Supplementary Material:
Modeling Addiction in terms of fluctuating neurotransmitters within the reward system

1. General

The bounding function σ(x) is defined as follow:

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

where ε is a random value, ∈ [−0.05, 0.05].

Notations Unless otherwise specified, the following holds for the entire document:

d is a time steps counter used by the continuous processes, which resets to 1 at every time t where the value G(t) changes from a state G(t) = 0, < 0, or > 0 to another state
t_G is the time when G(t) last changed state
ε_X is a random value applied to process X, $\varepsilon_X \in [-0.05, 0.05]$
τ_G is a binary variable, defined as:
$\tau_G = 0$ if maladaptive behavior where never expressed
$\tau_G = 1$ if maladaptive behavior where already expressed at least once
ω_X is the weight of the process X, $\omega_X \in [0, 1]$
M_X is the upper bound asymptote of the process X, $M_X \in]\mu_X , 1] \subseteq]0, 1]$
μ_X is the lower bound asymptote of the process X, $\mu_X \in [0, MX [\subseteq [0, 1[$
Π_X is a temporal constant which influences the behavior of the process X, $\in N^+$
β, γ and γ_n are constants $\in R^+$
P_X (t) is the uniformly distributed random function of process X, P_X (t) $\in [0, 1]$
θ_X is the constant probability that the discrete process X occurs at time t, $\theta_X \in [0, 1]$
d_Λ is a time steps counter used by the discrete processes, which resets to 1 when a discrete process is triggered (each discrete process has a distinct counter of this type)
δ_X is a constant for the discrete process X, $\in N^+$
ρ_X is a constant for the discrete process, $\rho_X \in [0, 1]$
Δ_i and Δ_d are the constant magnitudes of the discrete process's memories increases and decreases, $\{\Delta_i, \Delta_d\} \in N^+$ (different for each process)

Table 1: Behaviors of the continuous processes with respect to G(t) and d, when $\tau_G = 1$. The sign → stands for constant, and the signs ↗ and ↘ stand for exponentially increasing and decreasing.

	$G(t-1)=0$	$G(t-1)<0$	$G(t-1)>0$	
	$\forall d$	$\forall d$	$d \leq \Pi_X$	$d > \Pi_X$
$DA_b(t)$	→	↗	↘	
$GL_{PFC,b}(t)$	→	↘	↘	↗
$DA_p(t)$	→	↘	↘	↗
$GL_{PFCp}(t)$	→	↘	↘	↗
$GL_{PFC,c}(t)$	→	↘	↘	↗
$GL_{Amg,c}(t)$	→	↘	↘	↗
$GL_{HPC,c}(t)$	→	↘	↘	↗
$DA_c(t)$	→		↘	↗
$GL_{PFC,ic}(t)$	→	↘	↗	

About the continuous processes In Table 1 are summarized the continuous processes with respect to G(t) and the counter d, when $\tau_G = 1$.
The tendency of drug-seeking behavior G(t) is the output of the model, the variable τ_G describe whether the virtual subject already expressed maladaptive behavior, and the counter d is reset to 1 at every time t where the value G(t) changes state, from G(t) = 0, G(t) < 0, or G(t) > 0 to another state.
When $\tau_G = 0$ these processes stay constant over time (→).

About the discrete processes The following list describe when these processes can be triggered:

- Λ_{DP} can be triggered at time t if $\tau_G = 1$, $G(t-1) \geq 0$, and $P_{DP} \leq \theta_{DP}$
  This process influences $DA_p(t)$ and $GL_{PFC,p}(t)$
- Λ_{DC} can be triggered at time t if $\tau_G = 1$, and $P_{DC} \leq \theta_{DC}$
  This process influences $GL_{PFC,c}(t)$, $GL_{Amg,c}(t)$, $GL_{HPC,c}(t)$, and $DA_c(t)$
- Λ_S can be triggered at time t if $\tau_G = 1$, $G(t-1) \geq 0$, and $P_S \leq \theta_S$
  This process influences $DA_p(t)$ and $GL_{PFC,p}(t)$
- Λ_R can be triggered at time t if $\tau_G = 1$, $G(t-1) \leq 0$, and $P_R \leq \theta_R$
  This process influences $GL_{PFC,ic}(t)$

2. Continuous processes

2.1 DA_b - Basal Extracellular DA from the VTA

$$DA_b(t) \equiv X(t) = \begin{cases} \sigma\left[X(t-1)+\epsilon_X\right] & \text{if } \tau_G=0 \\ & \text{or } \tau_G=1 \text{ and } G(t\text{-}1)=0 \\ \sigma\left[[X(t_G)-\mu_X]\cdot e^{-\gamma\cdot d}+\mu_X+\epsilon_X\right] & \text{if } \tau_G=1 \text{ and } G(t\text{-}1)<0 \\ \sigma\left[X(t_G)\cdot e^{\beta\cdot d}+\epsilon_X\right] & \text{if } \tau_G=1 \text{ and } G(t\text{-}1)>0 \end{cases}$$

2.2 $GL_{PFC,b}$ - Basal Extracellular Glutamate from the PFC

$$GL_{PFC,b}(t) \equiv X(t) = \begin{cases} \sigma\left[X(t-1)+\epsilon_X\right] & \text{if } \tau_G=0 \\ & \text{or } \tau_G=1 \text{ and } G(t\text{-}1)=0 \\ \sigma\left[[X(t_G)-\mu_X]\cdot e^{-\gamma_n\cdot d}+\mu_X+\epsilon_X\right] & \text{if } \tau_G=1 \text{ and} \\ \quad \text{with} \gamma_n=\gamma_1 & \quad G(t\text{-}1)<0 \\ \quad \text{with} \gamma_n=\gamma_2 & \quad G(t\text{-}1)>0 \text{ and } d \le \Pi_X \\ \sigma\left[X(t_G)\cdot e^{\beta\cdot d}+\epsilon_X\right] & \text{if } \tau_G=1 \\ & \text{and } G(t\text{-}1)>0 \text{ and } d>\Pi_X \end{cases}$$

2.3 DA_p - Drug-Induced DA from the VTA

$$DA_p(t) \equiv X(t) = \begin{cases} \sigma\left[X(t-1)+\epsilon_X\right] & \text{if } \tau_G=0 \\ & \text{or } \tau_G=1 \text{ and } G(t\text{-}1)=0 \\ \sigma\left[M_X-[M_X-X(t_G)]\cdot e^{-\gamma_n\cdot d}+\epsilon_X\right] & \text{if } \tau_G=1 \text{ and} \\ \quad \text{with} \gamma_n=\gamma_1 & \quad G(t\text{-}1)<0 \\ \quad \text{with} \gamma_n=\gamma_2 & \quad G(t\text{-}1)>0 \text{ and } d \le \Pi_X \\ \sigma\left[M_X-[M_X-X(t_G+\Pi_X)]\cdot e^{\beta\cdot d}+\epsilon_X\right] & \text{if } \tau_G=1 \\ & \text{and } G(t\text{-}1)>0 \text{ and } d>\Pi_X \end{cases}$$

2.4 $GL_{PFC,p}$ - Drug-Induced Glutamate from the PFC

$$GL_{PFC,p}(t) \equiv X(t) = \begin{cases} \sigma\left[X(t-1) + \epsilon_X\right] & \text{if } \tau_G = 0 \\ & \text{or } \tau_G = 1 \text{ and } G(t\text{-}1) = 0 \\ \sigma\left[M_X - [M_X - X(t_G)] \cdot e^{-\gamma_n \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \text{ and} \\ \quad \text{with} \gamma_n = \gamma_1 & \quad G(t\text{-}1) < 0 \\ \quad \text{with} \gamma_n = \gamma_2 & \quad G(t\text{-}1) > 0 \text{ and } d \le \Pi_X \\ \sigma\left[M_X - [M_X - X(t_G + \Pi_X)] \cdot e^{\beta \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \\ & \text{and } G(t\text{-}1) > 0 \text{ and } d > \Pi_X \end{cases}$$

2.5 $GL_{N,c}$ - Saliency of Drug-Associated Cues (Glutamate)

$GL_{N,c} = \{GL_{PFC,c}, GL_{Amg,c}, GL_{HPC,c}\}$

$$GL_{N,c}(t) \equiv X(t) = \begin{cases} \sigma\left[X(t-1) + \epsilon_X\right] & \text{if } \tau_G = 0 \\ & \text{or } \tau_G = 1 \text{ and } G(t\text{-}1) = 0 \\ \sigma\left[M_X - [M_X - X(t_G)] \cdot e^{-\gamma_n \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \text{ and} \\ \quad \text{with} \gamma_n = \gamma_1 & \quad G(t\text{-}1) < 0 \\ \quad \text{with} \gamma_n = \gamma_2 & \quad G(t\text{-}1) > 0 \text{ and } d \le \Pi_X \\ \sigma\left[M_X - [M_X - X(t_G + \Pi_X)] \cdot e^{\beta \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \\ & \text{and } G(t\text{-}1) > 0 \text{ and } d > \Pi_X \end{cases}$$

2.6 DA_c - Saliency of Drug-Associated Cues (Dopamine)

$$DA_c(t) \equiv X(t) = \begin{cases} \sigma\left[X(t-1) + \epsilon_X\right] & \text{if } \tau_G = 0 \\ & \text{or } \tau_G = 1 \text{ and } G(t\text{-}1) \leq 0 \\ \sigma\left[M_X - [M_X - X(t_G)] \cdot e^{-\gamma \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \\ & \text{and } G(t\text{-}1) > 0 \text{ and } d \leq \Pi_X \\ \cdot\sigma\left[M_X - [M_X - X(t_G + \Pi_X)] \cdot e^{\beta \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \\ & \text{and } G(t\text{-}1) > 0 \text{ and } d > \Pi_X \end{cases}$$

2.7 $GL_{PFC,ic}$ - Harmful Consequences of Drug Consumption

$$GL_{PFC,ic}(t) \equiv X(t) = \begin{cases} \sigma\left[X(t-1) + \epsilon_X\right] & \text{if } \tau_G = 0 \\ & \text{or } \tau_G = 1 \text{ and } G(t\text{-}1) = 0 \\ \sigma\left[M_X - [M_X - X(t_G)] \cdot e^{-\gamma \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \text{ and } G(t\text{-}1) < 0 \\ \sigma\left[M_X - [M_X - X(t_G)] \cdot e^{\beta \cdot d} + \epsilon_X\right] & \text{if } \tau_G = 1 \text{ and } G(t\text{-}1) > 0 \end{cases}$$

3. Discrete processes

3.1 Λ_X - General definition

$$\Lambda_X(t) = \begin{cases} 1 & \text{if (*) or } d_\Lambda]1, \delta_X] \\ \max(0, \rho_X \cdot \Lambda_X(t-1)) & \text{if } d_\Lambda]\delta_X, \pi_X(t)] \\ 0 & \text{otherwise} \end{cases}$$

where

$$\pi_X(t) = \begin{cases} \pi_X(t-1) + \Delta_i & \text{if (*)} \\ \max(0, \pi_X(t-1) - \Delta_d) & \text{otherwise} \end{cases}$$

where (*) is the activation condition of the discrete process, as described below.

3.1.1 Λ_{DP} - Drug Priming

(*) stands for: $\tau_G = 1$ and $G(t-1) \geq 0$ and $P_{DP}(t) \leq \theta_{DP}$

3.1.2 Λ_{DC} - Drug-associated Cues

(*) stands for: $\tau_G = 1$ and $P_{DC}(t) \leq \theta_{DC}$

3.1.3 Λ_S - Stress

(*) stands for: $\tau_G = 1$ and $G(t-1) \geq 0$ and $P_S(t) \leq \theta_S$

3.1.4 Λ_R - Recovery

(*) stands for: $\tau_G = 1$ and $G(t-1) \leq 0$ and $P_R(t) \leq \theta_R$

4. Processes integration and output of the model

4.1 n - Input to the behavioral process

$$n(t)=\begin{cases} DA_b^{\omega}(t)+GL_{PFC,b}^{\omega}(t)-\widetilde{DA_p}(t)- & \text{if mod(t-1,24)=0} \\ \widetilde{GL_{PFC,p}}(t)-\widetilde{GL_{PFC,c}})(t)-\widetilde{GL_{Amg,c}}(t)- & \text{or } \Lambda_{DP}(t)\neq 0 \text{ or } \Lambda_{DC}(t)\neq 0 \\ \widetilde{GL_{HPC,c}}(t)-\widetilde{DA_c}(t)+\widetilde{GL_{PFC,ic}}(t) & \text{or } \Lambda_S(t)\neq 0 \text{ or } \Lambda_R(t)\neq 0 \\ n(t-1) & \text{otherwise} \end{cases}$$

where

$$DA_b^{\omega}(t)=\omega_X\cdot DA_b(t)$$

$$GL_{PFC,b}^{\omega}(t)=\omega_X\cdot GL_{PFC,b}(t)$$

$$\widetilde{DA_p}(t)=\omega_X\cdot DA_p(t)+\omega_{DP1}\cdot\Lambda_{DP}(t)+\omega_{S1}\cdot\Lambda_S(t)$$

$$\widetilde{GL_{PFC,p}}(t)=GL_{PFC,p}(t)+\omega_{DP2}\cdot\Lambda_{DP}(t)+\omega_{S2}\cdot\Lambda_S(t)$$

$$\widetilde{GL_{N,c}}(t)=GL_{N,c}(t)+\omega_{DCn}\cdot\Lambda_{DC}(t)$$

$$\widetilde{DA_c}(t)=DA_c(t)+\omega_{DC4}\cdot\Lambda_{DC}(t)$$

$$\widetilde{GL_{PFC,ic}}(t)=GL_{PFC,ic}(t)+\omega_R\cdot\Lambda_R(t)$$

with ω_{DCn} = {ω_{DC1}, ω_{DC2}, ω_{DC3}} for respectively $GL_{PFC,c}$, $GL_{Amg,c}$, and $GL_{HPC,c}$.
and

At the last active step of the acute processes Λ_{DP} and Λ_S (means at $d_\Lambda=\pi_X(t)$, with X={DP,S}) the value of $DA_p(t)$ is updated.

4.2 [*output*] G - Tendency of drug-seeking behavior

$$G(t)=\begin{cases}\tanh\left(\alpha\cdot G(t-1)+\beta\cdot n(t)-\gamma\right) & \text{if mod(t-1,24)=0 or } \Lambda_{DP}(t)\neq 0 \\ & \text{or } \Lambda_{DC}(t)\neq 0 \text{ or } \Lambda_{S}(t)\neq 0 \text{ or } \Lambda_{R}(t)\neq 0 \\ G(t-1) & \text{otherwise}\end{cases}$$

where

$\alpha, \beta \in [0, 1]$
γ is a constant:

$$\gamma=\frac{1}{2}\alpha-\frac{11}{2}\beta$$

$G(t) \in [-1, 1]$