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

1. General
The bounding function $\sigma(x)$ is defined as follow:

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

where $\varepsilon$ is a random value, $\in [-0.05, 0.05]$.

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 $G(t) = 0, < 0, \text{ or } > 0$ to another state $t_G$ is the time when $G(t)$ last changed state
- $\varepsilon_X$ is a random value applied to process $X$, $\varepsilon_X \in [-0.05, 0.05]$
- $\tau_G$ 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
- $\omega_X$ is the weight of the process $X$, $\omega_X \in [0, 1]$
- $M_X$ is the upper bound asymptote of the process $X$, $M_X \in [\mu_X, 1] \subseteq [0, 1]$
- $\mu_X$ is the lower bound asymptote of the process $X$, $\mu_X \in [0, M_X \subseteq [0, 1]$
- $\Pi_X$ is a temporal constant which influences the behavior of the process $X$, $\in \mathbb{N}^+$
- $\beta, \gamma$ and $\gamma_n$ are constants $\in \mathbb{R}^+$
- $P_X(t)$ is the uniformly distributed random function of process $X$, $P_X(t) \in [0, 1]$
- $\theta_X$ is the constant probability that the discrete process $X$ occurs at time $t$, $\theta_X \in [0, 1]$
- $d_A$ 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)
- $\delta_X$ is a constant for the discrete process $X$, $\in \mathbb{N}^+$
- $\rho_X$ is a constant for the discrete process, $\rho_X \in [0, 1]$
- $\Delta_i$ and $\Delta_d$ are the constant magnitudes of the discrete process’s memories increases and decreases, $\{\Delta_i, \Delta_d\} \in \mathbb{N}^+$ (different for each process)
Table 1: Behaviors of the continuous processes with respect to \( G(t) \) and \( d \), when \( \tau_G = 1 \). The sign \( \rightarrow \) stands for constant, and the signs \( \nearrow \) and \( \searrow \) stand for exponentially increasing and decreasing.

<table>
<thead>
<tr>
<th>( G(t - 1) )</th>
<th>( G(t - 1) &lt; 0 )</th>
<th>( G(t - 1) &gt; 0 )</th>
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</thead>
<tbody>
<tr>
<td>( \forall d )</td>
<td>( \forall d \leq \Pi_X )</td>
<td>( d &gt; \Pi_X )</td>
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<tr>
<td>( DA_p(t) )</td>
<td>( \rightarrow )</td>
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<tr>
<td>( GL_{PFC,p}(t) )</td>
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<td>( GL_{HPFC,c}(t) )</td>
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<tr>
<td>( DA_c(t) )</td>
<td>( \rightarrow )</td>
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<td>( GL_{PFC,ic}(t) )</td>
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</tbody>
</table>

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 \( \tau_G \) 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 (\( \rightarrow \)).

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

- \( \Lambda_{DP} \) 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 \( GL_{PFC,p}(t) \).
- \( \Lambda_{DC} \) can be triggered at time \( t \) if \( \tau_G = 1 \), and \( P_{DC} \leq \theta_{DC} \). This process influences \( GL_{PFC,d}(t) \), \( GL_{Amg,d}(t) \), \( GL_{HPFC,d}(t) \), and \( DA_c(t) \).
- \( \Lambda_S \) 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 \( GL_{PFC,p}(t) \).
- \( \Lambda_R \) 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<sub>b</sub> - Basal Extracellular DA from the VTA

\[
DA_{b}(t) \equiv X(t) = \begin{cases} 
\sigma[X(t-1) + \epsilon_X] & \text{if } \tau_G = 0 \\
\sigma[(X(t_G) - \mu_x) \cdot e^{-\gamma_n d} + \mu_x + \epsilon_X] & \text{if } \tau_G = 1 \text{ and } G(t-1) < 0 \\
\sigma[X(t_G) \cdot e^{\beta d} + \epsilon_X] & \text{if } \tau_G = 1 \text{ and } G(t-1) > 0 \\
\end{cases}
\]

2.2 GL<sub>PFC,b</sub> - Basal Extracellular Glutamate from the PFC

\[
GL_{PFC,b}(t) \equiv X(t) = \begin{cases} 
\sigma[X(t-1) + \epsilon_X] & \text{if } \tau_G = 0 \\
\sigma[(X(t_G) - \mu_x) \cdot e^{-\gamma_n d} + \mu_x + \epsilon_X] & \text{if } \tau_G = 1 \text{ and } G(t-1) < 0 \\
\sigma[X(t_G) \cdot e^{\beta d} + \epsilon_X] & \text{if } \tau_G = 1 \text{ and } G(t-1) > 0 \text{ and } d \leq \Pi_X \\
\end{cases}
\]

2.3 DA<sub>p</sub> - Drug-Induced DA from the VTA

\[
DA_{p}(t) \equiv X(t) = \begin{cases} 
\sigma[X(t-1) + \epsilon_X] & \text{if } \tau_G = 0 \\
\sigma[M_X - [M_X - X(t_G)] \cdot e^{-\gamma_n d} + \epsilon_X] & \text{if } \tau_G = 1 \text{ and } G(t-1) < 0 \\
\sigma[M_X - [M_X - X(t_G + \Pi_X)] \cdot e^{\beta d} + \epsilon_X] & \text{if } \tau_G = 1 \text{ and } G(t-1) > 0 \text{ and } d > \Pi_X \\
\end{cases}
\]
2.4 GL$\text{PFC}_p$ - Drug-Induced Glutamate from the PFC

\[ GL_{\text{PFC}_p}(t) \equiv X(t) = \begin{cases} 
\sigma[X(t-1)+\epsilon_X] & \text{if } \tau_g=0 \\
\sigma[M_X-[M_X-X(t_G)] \cdot e^{-\gamma_X d} + \epsilon_X] & \text{if } \tau_g=1 \text{ and } G(t-1)=0 \\
\text{with } \gamma_n=\gamma_1 & \text{if } G(t-1)<0 \\
\text{with } \gamma_n=\gamma_2 & \text{if } G(t-1)>0 \text{ and } d \leq \Pi_X \\
\sigma[M_X-[M_X-X(t_G+\Pi_X)] \cdot e^{\beta d} + \epsilon_X] & \text{if } \tau_g=1 \\
\text{if } G(t-1)>0 \text{ and } d > \Pi_X 
\end{cases} \]

2.5 GL$\text{N}_c$ - Saliency of Drug-Associated Cues (Glutamate)

GL$\text{N}_c = \{GL_{\text{PFC}_c}, GL_{\text{Amg}_c}, GL_{\text{HPC}_c}\}$

\[ GL_{\text{N}_c}(t) \equiv X(t) = \begin{cases} 
\sigma[X(t-1)+\epsilon_X] & \text{if } \tau_g=0 \\
\sigma[M_X-[M_X-X(t_G)] \cdot e^{-\gamma_X d} + \epsilon_X] & \text{if } \tau_g=1 \text{ and } G(t-1)=0 \\
\text{with } \gamma_n=\gamma_1 & \text{if } G(t-1)<0 \\
\text{with } \gamma_n=\gamma_2 & \text{if } G(t-1)>0 \text{ and } d \leq \Pi_X \\
\sigma[M_X-[M_X-X(t_G+\Pi_X)] \cdot e^{\beta d} + \epsilon_X] & \text{if } \tau_g=1 \\
\text{if } G(t-1)>0 \text{ and } d > \Pi_X 
\end{cases} \]
2.6 DA\textsubscript{e} - Saliency of Drug-Associated Cues (Dopamine)

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

2.7 GL\textsubscript{pFC,ic} - Harmful Consequences of Drug Consumption

\[ GL\textsubscript{pFC,ic}(t) \equiv X(t) = \begin{cases} 
\sigma[X(t-1) + \epsilon_x] & \text{if } \tau_G = 0 \text{ or } \tau_G = 1 \text{ and } G(t-1) = 0 \\
\sigma\left[M_X - \left[M_X - X(t_G)\right] \cdot e^{-\gamma d} + \epsilon_x\right] & \text{if } \tau_G = 1 \text{ and } G(t-1) < 0 \\
\sigma\left[M_X - \left[M_X - X(t_G)\right] \cdot e^{\beta d} + \epsilon_x\right] & \text{if } \tau_G = 1 \text{ and } G(t-1) > 0 
\end{cases} \]
3. Discrete processes

3.1 $\Lambda_X$ - General definition

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

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

3.1.2 $A_{DC}$ - Drug-associated Cues
(* stands for: $\tau_G = 1$ and $P_{DC}(t) \leq \theta_{DC}$

3.1.3 $A_S$ - Stress
(* stands for: $\tau_G = 1$ and $G(t-1) \geq 0$ and $P_S(t) \leq \theta_S$

3.1.4 $A_R$ - 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 Input to the behavioral process

\[
\begin{align*}
n(t) = & \begin{cases} 
DA_{b}^{\omega}(t) + GL_{PFC,b}^{\omega}(t) - \overline{DA}_p(t) - & \text{if } \text{mod}(t-1,24)=0 \\
GL_{PFC,p}(t) - GL_{PFC,x}(t) - GL_{Amg,x}(t) - & \text{or } \Lambda_{DP}(t) \neq 0 \text{ or } \Lambda_{DC}(t) \neq 0 \\
GL_{HPC,x}(t) - \overline{DA}_c(t) + GL_{PFC,ic}(t) & \text{or } \Lambda_{S}(t) \neq 0 \text{ or } \Lambda_{R}(t) \neq 0 \\
n(t-1) & \text{otherwise}
\end{cases}
\end{align*}
\]

where

\[
\begin{align*}
DA_{b}^{\omega}(t) &= \omega_{X} \cdot DA_{b}(t) \\
GL_{PFC,b}^{\omega}(t) &= \omega_{X} \cdot GL_{PFC,b}(t) \\
\overline{DA}_p(t) &= \omega_{X} \cdot DA_p(t) + \omega_{DP} \cdot \Lambda_{DP}(t) + \omega_{S1} \cdot \Lambda_{S}(t) \\
\overline{GL}_{PFC,p}(t) &= GL_{PFC,p}(t) + \omega_{DP} \cdot \Lambda_{DP}(t) + \omega_{S2} \cdot \Lambda_{S}(t) \\
\overline{GL}_{N,x}(t) &= GL_{N,x}(t) + \omega_{DC} \cdot \Lambda_{DC}(t) \\
\overline{DA}_c(t) &= DA_c(t) + \omega_{DC} \cdot \Lambda_{DC}(t) \\
\overline{GL}_{PFC,ic}(t) &= GL_{PFC,ic}(t) + \omega_{R} \cdot \Lambda_{R}(t)
\end{align*}
\]

with \(\omega_{DCn} = \{\omega_{DC1}, \omega_{DC2}, \omega_{DC3}\}\) for respectively \(\text{GL}_{PFC,c}, \text{GL}_{Amg,c}\), and \(\text{GL}_{HPC,c}\).

and

At the last active step of the acute processes \(\Lambda_{DP}\) and \(\Lambda_{S}\) (means at \(d_{X}=\pi_X(t)\), with \(X=\{DP,S\}\)) the value of \(DA_p(t)\) is updated.
4.2 [output] $G$ - Tendency of drug-seeking behavior

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

where

$\alpha, \beta \in [0, 1]$

$\gamma$ is a constant:

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

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