure phase, during which the subject increasingly enjoys drug effects. The second step is the wanting phase during which the subject changes behavior in order to obtain more and more of the drug. The parameter $c'(t)$ describes the sensitization (liking) process and the parameter $c''(t)$ describes the incentive (wanting) process:

$$c'(t) = \begin{cases} c'_h - (c'_h - c'_0)e^{-\gamma d} & \text{if } G(t) < 0 \\ & \text{and } \tau_G = 0 \\ & \\ c'_{l1} + |c'_{l1} - c'_0|e^{-\beta_1 d} & \text{if } G(t) < 0 \\ & \text{and } \tau_G = 1 \\ & \\ c'_{l2} + |c'_{l2} - c'_0|e^{-\beta_2 d} & \text{if } G(t) > 0 \\ & \text{and } \tau_G = 1 \\ & \\ c'(t-1) & \text{else} \end{cases} \tag{7}$$

and

$$c''(t) = \begin{cases} c''_{h1} - (c''_{h1} - c''_0)e^{-\gamma_1 d} & \text{if } G(t) < 0 \\ & \text{and } \tau_G = 0 \\ & \\ c''_{h2} - (c''_{h2} - c''_0)e^{-\gamma_2 d} & \text{if } G(t) < 0 \\ & \text{and } \tau_G = 1 \\ & \\ c''_l + |c''_l - c''_0|e^{-\beta d} & \text{if } G(t) > 0 \\ & \text{and } \tau_G = 1 \\ & \\ c''(t-1) & \text{else} \end{cases} \tag{8}$$

where c'_h, c'_{l1}, c'_{l2}, c''_{h1}, c''_{h2} and c''_l are maximal and minimal values of respectively $c'(t)$ and $c''(t)$; γ, γ_1, γ_2, β, β_1 and β_2 are constants; τ_G is a binary value set to 1 when $G(t) < 0$ for a number of time steps; d is the number of time steps after a change in the sign of $G(t)$ or the value of τ_G; $c'_0 = c'(d)$ and $c''_0 = c''(d)$. Random noise is added to both signals.

3 EXPERIMENTAL EVALUATION

Drinking, smoking, and drug use are serious problems among college students and can cause addiction. A preliminary experimental evaluation of our model has been performed in order to characterize such behavior. We begin by describing the onset and maintenance of addictive behavior in G.D., a college-age virtual male subject who had a healthy physical and mental development.

The evolution of G.D.'s inhibition $I(t)$ up to age 25 is shown in Figure 2. Here $i'(t)$ is the inhibition related to his neural development, and $i''(t)$ is the inhibition related to the social rules present in his environment. Note that the neural related inhibition $i'(t)$ undergoes an abrupt transformation after age 10, whereas the inhibition $i''(t)$ fluctuates between two exponential curves that represent the minimum and maximum inhibitions in G.D.'s social environment.

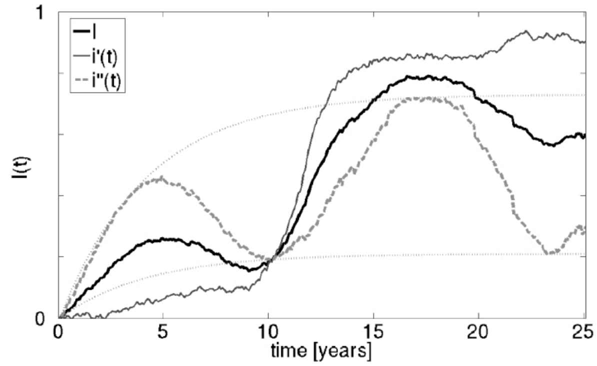

Figure 2: Evolution of G.D.'s inhibition $I(t)$ from birth to age 25: $i'(t)$ is the inhibition related to neural development, and $i''(t)$ is the inhibition related to the social environment.

G.D. had his first encounter with drugs at age 17. The evolution of his drug-seeking behavior $G(t)$ and his compulsion $C(t)$, between the ages of 16 and 18, are shown in Figure 3. Note that the sign of $G(t)$ changes form positive to negative at age 17, and how the incentive and sensitization processes $c'(t)$ and $c''(t)$ change their trajectories.

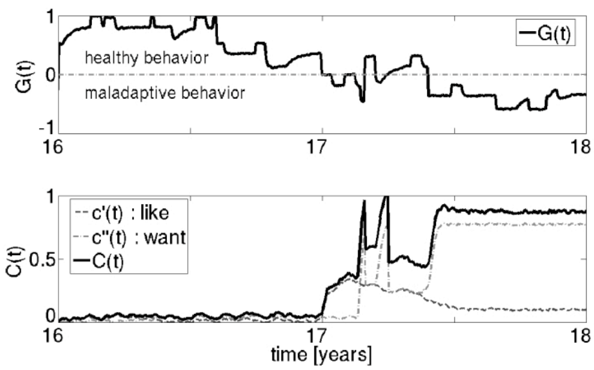

Figure 3: $G(t)$ (upper curve) and $C(t)$ (lower curve) for G.D. from age 16 to 18. Also included are incentive $c'(t)$ and the sensitization $c''(t)$ processes [Robinson and Berridge, 1993].

As a further check of the model, we used the same $I(t)$ and $C(t)$ signals and performed 10 different simulations to compute $G(t)$ and also the other signals. Figures 4 to 6 show the means of these signals as well as the standard errors of the mean (SEM). The evolution of G.D.'s internal processes $S(t)$, $P(t)$ and $D(t)$ at the age of 17 when he begins to take drugs and becomes addicted is shown in Figure 4. The level of negative consequences in areas such as health or social relations $P(t)$ and the dopamine-related craving $D(t)$ have low values at the beginning of the addictive experience, and then progressively increase to steady values.

In the years following his encounter with addiction, G.D. exemplifies the drug-seeking behavior of someone who is unsuccessfully trying to quit using drugs. This relapse pattern, which is a fundamental characteristic of addiction, is apparent in Figure 5, which shows the mean values of $G(t)$ over 10 simulations and the corresponding SEM, from age 19 to 21.

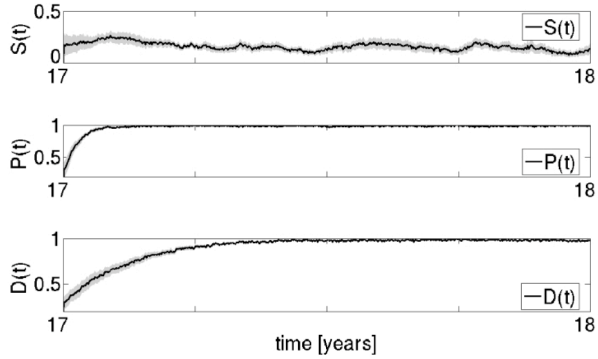

Figure 4: Means and SEMs of the internal processes $S(t)$, $P(t)$, and $D(t)$ for G.D. from age 17 to 18 (10 simulations).

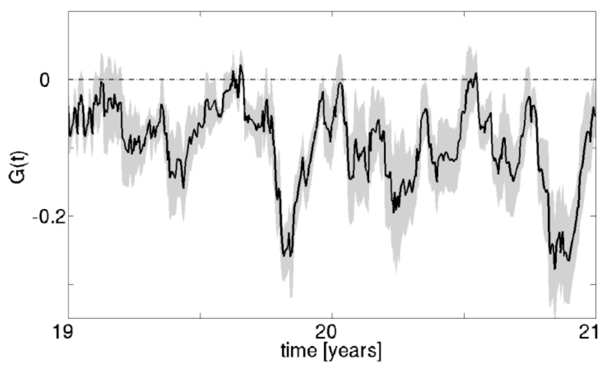

Figure 5: $G(t)$ mean and SEM for 10 simulations. Between ages 19 to 21, G.D. shows a continuous relapse pattern of a person unsuccessfully trying to escape from drug-seeking behavior.

G.D.'s internal processes for this same period are shown in Figure 6. Acute traumas $A_P(t)$ bring him towards a healthy behavior, but he is unable to overcome addiction because of the drug-associated cues $Q(t)$. As $G(t) < 0$ the value of $q(t)$ increases, and $A_S(t)$ and $A_D(t)$ can not occur.

This particular case exemplifies a college-age student who has his first encounter with drugs at the age of 17. Initially G.D. enjoyed the drug, but his enjoyment progressively decreased as his desire increased. This dynamic behavior is due to the negative effect of $Q(t)$ being stronger than the positive effect of $A_P(t)$.

Our model is not limited to monotonic non-reversible processes. Another example with a healthier dynamic is shown in Figure 7. In this case, the virtual male subject, we call V.R. has job-related difficulties following his 36th birthday. The acute stress episodes he experiences at his workplace makes V.R. more vulnerable to addiction. Over a period of several days, his $G(t)$ value decreases and becomes negative, but acute episodes of pain make his $G(t)$ value positive again and his behavior is healthy again.

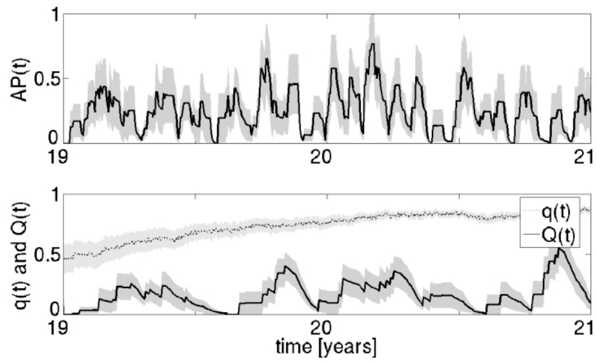

Figure 6: Acute pain $A_P(t)$ (upper curve), and drug-associated cues $Q(t)$ and their saliency value $q(t)$ (lower curves) mean and SEM over 10 simulations for G.D. between ages 19 to 21.

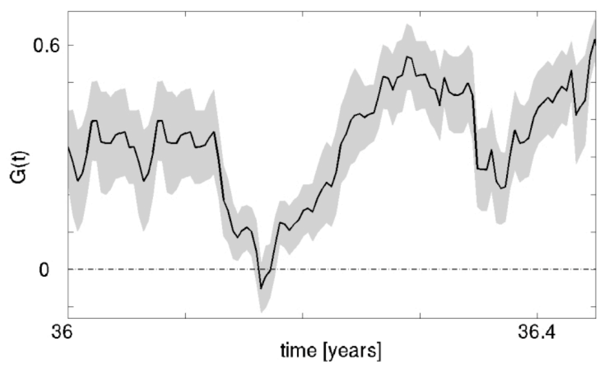

Figure 7: $G(t)$ mean and SEM over 10 simulations for V.R. for 5 months following his 36th birthday. His drug-seeking behavior changes from healthy to maladaptive and back to healthy.

4 DISCUSSION

The present paper introduces a multi-scale approach to the modeling of addiction while also incorporating time dependence to the inhibition and the compulsion processes. A fundamental issue is evaluating the model's ability to mimic experimental data. The first step in this endeavor is to assess whether the calculated likelihood of drug-seeking behavior $G(t)$ is suitable for describing actual addictive behavior.

Computed values for the likelihood of drug-seeking $G(t)$ give rise to specific patterns or trajectories of behavior. For example, it was shown that over 4 years, a group of college-age occasional smokers is likely to evolve into three categories: 45% of the subjects are likely to become nonsmokers, 35% occasional smokers, and 20% daily smokers [Kenford et al., 2005]. Another investigation classifies drinking trajectories of first year college students into five groups: light drinkers the whole year (light-stable), light drinkers the whole year but with a considerable increase during holidays (light-stable plus high holiday), initial moderate drinkers who increased their consumption during the year (medium-increasing), initial heavy drinkers who decreased their consumption during the year (high-decreasing), and finally heavy drinkers during the whole year (heavy-stable) [Greenbaum et al., 2005].

The drug-seeking behavior profile of virtual subject G.D. presented in Figure 5 suggests a person in the "light-stable plus high holiday" group cited above. This parallelism can be made under the assumption that G.D.'s birthday is in September. Within this context, associations between local minima of $G(t)$ and holiday periods seem reasonable with respect to time and the absolute values of $G(t)$. The two local minima prior to G.D.'s 20^{th} and 21^{th} birthdays may be considered to occur in the summer, and the two local minima around ages 19.5 and 20.5 during winter breaks. Also associations between local maxima of $G(t)$ and particularly intense periods of the school year seem reasonable. Local maxima prior to G.D.'s 20^{th} and 21^{th} birthdays may be considered to occur during examination periods. It is reasonable to associate G.D.'s profile with the profile of a student which tends to decrease his drinking consumption during periods requiring more responsibility, and to increase consumption during more serene periods.

Preliminary results presented in this paper suggest that the "dynamical addict" model could provide a complementary view to existing computational models toward a better understanding of addiction and its dynamical properties. Future work will concentrate on more extensive comparisons with real data as well as the integration of an additional neurophysiological scale.

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References

[Ahmed et al., 2007] Ahmed, S. H., Bobashev, G., and Gutkin, B. S. (2007). The simulation of addiction: Pharmacological and neurocomputational models of drug self-administration. *Drug Alcohol Depen*, 90(2-3):304–311.

[Aston-Jones and Harris, 2004] Aston-Jones, G. and Harris, G. C. (2004). Brain substrates for increased drug seeking during protracted withdrawal. *Neuropharmacology*, 47 Suppl 1:167–79.

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

[Blakemore and Choudhury, 2006] Blakemore, S.-J. and Choudhury, S. (2006). Development of the adolescent brain: implications for executive function and social cognition. *J Child Psychol Psychiatry*, 47(17):296–312.

[Bradby and Williams, 2006] Bradby, H. and Williams, R. (2006). Is religion or culture the key feature in changes in substance use after leaving school? young punjabis and a comparison group in glasgow. *Ethn Health*, 11(3):307–24.

[Costa, 2008] Costa, A. M. (2008). Executive summary. In *Office on Drugs and Crime World Drug Report 2008*. United Nations.

[De Alba et al., 2004] De Alba, I., Samet, J. H., and Saitz, R. (2004). Burden of medical illness in drug- and alcohol-dependent persons without primary care. *Am J Addict*, 13(1):33–45.

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

[Durston et al., 2002] Durston, S., Thomas, K. M., Yang, Y., Ulug, A. M., Zimmerman, R. D., and Casey, B. J. (2002). A neural basis for the development of inhibitory control. *Dev Sci*, 5(4):F9–F16.

[Erb et al., 1996] Erb, S., Shaham, Y., and Stewart, J. (1996). Stress reinstates cocaine-seeking behavior after prolonged extinction and a drug-free period. *Psychopharmacology (Berl)*, 128(4):408–12.

[Greenbaum et al., 2005] Greenbaum, P. E., Boca, F. K. D., Darkes, J., and Goldman, C.-P. W. M. S. (2005). Variation in the drinking trajectories of freshmen college students. *J Consult Clin Psychol*, 73(2):229–238.

[Hodgins et al., 1995] Hodgins, D. C., el Guebaly, N., and Armstrong, S. (1995). Prospective and retrospective reports of mood states before relapse to substance use. *J Consult Clin Psychol*, 63(3):400–7.

[Hyman, 2005] Hyman, S. E. (2005). Addiction: a disease of learning and memory. *Am J Psychiatry*, 162(8):1414–22.

[Interlandi, 2008] Interlandi, J. (2008). What addicts need. *Newsweek*, March 3:36–42.

[Kenford et al., 2005] Kenford, S. L., Wetter, D. W., Welsch, S. K., Smith, S. S., Fiore, M. C., and Baker, T. B. (2005). Progression of college-age cigarette samplers: What influences outcome. *Addict Behav*, 30(2):285–294.

[Koob and Le Moal, 2001] Koob, G. F. and Le Moal, M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, 24(2):97–129.

[Leon-Carrion et al., 2004] Leon-Carrion, J., Garcia-Orza, J., and Perez-Santamaria, F. J. (2004). Development of the inhibitory component of the executive functions in children and adolescents. *Int J Neurosci*, 114(10):1291–311.

[Robinson and Berridge, 1993] Robinson, T. E. and Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Rev*, 18(3):247–91.

[Robinson and Berridge, 2003] Robinson, T. E. and Berridge, K. C. (2003). Addiction. *Annu Rev Psychol*, 54:25–53.

[See, 2002] See, R. E. (2002). Neural substrates of conditioned-cued relapse to drug-seeking behavior. *Pharmacol Biochem Behav*, 71(3):517–29.

[Siegelmann, 2008] Siegelmann, H. T. (2008). Dynamical addict: cessation, relapse, and possible recovery. *Submitted*.

[Sinha et al., 2000] Sinha, R., Fuse, T., Aubin, L. R., and O'Malley, S. S. (2000). Psychological stress, drug-related cues and cocaine craving. *Psychopharmacology (Berl)*, 152(2):140–8.

[Sobell et al., 2000] Sobell, L. C., Ellingstad, T. P., and Sobell, M. B. (2000). Natural recovery from alcohol and drug problems: methodological review of the research with suggestions for future directions. *Addiction*, 95(5):749–764.

[Spealman et al., 1999] Spealman, R. D., Barrett-Larimore, R. L., Rowlett, J. K., Platt, D. M., and Khroyan, T. V. (1999). Pharmacological and environmental determinants of relapse to cocaine-seeking behavior. *Pharmacol Biochem Behav*, 64(2):327–36.

[Stewart, 2000] Stewart, J. (2000). Pathways to relapse: the neurobiology of drug- and stress-induced relapse to drug-taking. *J Psychiatry Neurosci*, 25(2):125–36.

[Winick, 1962] Winick, C. (1962). Maturing out of narcotic addiction. *The United Nations Office on Drugs and Crime (UNODC) Bulletin on Narcotics*, 1962(1):1–7.

APPENDIX

This Appendix contains the mathematical details for the internal and external processes in Section 2.1.

The bounding function σ is defined as:

$$\sigma(x) = \begin{cases} 0 & \text{if } x < 0 \\ x & \text{if } x \in [0,1] \\ 1 & \text{if } x > 1 \end{cases}$$

In the following, $\nu(\in [-0.05, 0.05])$ denotes the uniform noise that is different for every signal at each time step t.

The internal processes in the NepS are computed as follows:

S - stress

$$S(t) = \begin{cases} \sigma[1 - (1 - S_0) \cdot e^{-\beta_S \cdot d} + \nu] & \text{if } G > 0 \\ \sigma[S(t-1) + \nu] & \text{if } G = 0 \\ \sigma[S_0 \cdot e^{-\gamma_S \cdot d} + \nu] & \text{if } G < 0 \end{cases}$$

where t_c is the time of last change of sign of G; S_0 is the value of $S(t_c)$; β_S is the exponential constant of S when $G > 0$; γ_S is the exponential constant of S when $G < 0$; d is the number of steps after t_c; $d \in \mathbb{N}$; $S \in [0, 1]$.

P - pain

$$P(t) = \begin{cases} \sigma[P_0 \cdot e^{-\beta_P \cdot d} + \nu] & \text{if } G > 0 \\ \sigma[P(t-1) + \nu] & \text{if } G = 0 \\ \sigma[1 - (1 - P_0) \cdot e^{-\gamma_P \cdot d} + \nu] & \text{if } G < 0 \end{cases}$$

where t_c is the time of last change of sign of G; P_0 is the value of $P(t_c)$; β_P is the exponential constant of P when $G > 0$; γ_P is the exponential constant of P when $G < 0$; d is the number of steps after t_c; $d \in \mathbb{N}$; $P \in [0, 1]$.

D - dopamine related craving

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

where t_c is the time of last change of sign of G; D_0 is the value of $D(t_c)$; τ is the number of time steps in which the dopamine related craving increases after there is no drug consumption; $D_0^{'}$ is the value of $D(t)$ at $t = \tau$; β_D is the exponential constant of D when $G > 0$; γ_D is the exponential constant of D when $G < 0$; d is the number of steps after t_c; $d \in \mathbb{N}$; $D \in [0, 1]$.

q - saliency to drug cues

$$q(t) = \begin{cases} \sigma[q(t-1) + \nu] & \text{if } \{G > 0 \\ & \text{and } d \in [1, \tau]\} \\ & \text{or if } G = 0 \\ \\ \sigma[q_0^{'} \cdot e^{-\beta_q \cdot d} + \nu] & \text{if } G > 0 \\ & \text{and } d > \tau \\ \\ \sigma[1 - (1 - q_0) \cdot e^{-\gamma_q \cdot d} + \nu] & \text{if } G < 0 \end{cases}$$

where t_c is the time of last change of sign of G; q_0 is the value of $q(t_c)$; τ is the number of time steps in which saliency to drug cues does not decrease even that there is no drug consumption; $q_0^{'}$ is the value of $q(t)$ when $t = \tau$; β_q is the exponential constant of q when $G > 0$; γ_q is the exponential constant of q when $G < 0$; d is the number of steps after t_c; $d \in \mathbb{N}$; $q \in [0, 1]$.

The external processes in the NepS are computed as follows:

A_S - acute shock

$$A_S(t) = \begin{cases} A_{S_0} & \text{if } \{G > 0 \\ & \text{and } b_S(t) = 1\} \\ & \text{or } t_S \in [1, \tau_1] \\ \\ \rho_S \cdot A_S(t-1) & \text{if } t_S \in [\tau_1, \tau_2] \\ \\ 0 & \text{else} \end{cases}$$

where $b_S(t)$ is a Boolean variable $\in \{0,1\}$; $b_S(t) = 1$ means that a shock begins at time t; A_{S_0} is a constant; ρ_S is a constant < 1; t_0 is the starting time of a shock; $t_S \in \mathbb{N}$ is the number of steps after t_0; τ_1 is the number of time steps in which the shock effect is constant; τ_2 is the number of time steps in which the shock effect is decreasing $(\tau_2 > \tau_1)$; $A_S \in [0, A_{S_0}]$.

A_P and A_D - acute trauma and acute priming to drugs

The signals A_S, A_P, and A_D are mathematically very similar. The main difference is that an event A_P can start only when $G < 0$, but events A_S and A_D can start only when $G > 0$.

Q - encountering drug cues

$$Q(t) = \begin{cases} q(t) & \text{if } b_Q(t) = 1 \\ Q(t-1) & \text{if } t_Q \in [1, \tau_1] \\ \rho_Q \cdot Q(t-1) & \text{if } t_Q \in [\tau_1, \tau_2] \\ 0 & \text{else} \end{cases}$$

where $b_Q(t)$ is a Boolean variable $\in \{0,1\}$; $b_Q(t) = 1$ means that a cue begins at time t; ρ_Q is a constant > 1; t_0 is the starting time of a cue; $t_Q \in \mathbb{N}$ is the number of steps after t_0; τ_1 is the number of time steps in which the cue effect is constant; τ_2 is the number of time steps in which the cue effect is decreasing $(\tau_2 > \tau_1)$; $Q \in [0, \rho_Q]$.