A mathematical model of reward-mediated learning in drug addiction

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ABSTRACT

Substances of abuse are known to activate and disrupt neuronal circuits in the brain reward system. We propose a simple and easily interpretable dynamical systems model to describe the neurobiology of drug addiction that incorporates the psychiatric concepts of reward prediction error, drug-induced incentive salience, and opponent process theory. Drug-induced dopamine releases activate a biphasic reward response with pleasurable, positive "a-processes" (euphoria, rush) followed by unpleasant, negative "b-processes" (cravings, withdrawal). Neuroadaptive processes triggered by successive intakes enhance the negative component of the reward response, which the user compensates for by increasing drug dose and/or intake frequency. This positive feedback between physiological changes and drug self-administration leads to habituation, tolerance, and, eventually, to full addiction. Our model gives rise to qualitatively different pathways to addiction that can represent a diverse set of user profiles (genetics, age) and drug potencies. We find that users who have, or neuroadaptively develop, a strong b-process response to drug consumption are most at risk for addiction. Finally, we include possible mechanisms to mitigate withdrawal symptoms, such as through the use of methadone or other auxiliary drugs used in detoxification.

Drug abuse has been dramatically increasing worldwide over the last 20 years. Despite attempts to implement effective prevention programs, treatment options, and legislation, drug poisoning remains a leading cause of injury-related death in the United States, with a record of 100 000 fatal overdoses recorded in 2020. Understanding how addiction to illicit substances develops is of crucial importance in trying to develop clinical, pharmaceutical, or behavioral intervention. The neurobiological basis of drug addiction is centered on disruptions to the dopamine system in the brain reward pathway of users, which lead to neuroadaptive changes and the need for larger or more frequent intakes to avoid withdrawal symptoms. Despite the many qualitative descriptions of the pathway to addiction, a concise mathematical representation of the process is still lacking. We propose a unified, easily interpretable dynamical systems model that includes the concepts of reward prediction error (RPE), drug-induced incentive salience (IST), and opponent process theory (OPT). Specifically, we introduce a time-dependent reward function associated with each drug intake. Physiological parameters evolve through neuroadaptation, consistently with OPT, while user-regulated drug intake is dependent on the most recent reward prediction, consistent with RPE. Our model yields different distinct stages of the addiction process that are cycled via a dynamical recursion. Individual-specific parameters may be tuned to represent different drug potencies, age, or genetic predispositions. Rich features emerge, such as monotonically convergent or damped oscillatory (yo-yo) progression toward full addiction. Finally, our model can be used to explore detoxification strategies.

I. INTRODUCTION

Despite decades of medical, political, and legal efforts, substance abuse remains a major issue worldwide. The annual number of overdose deaths in the United States has risen from about 20 000 in 2000 to over 70 000 in 2019,[1] resulting in the highest drug mortality rate in the world at an economic cost of at least 740 billion USD per year.[2]

Our understanding of addiction, why and how it emerges, is still incomplete, although several mechanisms of action have been identified[3,4] and modeled.[5,6] Addictive substances hijack the mesocorticolimbic pathways that govern our response to primary rewards such as food, drink, and sex. Under normal conditions, primary rewards increase levels of dopamine, the main neurotransmitter in the brain reward system. Dopamine-strengthened neuronal connections encode information on the reward and its utility,[7,8] while its release in the mesocorticolimbic pathways regulates incentive salience, the want and seeking of rewards.[9,10] To optimize future responses, dopaminergic neurons respond differently to rewards that deviate from expectations.[11–13] The reward prediction error (RPE) quantifies the discrepancy between a reward and its prediction and plays a major role in learning: neural activity increases if the reward is greater than expected (positive RPE) and decreases otherwise (negative RPE).[14–16] The RPE embodies reinforcement learning, a key concept in psychology that has been modeled and applied to many contexts, including drug addiction.[5]

The effects of addictive drugs on the brain are similar to that of primary rewards; drugs, however, amplify desires in abnormal ways. Viewed as rewards, cocaine, amphetamines, and morphine act faster and increase dopamine levels two to ten times more than food or sex,[17–19] exaggerating the brain's response to any drug-related cue. The operational mechanisms of each drug type may be different, for example, cocaine blocks the reuptake of dopamine, whereas heroin binds to mu-opioid receptors that directly stimulate the release of dopamine. Other molecular targets of drugs of abuse include the neurotransmitters endorphin and enkephalin (particularly, in the case of prescription opioids) and norepinephrine and glutamate.[20,21] Signaling between different neurotransmitter types frequently leads to secondary effects. Whether directly or indirectly activated, the most common feature of drug intake is a dramatic increase in dopamine signaling in the nucleus accumbens (NAc),[22] which is the process we will focus on in our modeling.

Incentive sensitization theory (IST) formalizes the concepts illustrated above.[23] Another relevant psychological concept is the opponent process theory (OPT), whereby every emotional experience, pleasant or unpleasant, is followed by a counteracting response to restore homeostasis. Within OPT, the consumption of drugs induces an "a-process," marked by euphoria, rush, and pleasure, later compensated by a "b-process" marked by withdrawal symptoms and craving.[24,25] For beginners, the pleasant a-process is more intense and lasts longer than the unpleasant b-process. Continued use leads to neuroadaptation, with the b-process appearing earlier and lasting longer. Tolerance and dependence set in Refs. 26 and 27 as drug consumption becomes predominantly unpleasant.[28] Examples of drug-dependent neuroadaptation include the reduction of postsynaptic D_2 dopamine receptors,[29] neuronal axotomy,[30] decreased dopamine neuron firing,[31] increases in the number of AMPA receptors,[32] and activation of D1-like receptors.[33] Central among the brain tissues responding to drug use is the ventral tegmental area (VTA) whose dopaminergic neurons project to the nucleus accumbens (NAc) shell and to the ventral pallidum (VP), two of the brain's pleasure centers associated with the a-process. The neurobiological source of the b-process has been identified with the subsequent activation of several stress circuits controlled by the extended amygdala and the hypothalamus, disrupting the release of stress related hormones or peptides such as CRH, norepinephrine, dynorphin, or hypocretin, leading to aversive feelings.[24,34–36]

How drugs impact the brain reward system has been mathematically studied using dynamical systems,[5,37–41] real-time neural networks,[42,43] temporal-difference reinforcement learning,[44] and model-free learning models.[45] While these models explain certain observed features of the addiction process, a simpler, yet explicit quantitative framework that unifies concepts from RPE, IST, and OPT and allostasis is still lacking. Here, we construct and analyze a proof-of-principle mathematical model of the onset of drug addiction, resolved at the individual drug intake time scale. Neuroadaptation is represented by changes in physiological parameters consistent with RPE and OPT, informing changes to user behavior. These changes induce further neuroadaptation, creating a feedback loop that may lead to full addiction. We introduce measures to quantify the overall reward resulting from a single drug intake and for the reward prediction error; addiction is mathematically defined as the state in which the overall reward is negative and the reward prediction error is below a given threshold. These formulations allow us to predict the unfolding of the addiction process depending on the specific physiology and neuroadaptive profile of the user. Specifically, we find that, given the same drug, users who are more sensitive to neuroadaptive changes in the b-process (or who have an initially elevated b-process response) are the ones whose progression to addiction is faster than those who are less reactive. These more resilient users may also display reward prediction errors that oscillate in value with each drug intake before permanently crossing the threshold to addiction ("yo-yo" dynamics).

II. MATHEMATICAL MODEL

A. Dopamine release

We begin by describing the time-dependent activity $D(t)$ (e.g., firing rate) of dopaminergic neurons in the reward system in response to the dopamine release that follows a single, initial drug intake. Other rewards such as food, sex, etc., also stimulate dopamine release, however, it is known that drug-induced dopamine release is an order of magnitude larger than what stimulated by "natural" rewards.[17] Experimental measurements show a rapid rise in activity within a few minutes of intravenous drug administration,[46,47] followed by an exponential decay over 1-5 h.[17] We propose

$$D(t) = \Delta e^{-\delta t}, \tag{1}$$

where Δ is the magnitude of the dopamine response and $1/\delta$ is the effective dopamine residence time, which includes the clearance time of dopamine-stimulating drugs; typically, $\delta \sim 0.2\text{–}1\,\mathrm{h}^{-1}$. For simplicity, we measure time in units of δ, rescale $t' \to \delta t$, drop the prime notation, and set $D(t) = \Delta e^{-t}$. Since dopamine release is triggered by drug intake, we, henceforth, use Δ as a proxy for drug dosage. Although more complex pharmacokinetic models have been developed to connect drug dose to dopamine activity,[48] the time dependence of dopamine activity qualitatively resembles a decaying exponential except at very short times.

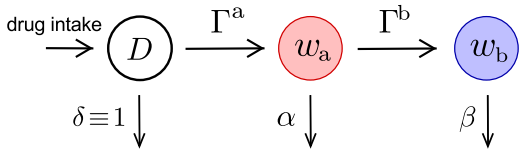

FIG. 1. Schematic of a- and b-processes. Drug use activates the dopaminergic neurons, which, in turn, activate the hedonic hotspots in the nucleus accumbens that mediate the pleasurable "a-processes" w_a, leading to euphoria and bliss. Unpleasurable "b-processes" w_b may follow, accompanied by cravings and withdrawal symptoms. The relative magnitude of the two $w_{a,b}$ experiences may vary among individuals and may depend on the stage of addiction. Dopamine-induced activity is modeled as $D(t) = \Delta e^{-\delta t}$ where Δ is a proxy for drug dosing and δ its typical degradation rate. The overall a-process is activated by $D(t)$ via the prefactor Γ^a, whereas the overall b-process is activated by the a-process via the prefactor Γ^b. The activity of the a- and b-processes decay with rates α and β, respectively.

B. Single-dose drug-induced a- and b-processes

According to OPT and as described above, drug-induced dopamine activity $D(t)$ induces a pleasurable a-process, $w_a(t)$, which, in turn, activates an unpleasant b-process, $w_b(t)$ (see Fig. 1). We propose a deterministic model for $w_{a,b}(t)$ that incorporates simple integrate-and-fire dynamics

$$\frac{dw_a(t)}{dt} = -\alpha w_a(t) + \Gamma^a D(t), \tag{2}$$

$$\frac{dw_b(t)}{dt} = -\beta w_b(t) - \Gamma^b w_a(t), \tag{3}$$

where Γ^a and Γ^b represent the coupling of $D(t)$ to $w_a(t)$ and of $w_a(t)$ to $w_b(t)$, respectively. The intrinsic decay rates of the a- and b-processes are denoted α and β. The effects of intermittent natural rewards that induce dopamine release can be incorporated by including an extra source to $w_a(t)$ in the form of a periodic or a randomly fluctuating term. These non-drug terms would be much smaller in magnitude than the drug source $D(t)$, since drug induced stimuli are much larger than non-drug ones.[17] The periodic part may represent, say, eating at regular intervals, whereas the fluctuating part might describe all other non-drug, pleasurable experiences that occur at random times. Thus, a stochastic model might yield a more complete description of the brain reward system and its many inputs but we shall limit this study to the deterministic response from well-defined drug intakes as presented in Eqs. (2) and (3).

The $w_{a,b}(t)$ processes generate the brain reward system's perception of the drug. While further complex processing and filtering of $w_{a,b}(t)$ may be at play, we assume they are summed to yield the dynamic, time-dependent response $w(t|\theta) = w_a(t) + w_b(t)$, where $\theta = \{\Delta, \alpha, \Gamma^a, \beta, \Gamma^b\}$ are the parameters associated with the reward perception process. Upon solving Eqs. (2) and (3), we find the dynamic response $w(t|\theta)$ following a single, isolated dopamine release and/or drug intake

$$w(t|\theta) = \frac{\Gamma^a \Delta}{\alpha - 1}\left[\left(1 - \frac{\Gamma^b}{\beta - 1}\right)e^{-t} - \left(1 - \frac{\Gamma^b}{\beta - \alpha}\right)e^{-\alpha t} - \left(\frac{\Gamma^b}{\beta - \alpha} - \frac{\Gamma^b}{\beta - 1}\right)e^{-\beta t}\right]. \tag{4}$$

The time-integrated net response

$$W(\theta) = \int_0^\infty w(t|\theta)dt = \frac{\Gamma^a \Delta}{\alpha}\left(1 - \frac{\Gamma^b}{\beta}\right), \tag{5}$$

associated with a single, isolated dopamine release and/or drug intake can be interpreted as a memory of the experience and can be used as a benchmark for future decision-making. Note that the amplitude factor Γ^a in Eqs. (4) and (5) adjusts the "hedonic" scale of $w(t|\theta)$ and $W(\theta)$.

In Fig. 2(a), we plot $w(t|\theta)$ for $\Delta = 1, \alpha = 0.5, \Gamma^a = 1, \Gamma^b = 0.8$, and $\beta = 1.5$ (orange curve I), $\beta = 0.9$ (green curve II), and $\beta = 0.45$ (blue curve III). These representative response curves $w(t|\theta)$ are (I) always positive, (II) turning negative with positive integral $W(\theta) > 0$, and (III) turning negative with negative integral $W(\theta) < 0$. Type I responses are typical of healthy, naïve users who for the most part experience only the pleasurable a-process. For smaller β, larger Γ^b, and/or larger α ($\Gamma^b < \beta < \Gamma^b + \alpha$), $w(t|\theta)$ exhibits a type II response, which is negative at late times but yields a positive net response $W(\theta) > 0$. For even smaller β and/or larger Γ^b, the response is type III: the negative b-process overtakes the a-process and the overall experience is negative with $W(\theta) < 0$. Type II and type III responses are typical of moderate and addicted users, respectively. Figure 2(b) shows the density plot of the time t^* when the dynamic response $w(t^*|\theta) = 0$, as a function of β and Γ^b at $\alpha = 0.5$. For $\beta \geq \Gamma^b + \alpha$, there are no finite solutions t^* to $w(t^*|\theta) = 0$; in this regime, the dynamic response is always positive as represented by the type I curve in Fig. 2(a). For $\beta < \Gamma^b + \alpha$, t^* is positive and finite and decreases as β decreases or Γ^b increases, indicating a stronger overall b-process. Examples are the type II and type III curves in Fig. 2(a).

What we have described so far is a simple single-dose picture of the reward response. In Sec. II C, we build on it to describe addiction as a progression of multiple drug intakes that induce neuroadaptive changes to the physiological parameters, β and Γ^b, and behavioral changes to the user that shift the net response from type I to type III.

C. Successive drug intakes

We now consider successive drug intakes i taken at times T_i with the first dose taken at $T_1 = 0$ and the most recent one at T_k. For finite T_k, the total time-dependent response is a superposition of the time-shifted responses in Eq. (4),

$$w(t|\{\theta_{i\leq k}\}) = \sum_{i=1}^{k} w(t - T_i|\theta_i), \quad T_1 \equiv 0, \quad T_k < t < T_{k+1}, \tag{6}$$

where $\theta_i = \{\Delta_i, \alpha_i, \Gamma_i^a, \beta_i, \Gamma_i^b\}$ are the parameters of the system following intake i. The doses Δ_i and intake times T_i are primarily user-controlled. We assume the other parameters $\{\alpha_i, \Gamma_i^a, \beta_i, \Gamma_i^b\}$

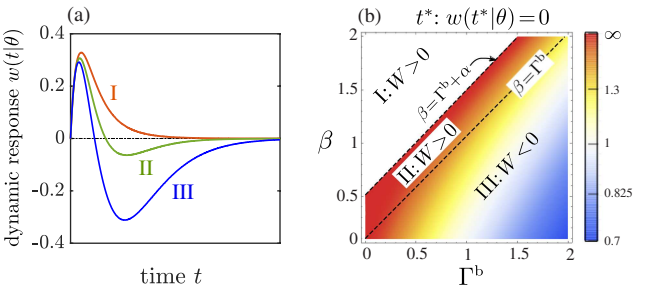

FIG. 2. (a) Three examples of time-dependent response $w(t|\theta)$ associated with a single, isolated dopamine hit. We fix $\theta = \{\Delta = 1, \alpha = 0.5, \Gamma^a = 1, \beta, \Gamma^b = 0.8\}$ and plot Eq. (4) for three different values of β showing a response that is always positive (I: $\beta = 1.5$, orange), a response that can become negative (II: $\beta = 0.9$, green), and one with a negative total reward (III: $\beta = 0.45$, blue). (b) Density plot representing the values of the time t^* associated with the solution to the transcendental equation $w(t^*|\theta) = 0$ as a function of β and Γ^b for $\alpha = 0.5$. The white parameter region does not admit a finite solution to t^* [$w(t|\theta)$ is always positive].

evolve in a step-wise fashion due to dopamine-induced neuroadaptive changes, such as long-term potentiation or other long-lasting physiological, tissue-level, or biochemical processes. The total net response after the last dose at time T_k can be defined as an integral over $w(t|\{\theta_{i\le k}\})$ starting from T_k until the current time t. Thus, the net response associated with dose k is

$$W_k(t|\{\theta_{i\le k}, T_{i\le k}\}) = \int_{T_k}^{t} w(t'|\{\theta_{i\le k}\})\, \mathrm{d}t', \tag{7}$$

where $T_k < t < T_{k+1}$ and T_{k+1} is the time of the next dose, if it occurs. Using Eqs. (4) and (7), we find

$$\begin{aligned} W_k(t|\{\theta_{i\le k}, T_{i\le k}\}) = &\sum_{i=1}^{k} C_i (e^{-(T_k - T_i)} - e^{-(t-T_i)}) \\ &+ \sum_{i=1}^{k} C_i^{\alpha} (e^{-\alpha_i (T_k - T_i)} - e^{-\alpha_i (t-T_i)}) \\ &+ \sum_{i=1}^{k} C_i^{\beta} (e^{-\beta_i (T_k - T_i)} - e^{-\beta_i (t-T_i)}), \end{aligned} \tag{8}$$

where

$$\begin{aligned} C_i &\equiv \frac{\Gamma_i^a \Delta_i}{\alpha_i - 1}\left(1 - \frac{\Gamma_i^b}{\beta_i - 1}\right), \\ C_i^{\alpha} &\equiv \frac{\Gamma_i^a \Delta_i}{\alpha_i - 1}\frac{1}{\alpha_i}\left(\frac{\Gamma_i^b}{\beta_i - \alpha_i} - 1\right), \\ C_i^{\beta} &\equiv \frac{\Gamma_i^a \Delta_i}{\alpha_i - 1}\frac{1}{\beta_i}\left(\frac{\Gamma_i^b}{\beta_i - 1} - \frac{\Gamma_i^b}{\beta_i - \alpha_i}\right). \end{aligned} \tag{9}$$

If drug intakes are well-separated ($T_{i+1} - T_i \to \infty$) with no residual effects from previous doses, the net response between T_k and T_{k+1} is $W_k(T_{k+1}|\{\theta_{i\le k}, T_{i\le k}\}) \to \Gamma_k^a \Delta_k (1 - \Gamma_k^b/\beta_k)/\alpha_k$, the result given in Eq. (5).

D. Reward prediction error (RPE) and behavioral changes

To construct the total time-dependent response for multiple drug intakes $w(t|\{\theta_{i\le k}\})$ in Eq. (6), we must describe the evolution of the user-controlled variables $\{\Delta_i, T_i\}$ and of the neuroadaptive parameters $\{\alpha_i, \Gamma_i^a, \beta_i, \Gamma_i^b\}$ as a function of the number of intakes i. In this section, we provide a mathematical description of the RPE, the difference between the expected and received rewards associated with each drug intake. The RPE is a key component of learning and decision-making; here, it will be assumed to regulate the specific decision of the user to change (or not) the next drug dose Δ_{k+1} of intake $k+1$.

The expected response of a drug intake depends on the user's prior history, experiences, and cues of upcoming rewards. The expectation may be different from the actual, obtained response leading to an error, the RPE. For simplicity, we represent the RPE_k following intake k, and just before intake $k+1$, as the difference between the most recent net response W_k and the prior one W_{k-1},

$$\begin{aligned} \mathrm{RPE}_k \equiv\ & W_k(T_{k+1}|\{\theta_{i\le k}, T_{i\le k}\}) \\ & - \gamma_{k-1} W_{k-1}(T_k|\{\theta_{i\le k-1}, T_{i\le k-1}\}) - C_{k+1}, \end{aligned} \tag{10}$$

weighted by a factor $\gamma_{k-1} < 1$ that discounts the previous net response W_{k-1} and that may incorporate memory effects. RPEs that rely on responses associated with drug doses further in the past can also be used to reflect longer memory of the reward.[37] The term C_{k+1} is a history-independent cue associated with the upcoming $k+1$th intake. Examples of cues include seeing or smelling the drug, or preparing for its consumption. Without loss of generality, we assume $C_k = 0$ by shifting the baseline value of the RPE. An example of a negative RPE is shown in Fig. 3, where $\mathrm{RPE}_3 < 0$, indicating unmet expectations from intake 3. As defined in Eq. (10), a positive RPE_k arises if $W_k > \gamma_{k-1} W_{k-1}$, raising expectations for future intakes. This increased expectation may represent habituation, whereby continued use generates a desire for greater net responses. The value of RPE_k will be used in Sec. II F to determine if a behavioral change, such as a change in dose Δ_{k+1}, is elicited.

E. Neuroadaptation and parameter changes

In addition to $\{\Delta_i T_i\}$, the time-dependent response $w(t|\{\theta_{i\le k}\})$ also depends on the physiological parameters $\{\alpha_i, \Gamma_i^a, \beta_i, \Gamma_i^b\}$. Changes in these quantities can be driven by neuroadaptive processes following each drug intake and can depend on the specific characteristics (age, gender, constitution, genetic makeup) of each user. These neuroadaptive processes are complex and difficult to model, so we simplify matters by assuming that $\{\alpha_i, \Gamma_i^a, \beta_i, \Gamma_i^b\}$ change only in response to each drug-induced dopamine release Δ_i at T_i. To be consistent with OPT and observations, neuroadaptive changes should increase the effects of the negative b-process relative to those of the positive a-process as addiction progresses. This can be achieved through a decrease in β_i and/or an increase in Γ_i^b. In principle, changes in α_i arising from tolerance (that shortens the "high" and affects the relative strengths of the a- and b-processes) can also be modeled, but since changes to $\Gamma_i^a \Delta_i/(\alpha_i - 1)$ only rescale $w(t)$, we fix $\alpha_i = \alpha$ and $\Gamma_i^a = \Gamma^a$ to constant values. Thus, we let Δ_i drive neuroadaptive changes in β_{i+1} and Γ_{i+1}^b according to the simplest

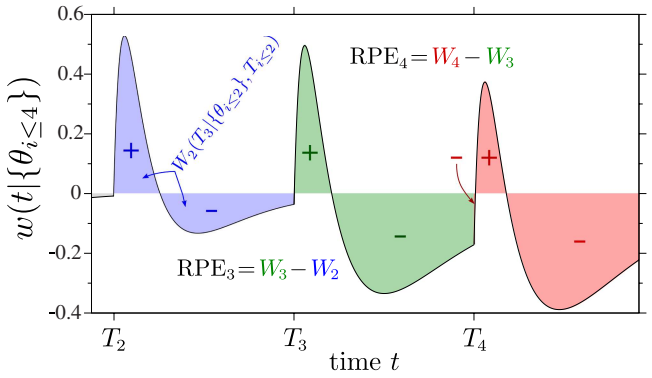

FIG. 3. Time-dependent response $w(t)$ resulting from multiple drug intakes at times $T_1 = 0$ (not shown), T_2, T_3, and T_4. Each dopamine release elicits an a- and b-process response, which can be concatenated [Eq. (6)]. The net reward W_k associated with dose k is defined as the integral of $w(t|\{\theta_{i\le k}\})$ from time T_k to T_{k+1} and may depend on $\theta_{i\le k}$ since the a- and b-processes triggered by previous drug intakes may not have fully dissipated. For small β_i, b-processes relax slowly, making the response to appear to reach a lower homeostatic value. The small β regime resembles the allostatic effect on time scales $\lesssim 1/\beta$. In this limit, repeated drug doses successively drive the reward response negative pushing the user to experience increasingly intense withdrawal symptoms. In these plots, $\Delta = 1, \alpha = 0.2, \Gamma^{\mathrm{a}} = 1, \Gamma^{\mathrm{b}} = 0.2$ and $\beta_1 = 0.3$, $\beta_2 = 0.2$, $\beta_3 = 0.1$, and $\beta_4 = 0.1$ for intakes at 0, T, $2T$, and $3T$, respectively. The RPE is defined by the difference between two consecutive time-integrated responses $W_k - W_{k-1}$.

rule consistent with OPT,

$$\beta_{i+1} = \beta_i(1 - B\Delta_{i+1}), \quad \Gamma^{\mathrm{b}}_{i+1} = \Gamma^{\mathrm{b}}_i(1 + G\Delta_{i+1}). \tag{11}$$

Here, B and G are parameter-change sensitivities that may depend on i, β_i, Γ^{b}_i, and Δ_i, but that we assume to be constant, with the caveat that B is small enough that for all values of i, $B\Delta_i < 1$. Equation (11) implies that β_i and Γ^{b}_i are represented by piecewise constant values that change after each drug intake. Note that after a sufficient number of intakes β_i becomes very small and the negative response persists for a long time, yielding an apparent "allostatic" state.[49] In the above recursion Eq. (11), the drug doses Δ_i may be assumed fixed or may evolve according to models that involve the RPE.

We now incorporate the ingredients described above into a dynamical model that generates trajectories to addiction. In this model, the neuroadaptative evolution of the physiological parameters induces changes to the reward responses, which, in turn, modify the RPE and lead to user behavioral changes such as increases in drug dose or intake frequency to boost the pleasurable a-process. Despite these user-controlled changes, the evolving neurophysiological parameters may eventually lead to negative net responses and RPEs. We, thus, define addiction as a state marked by persistently negative $\mathrm{RPE}_i < 0$ and negative net responses $W_i < 0$ that arise for intakes at or greater than a critical number $i \ge k^*$.

F. Evolution of intake doses

We first consider the case where the intake times $T_i = (i-1)T$ are perfectly periodic with interval T and study the evolution of the most recent dose Δ_k to the next one Δ_{k+1}. Although more intense dopamine activity may be stimulated by a larger Δ_{k+1} [according to Eq. (4) for well spaced intakes], the resulting net response W_{k+1} may not necessarily be larger than W_k since W_{k+1} depends not only on dose but also on the neuroadaptive parameters $\{\alpha_{k+1}, \Gamma^{\mathrm{a}}_{k+1}, \beta_{k+1}, \Gamma^{\mathrm{b}}_{k+1}\}$ over which the user has no direct control. Thus, scenarios may arise in which although the drug dose increases, the RPE remains negative and user expectations are not met. We assume that if the RPE > 0, the user will not alter the drug dose; however, if RPE < 0, the user will increase it. To concretely model this behavior and allow variable Δ_k, we augment the recursion relations (11) as follows:

$$\Delta_{k+1} = \Delta_k + \sigma H(\mathrm{RPE}_k), \quad H(x) = \begin{cases} 1, & x \le R_{\mathrm{c}}, \\ \frac{x}{R_{\mathrm{c}}}, & R_{\mathrm{c}} < x < 0, \\ 0, & x \ge 0, \end{cases} \tag{12}$$

where σ is the maximal dose-change and $H(x)$ dictates how doses increase as a function of RPE_k. We choose the simple form in Eq. (12) representing a graded switching function with threshold $R_{\mathrm{c}}/2$. We use the representation of RPE_k given in Eq. (10) in which for simplicity we set $\gamma_{k-1} = 1$ and $C_{k+1} = 0$. Finally, note that the argument of H in Eq. (12), RPE_k, depends on the drug intake period T and the dose Δ_k through $W_k(T_{k+1}|\{\theta_{i\le k}, T_{i\le k}\})$, which makes the evolution Eq. (12) non-linear.

In our model, changes to the neuroadaptive parameters $\beta_{i+1}, \Gamma^{\mathrm{b}}_{i+1}$ at intake $i+1$ carry a linear dependence on the dosage Δ_{i+1}, according to Eq. (11). We adopted this choice for simplicity; however, more complex forms for the evolution of $\beta_{i+1}, \Gamma^{\mathrm{b}}_{i+1}$, and Δ_{i+1} can be used to study a wider range of scenarios.

Specifically, the parameters coefficients B, G in Eq. (11) could be modeled to be functions of intake number or time on drugs, through forms that depend on the genetics of age of the user. Such refinements may be important especially if one is interested in the long-term dynamics of drug consumption, or in comparing responses among different user types. For example, it is well known that drugs of abuse can significantly impact the still-maturing and, thus, vulnerable, adolescent brain and cause severe, long-term damage.[50] Equation (11) can also be modified to include saturation or recovery of the baseline values of $\beta_{i+1}, \Gamma^{\mathrm{b}}_{i+1}$ if the user stops using drugs. Other nonlinearities may be introduced to represent distinct neuroadaptive regimes. These could be stages of more (or less) impactful changes once a given threshold of, say, drug dose, cumulative drug dose, or reward value is reached.[51] These choices may lead to non-trivial dynamics involving $\beta, \Gamma_{\mathrm{b}}, \Delta$ as well as the RPE, and possibly lead to chaotic behaviors,[52] as proposed in the context of alcohol addiction.[53–55]

III. RESULTS

We now study the effects of multiple intakes utilizing the full model given by Eqs. (7)–(9) and Eqs. (10)–(12). We set $\alpha_i = 0.3, \Gamma^{\mathrm{a}}_i = 1, R_{\mathrm{c}} = -0.05, \sigma = 0.1$, initialize the system with $\{\beta_1, \Gamma^{\mathrm{b}}_1, \Delta_1, \mathrm{RPE}_1\} = \{0.5, 0.1, 1, 0\}$. Upon specifying B, G we can find the first net response $W_1(T_2|\{\theta_1, T_1\})$ per Eq. (7).

We let the second dose $\Delta_2 = 1$ and generate $\{\beta_2, \Gamma_2^b\}$ from Eq. (11) and $W_2(T_3|\{\theta_{i\le 2}, T_{i\le 2}\})$ from Eq. (7), yielding $\mathrm{RPE}_2 = W_2(T_3|\{\theta_{i\le 2}, T_{i\le 2}\}) - W_1(T_2|\{\theta_1, T_1\})$. The next dose Δ_3 is then determined through Eq. (12), and so on. To illustrate responses to multiple fixed-period intakes, we must specify the dimensionless time T between drug intakes relative to the drug-induced dopamine mean residence times. In Fig. 4, we assume the inter-intake period T to be six times the effective dopamine residence time $1/\delta$. Thus, if $\delta \approx 0.25$/h, daily drug dosing (once every 24 h) corresponds to $T = 6$.

Figure 4(a) shows the total time-dependent response $w(t|\{\theta_i\})$ under three sets of parameters, $B = 0.05, G = 0$ (Case 1, solid black curve), $B = 0, G = 0.05$ (Case 2, dashed green curve), and $B = G = 0.05$ (Case 3, solid red curve). We see that under neuroadaptation of both parameters β and Γ^b (Case 3), the transition to addiction occurs much faster (red curve), with a shorter plateau in W_k and a quicker drop in RPE_k. In general, a larger Γ^b relative to Γ^a depresses the time-dependent dynamical response $w(t|\{\theta_i\})$ and the net response W. Larger α and β lead to more transient responses that display less overlap between intakes provided T is fixed. Smaller β leads to longer lasting b-processes that overlap across successive intakes.

In Fig. 5, we explore the effects of varying the duration of the a-process by setting $\beta_1 = 0.5, \sigma = 0.05, \Gamma^a = 1, \Gamma_1^b = 0.1$, $B = 0.05, G = 0$, and changing α. In Cases 4 (solid black curves), 5 (dashed green curves), and 6 (solid red curves), we set $\alpha = 0.05, 0.2, 0.7$ to represent long-lasting, intermediate, and short-lived a-processes, respectively. As shown in Fig. 5(a), a smaller α results in more overlap of positive responses w_a and as a result, more positive overall response $w(t|\theta_{i\le k})$. Different values of α do not seem to appreciably change the number of intakes at which $w(t|\theta_{i\le k})$ becomes negative. The evolution of β_k and Δ_k are nearly indistinguishable for all three cases as shown in Figs. 5(b) and 5(c).

It is worth noting that, as shown in Fig. 5(c), the net responses W_k in Cases 4, 5, 6 reach long-lasting plateaus before starting to decrease, between intakes $k = 30$ and $k = 35$. The corresponding RPEs shown in Fig. 5(d) fluctuate around zero in all cases until relatively large intake numbers k are reached, indicating "high-functioning" users. Eventually, however, the RPEs decrease and become negative as well. However, the quickest descent of the RPE_k toward negative values is observed for the longest lived a-process, Case 4 for $\alpha = 0.05$, whereas the most stable RPE_k arises for the shortest lived a-processes, Case 6 for $\alpha = 0.7$, although the associated W_k exhibits a smaller amplitude. These results indicate that the sensitivity of the responses, W_k, and RPE_k to changes in α are nonlinear and involve a subtle interplay between the overlap of the a- and b-processes, the amplitude Γ^b of the b-process, and the definition of the RPE.

The cases described above are illustrative of how different user-specific parameters (B, G, σ, α), and initial conditions (β_1, Γ_1^b) yield qualitatively different paths to addiction. Cases 1, 2, and 3 reveal the effects of higher neuroadaptive sensitivity (Case 3, $B = G = 0.05$), whereby the onset of addiction is dramatically faster. Cases 4, 5, and 6 compare scenarios in which the trajectories of the neuroadaptive parameter β_k and intake dose Δ_k do not substantially differ but can nonetheless lead to qualitative differences in the magnitudes of the integrated response W_k, the drop-off point of the RPE_k, and the intake at which addiction occurs. The "yo-yo" behavior of RPE_k is typically seen for users who are allowed to adjust their doses through Eq. (12).

A. Evolution of intake timing

We now consider the case where drug doses are equal for all intakes $\Delta_i \equiv \Delta = 1$, but the user-controlled intake times T_i does not define a periodic sequence. Since Δ is constant, the recursion relations (11) are explicitly solved by $\beta_i = \beta_1(1 - B\Delta)^{i-1}$ and $\Gamma_i^b = \Gamma_1^b(1 + G\Delta)^{i-1}$ under the assumption $B\Delta < 1$. These expressions represent exponential decreases and increases in β_i and Γ_i^b, respectively. Similar to how drug doses were determined, we now assume that the user's decision of when to next take drugs depends on the RPE defined in Eq. (10). Here, we set $C_{k+1} = 0$ but keep the discount term $\gamma_{k-1} \le 1$. We also assume that the next $(k+1)$th intake occurs when $\mathrm{RPE}_k(t)$ declines to the threshold value R_c, representing the onset of unpleasant effects after the high following intake k. Thus, T_{k+1} can be determined by the real root of $\mathrm{RPE}_k(T_{k+1}) = R_c$, which, using the definition of RPE_k, reads

$$W_k(T_{k+1}|\{\theta_{i\le k}, T_{i\le k}\}) - \gamma_{k-1} W_{k-1}(T_k|\{\theta_{i\le k-1}, T_{i\le k-1}\}) = R_c. \quad (13)$$

This equation must be solved on the decreasing branch of the RPE_k curve as the user takes the next dose to alleviate the decreasing net response. The user is "initialized" with daily intakes (of period $T = 6$ in non-dimensional units) until a real solution arises from Eq. (13), indicating a user who adjusts their intake timing to avoid unpleasant effects. If at any time $\mathrm{RPE}_k = R_c$ again exhibits no real solution, we simply add T to the last intake time T_k so that $T_{k+1} = T_k + T$. In this case, the user is satisfied with the effects of the kth intake and can return to his or her daily routine of drug consumption. For concreteness, we set $\Delta_k = \Gamma^a = 1, \alpha = 0.1, B = G = 0.01, \beta_1 = \Gamma_1^b = 0.5$ and evaluate $W_1(T_2 = 6)$. We then generate $\{\beta_2, \Gamma_2^b\}$ according to the exponential solutions to Eq. (11). The time of the third intake T_3 is then found by solving $W_2(T_3|\{\theta_{i\le 2}, T_{i\le 2}\}) - \gamma_1 W_1(T_2|\{\theta_1, T_1 = 0\}) = R_c$, and so on.

In Fig. 6, we consider three scenarios representing different levels of memory of the previous intake reflected by different values of γ_{k-1} in Eq. (10). In Case 1T (solid black curve), we set $\gamma_{k-1} = 0$ to describe a user who does not remember the response from any previous dose and only uses the current net response $W_k(t)$ to determine the next intake at time T_{k+1}. As shown in Fig. 6(a), the intakes become successively more frequent giving rise to a sharp decline in the dynamic response $w(t|\theta_{i\le k})$ after about $t \approx 65$, about a week if $T = 6$ corresponds to 24 h. In Case 2T (dashed green curve), we set $\gamma_k = 0.5$ to describe a user who weights the net response of the previous intake, W_{k-1} half as much as that relative to the current intake, W_k. In this case, full addiction occurs at intake $k = 4$ (not explicitly shown) at time $t \approx 20$, about three days. In Case 3T (solid red curve), $\gamma_k = 1$ and the user fully remembers the response associated with the previous dose in his or her determination of the next intake. In this case, the response decreases more slowly than in Cases 1T and 2T. The decreases occur later than when $\gamma = 0.5$ but earlier than when $\gamma_k = 0$. In Fig. 6(b), we plot $T_{k+1} - T_k$ for all three cases which show subtle differences in timing associated with the three qualitatively different cases. In Case 3T, the slower decrease in successive

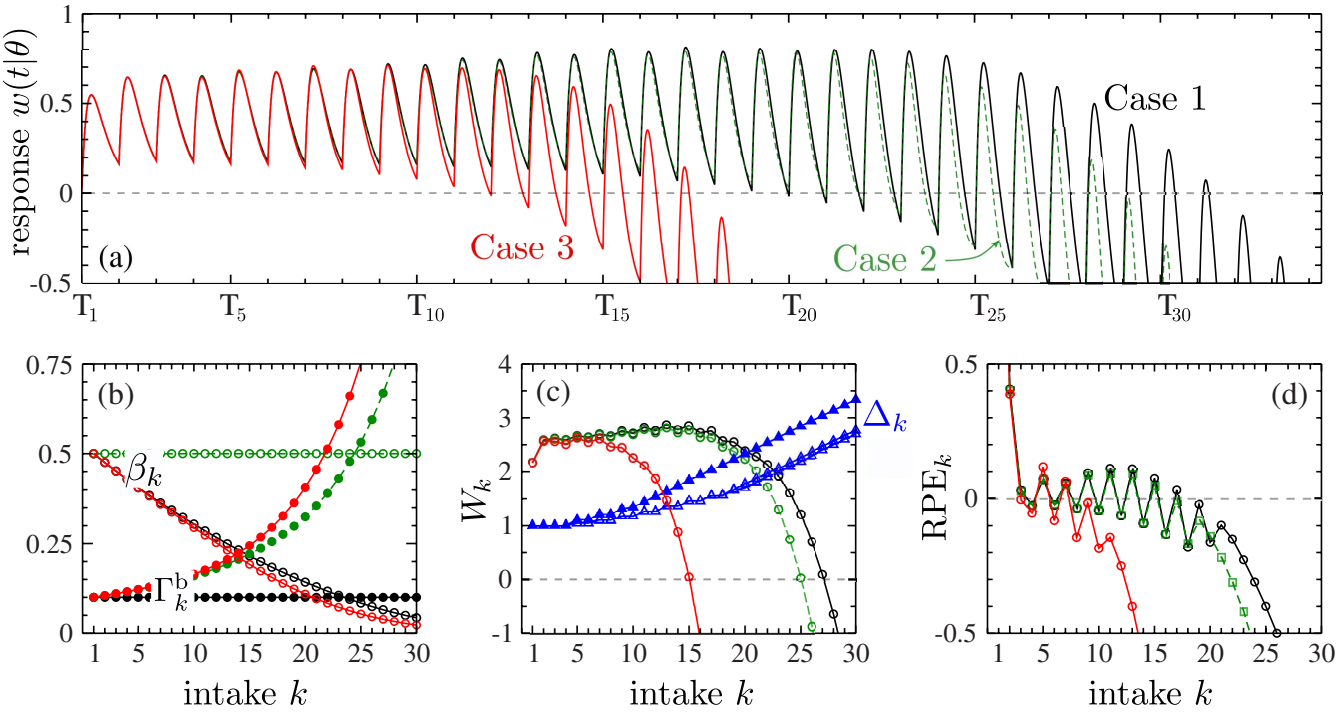

FIG. 4. (a) The time-dependent response resulting from multiple drug intakes with varying Δ_k for three scenarios. In Case 1 (solid black curve), we set $B = 0.05$, $G = 0$, while in Case 2 (dashed green curve), $B = 0$, $G = 0.05$. Finally, in Case 3 (solid red curve), $B = G = 0.05$. The interval between two consecutive intakes in these examples is $T = T_{k+1} - T_k = 6$. The effects of neuroadaptation when both β_k and Γ_k^b evolve are synergistic as Case 3 leads to addiction after significantly fewer intakes. (b) Evolution of the parameters β_k (open circles, solid curves) and Γ_k^b (filled circles, dashed curves) for Cases 1, 2, and 3. (c) Evolution of the integrated response and intake doses Δ_k [blue triangles, Eq. (12)] associated with intake k for each of the three cases. The evolution of Δ_k is similar for Cases 1 and 2, while Δ_k for Case 3 rises faster and might describe a highly addictive drug that results in addiction after a smaller number of doses. The integrated responses W_k become negative at about intake $k \approx 27$, 26, and 16 for Cases 1, 2, and 3, respectively. (d) The RPE_k as a function of the intake k exhibit oscillations with increasing then decreasing amplitude before monotonically decreasing well below zero at intakes $k \approx 20$, 18, and 10 for Cases 1, 2, and 3, respectively. In all cases, the user experiences a "yo-yo" progression to addiction. Since in all cases, W_k becomes negative after the RPE, addiction occurs when $W_k < 0$ at intakes $k^* \approx 27$, 26, and 16, respectively.

T_ks for large k results from the slower drop-off of $w(t|\theta_{i\le k})$ at long times.

Since by construction, $RPE_k(T_{k+1}) = R_c < 0$ for all k, addiction is reached at intake k^* such that $W_{k^*} < 0$. If the first $i \le i^*$ intakes are taken at fixed times $T_i = (i-1)T$ because Eq. (13) has not yet generated a real root, the first intake for which $W_{k^*} < 0$ occurs at $k^* \approx i^* + j^*$, where j^* is found by the lowest integer j such that

$$\sum_{\ell=1}^{j-2} \gamma^{-\ell} > -\frac{W_{i^*}}{R_c} \tag{14}$$

for constant $\gamma_k = \gamma$. A related form can be easily derived when γ_k depends on k. For Cases 1T, 2T, and 3T shown here, $k^* \approx 2, 4, 10$, respectively. In general, we find that the iteration of Eq. (13) continues until either the inter-intake times $T_{k+1} - T_k \to 0$, or no positive real root can be found, indicating an RPE that is permanently below the threshold value R_c and that the user's expectation can never be met. The loss of the root is more likely to arise when β_k and Γ_1^b are small but always occurs after $W < 0$ and RPE < 0 (addiction).

The above examples show that the protracted use of drugs leads to neuroadaptive decreases in β and more slowly decaying b-processes. In the limiting case $\beta \to 0$, the user appears to be in an allostatic state, with near-permanently damaged brain circuits and altered reward response baseline levels. Note that a true allostatic state can be defined within our model by replacing $-\beta w_b(t)$ in Eq. (3) with a term such as $-\beta(w_b(t) + w_\infty)$. The infinite time response would then relax to $w_b(t \to \infty) \to -w_\infty$. This new baseline level may itself evolve after repeated intakes via neuroadaptive processes similar to those represented by Eq. (11).

B. Mitigation through agonist intervention

Our model provides a framework to study detoxification strategies where dosing of substitutes, such as methadone in the case of heroin addiction, can be calibrated to alleviate withdrawal symptoms without producing euphoric effects.[56] We assume an "auxiliary" drug, such as methadone, operates on a related, but different, pathway of the brain reward system relative to the ones stimulating

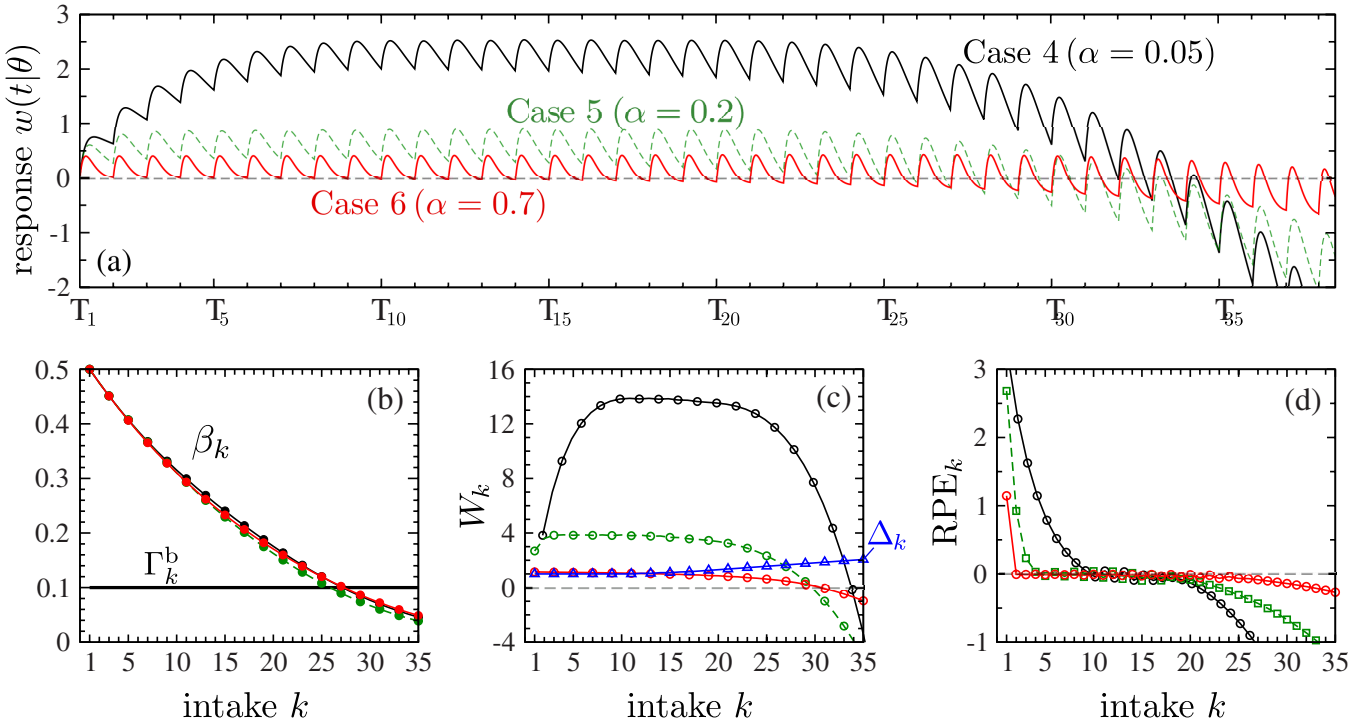

FIG. 5. (a) The time-dependent response resulting from multiple drug intakes at times $T_i = (i-1)6$ with user-adjusted Δ_i for three additional scenarios corresponding to different durations $1/\alpha$ of the a-process. In Case 4 (black solid curve), we keep $\beta_1 = 0.5, \Gamma^a = 1, \Gamma_1^b = 0.1, \sigma = B = 0.05, G = 0$ but assume a long-lasting a-process by setting $\alpha = 0.05$. In Cases 5 (green dashed curve) and 6 (solid red curve), we use $\alpha = 0.2$ and $\alpha = 0.7$, respectively. The corresponding β_k and Γ_k^b for these cases are nearly indistinguishable, as shown in (b). The corresponding doses (blue triangles) shown in (c) are also indistinguishable. The integrated responses W_k for these three cases reach long-lived plateaus of different amplitudes. The associated RPEs are also qualitatively different, as shown in (d). In all cases, the RPEs hover around small values for many intakes. Note while longer lasting a-processes generate higher values of W_k, the corresponding RPEs decrease faster. Addiction in these three cases occur at $k^* \approx 33$, 30, and 31 when $W_k < 0$ since $\mathrm{RPE}_k < 0$ occurs at $k \approx 11$, 5, and 2.

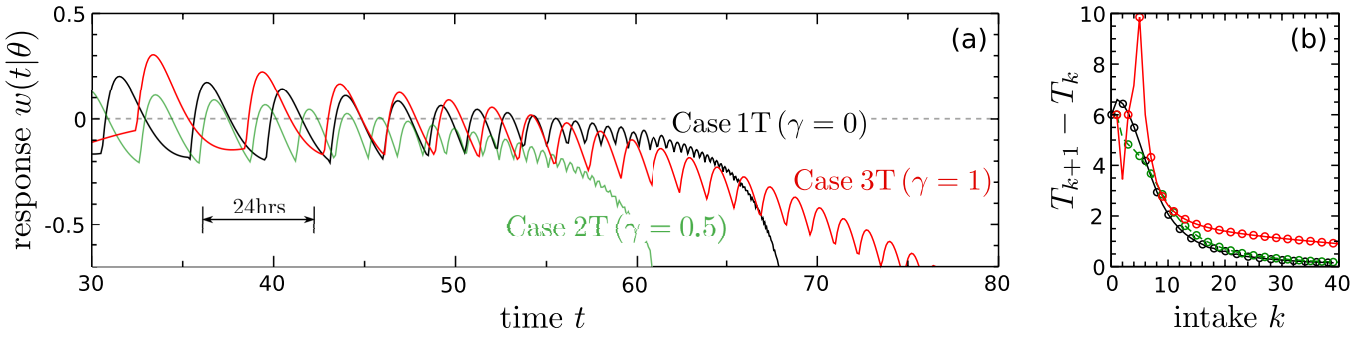

FIG. 6. (a) Time-dependent response curves resulting from multiple drug intakes with varying T_k are generated using $\alpha = 0.5, \Gamma^a = 1, B = G = 0.01$, and $\beta_1 = \Gamma_1^b = 0.5$. Case 1T (solid black curve) assumes $\gamma_k = \gamma = 0$ and no memory before the last intake, while Cases 2T (solid black curve) and 3T (dashed red curve) assume intermediate and strong memory, $\gamma_k = \gamma = 0.5$ and $\gamma_k = \gamma = 1$, respectively. Note that qualitatively, the decreasing trend is nonmonotonic in the memory γ_k. (b) Time separations $T_{k+1} - T_k$ between two consecutive intakes for the three cases.

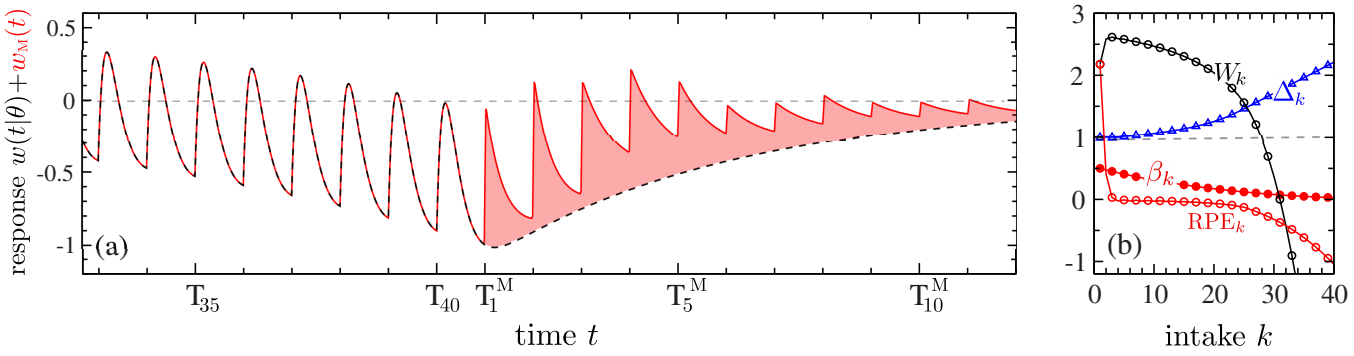

FIG. 7. (a) Time-dependent response $w(t|\theta)$ (black dashed curve) with the superimposed methadone contribution $w_M(t)$ (red solid curve). The time-dependent response in the absence of methadone returns to the baseline over a timescale $\sim 1/\beta_{40}$, producing unpleasant withdrawal symptoms during this time. Methadone treatment ($+w_M(t)$) adds to the response reducing the negative effects of b-processes by an amount indicated by the red shaded area. (b) β_k, Δ_k, W_k, and RPE_k associated with the drug sequence prior to the administration of methadone.

the a- and b-processes described in Eqs. (2) and (3). This auxiliary drug may generate a separate reward response which itself may evolve according to neuroadaptation or interactions with other neural networks. We denote the additional reward response $w_M(t)$ so that, within the context of our model, the overall user perception is given by the sum $w_a + w_b + w_M$. Positive values $w_M > 0$ shift the overall response toward the homeostatic baseline, reducing withdrawal symptoms. If neurocircuits are not permanently damaged, our results imply that an ideal treatment consists of applying a large enough $w_M > 0$ that mitigates the negative response w_b over a timescale $\sim 1/\beta_k$, where β_k is the value of the b-process decay rate at the time of the last intake.

To be concrete, we model a hypothetical heroin addiction via an intake sequence associated with $\alpha = 0.3, \beta_1 = 0.5, \Gamma^a = 1, \Gamma^b = 0.1, B = 0.05, G = 0, \sigma = 0.05, R_c = -0.05$, and $T = 6$. In Fig. 7, we show the response starting at $t \approx 200$ corresponding to approximately intake 33 (in this example, full addiction occurred at intake $k^* = 32$). We assume the user subsequently ceases heroin consumption at intake $k = 40$ where $\beta_{40} \approx 0.02$ and $\Delta_{40} \approx 2.3$. The user is then assumed to start a methadone maintenance treatment following a protocol of Δ_k^M doses at prescribed times T_k^M. We model the methadone response as

$$w_M(T_k^M < t < T_{k+1}^M | \Delta_{i\le k}^M, \delta_{i\le k}^M, T_{i\le k}^M) = \sum_{i=1}^{k} \Delta_i^M e^{-\delta_i^M (t - T_i^M)}, \quad (15)$$

where the dimensionless decay rates δ_i^M are measured relative to the overall dopamine clearance rate δ discussed in Eq. (1). Equation (15) is a succinct representation of the user perception of methadone; $1/\delta_i^M$ represents an effective lifetime that depends on the decay of methadone in the body and of the effects of the associated reward. A more complex model can be developed along the lines of Eq. (2). The lifetime of methadone in the body changes as treatment progresses, and ranges from initial values of 10–20 h to 25–30 h in the maintenance phase. In clinical settings, Δ_k^M also typically increases;[57] for example, the first methadone doses range between 10 and 30 mg, while later doses are increased to about 60–120 mg. Methadone dosage can also depend on the user's history of opioid use.

In our model, we apply 11 daily methadone doses, with the drug administered at periodic intervals of $T = 6$ starting at time $t = 246$, a day after the last $k = 40$ heroin intake at $t = 240$. We assume that the methadone doses follow the sequence $\Delta_i^M = \{1, 1, 0.8, 0.6, 0.4, 0.2, 0.2, 0.2, 0.1, 0.1, 0.1\}$ and that neuroadaptation increases the methadone timescale from about 10 to 27 h leading to $\delta_i^M = \{0.4, 0.4, 0.2, 0.2, 0.2, 0.15, 0.15, 0.15, 0.15, 0.15, 0.15\}$. Figure 7 shows the methadone-induced response $w_M(t)$ (red curve) added to the drug-induced response (black dashed curve).

Note that without methadone treatment, once heroin consumption ceases after intake $k = 40$, the time-dependent reward response (black dashed curve) resembles an allostatic load which returns to the baseline over a long timescale $\sim 1/\beta_{40} \approx 50$, over a week. The methadone-derived response $w_M(t)$ (red curve) alleviates much of the negative b-process and associated withdrawal symptoms. The net time-integrated reduction in withdrawal symptoms is represented by the red shaded area between the $w_a + w_b$ and the $w_a + w_b + w_M$ curves as shown in Fig. 7.

Although methadone is used to treat addiction, it is an opioid agonist and can itself induce addiction through w_M, which may also trigger its own b-processes. This is especially true if methadone is taken in an uncontrolled manner and may explain why often suboptimal doses are administered.[58] Thus, control of $w_M(t)$ is crucial in using methadone as a treatment. An ideal protocol would calibrate doses and timing to alleviate the negative response as much as possible, but would also prevent the induction of methadone-associated b-processes, or other interactions with addictive pathways. One can also explore the consequences of irregular methadone intakes or nonadherence to specific detoxification protocols.[59]

IV. DISCUSSION AND CONCLUSIONS

We constructed a quantitative framework for the evolution of drug addiction based on concepts from IST, OPT, and where drug dosages depend on the RPE. Our goal was to develop an explicit model that incorporates these key ingredients in a simple and clear way, without invoking a large number of parameters. Although many models that include action choice have been developed,[37,60]

our work assumes only one dominant action (drug taking) that emerges from the background response to all other routine rewards. We are thus assuming that the response to these "normal" rewards has already been subtracted from the drug-specific response $w_a + w_b$. A much richer stochastic model can be developed by considering fluctuating responses from routine rewards.

In our model, repeated intakes lead to overall negative reward responses due to neuroadaptive processes that lessen drug-induced pleasurable effects. To counterbalance this shift, the user actively seeks higher rewards by increasing drug dose, intake frequency, or both. These behaviors create a feedback loop that induces further neuroadaptive changes and that eventually lead to an addicted state. Our model captures the well-known phenomenon of tolerance by allowing expectations to increase after a drug intake, which, in turn, leads the user to increase the dosage as an attempt to meet the new expectation level. Mathematically this is represented by allowing the RPE to fall below a critical threshold value. Our model can also explain the increased frequency of drug intaking by dictating that the user takes a new dose once the RPE reaches the critical threshold value. A more realistic description would define an objective function that allows the user to both increase drug dosage and to take it more often.

How addiction unfolds depends on the specific physiology and neuroadaptive response of the user. Within our simple mathematical model, the path to addiction depends on the sequence of representative parameters that change with each drug intake i. These parameters represent neuroadaptive characteristics such as $\{\alpha_i, \Gamma_i^a, \beta_i, \Gamma_i^b\}$ that appear in Eqs. (2) and (3) as well as user-controlled dosing Δ_i and timing T_i that dictate the evolution of the RPE. In our analyses, we fixed α_i and Γ_i^a and proposed simple recursion relations for Δ_i, β_i, and Γ_i^b that evolve consistently with OPT. Specifically, this scheme represents b-processes becoming more prominent as drug addiction unfolds. If a user is genetically predisposed to addiction or if the drug is highly addictive, as in the case of methamphetamines, the parameters R_c and σ, and B and G that drive the evolution of the b-process will be larger and the number of intakes necessary to reach the addicted state will be few. For more resistant users and/or slowly addictive substances such as cannabinoids, R_c, σ, B, and/or G will be smaller, leading to a more drawn-out addiction process that includes damped oscillatory progression of the RPE. We also find that reaching the addicted state will require less intakes if the onset value of $\Gamma_b/\beta > 1$, implying an initially strong and persistent b-process. These results allow us to predict that the most at-risk users are those who are most reactive to changes in the b-process and (assuming that the brain processes all rewards through the same pathway) those who manifest elevated b-process responses even prior to drug intaking. Although there are not many studies connecting personality traits with addiction,[61] our finding is consistent with reports of neurotic individuals being among the most at risk for drug addiction.[62] One of the main hallmarks of neuroticism in fact is for negative effects, such as the ones expressed by the b-process, to be more pronounced.[63,64]

One simplification of our analysis is that we considered either variable doses Δ_i administered at periodic intervals T or constant doses Δ taken at non-uniformly spaced timings T_i. A more comprehensive study would allow for the RPE to dictate both dosages Δ_i and timings T_i as a function of expectations built on previous drug intakes, without fixing either *a priori*.

A number of refinements to our model can be straightforwardly incorporated. For example, instead of a sequential response to drug intake, where w_b is triggered by w_a, one could consider a parallel response where the drug-induced dopamine surge triggers both w_a and w_b. Similarly, we could consider a networked response, with several pleasurable and aversive neuronal centers being activated and/or stimulating one another. Alternatively, one could consider a multicomponent reward response that depends on neuronal sets differentially activated by multiple drugs. To study this case, one would need to derive a single-output reward response from a high-dimensional multi-drug input. If the multiple drugs lead to neuroadaptive changes in the relaxation rates α and β, their effects on the rewards w_a and w_b would be multiplicative. Different drugs may have different *in vivo* clearance rates and drive dopamine release with different durations leading to different dopamine residence times $1/\delta^{(j)}$. They may also activate different sets of neurons that contribute to the a- and b-processes w_a and w_b additively through the weights Γ^a and Γ^b. Thus, multiple drugs potentially administered at different times can contribute to the overall response both additively and multiplicatively, leading to rich dynamical behavior of the brain reward system. The inclusion of broader action classes (or "policies") can also be incorporated using a more formal framework from reinforced learning.[38]

Another possible approach would be to include continuous-time evolution of the parameters $\{\alpha, \Gamma^a, \beta, \Gamma^b\}$ or to include more realistic forms for the RPE such as a convolution of a memory kernel with $w_a + w_b$ as motivated from data.[37,44] More complex nonlinear evolution of parameters could also be considered which could give rise to sharper transitions into an addictive state[37] and to chaotic behaviors.[52,55] Sharper transitions would be partially mitigated by an RPE definition where current rewards are compared with averages over past periods. Although we assumed a well-defined "deterministic" behavioral rule for changing drug dose and intake timing, prolonged drug use can lead to dysfunction in decision-making and unpredictable and random behavioral changes,[65] justifying nonlinear dynamics and/or stochasticity in the definition of an effective RPE. Note that this stochasticity applied to the RPE would be different from adding noise to $D(t)$ and treating Eqs. (2) and (3) stochastically (e.g., as a Langevin equation). One can also examine in more detail the intake-dependent additive cue in Eq. (10) to predict how the RPE changes when moving from a controlled drug-taking environment (where cues such as location, paraphernalia, and accessibility are constant) to a more random one (where cues may vary in time and across intakes). Cues can also trigger dopamine releases without any actual drug intaking[66] and can lead to relapses after long periods of abstinence when the memory of previous intakes has subsided. Finally, our model can be generalized to other forms of chemical or behavioral addictions, such as alcoholism, gambling, or social-media addiction.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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