Non-linear stochastic model for dopamine cycle

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Dopamine

- **neurotransmitter** is a chemical messengers in the brain that help transmit signals between neurons
- **dopamine** is a crucial **neurotransmitter** that plays a central role in various aspects of brain functions, including reward processing, motivation, learning, and movement control
- its intricate involvement in these biological processes has made it a subject of extensive research across multiple disciplines, ranging from neuroscience and psychology to computational modeling

- for example, **non-linear ODE model** describing synthesis, storage, release, uptake and metabolism of dopamine in dopaminergic nerve terminal of the rat striatum is introduced in

J. B. Justice Jr., L. C. Nicolaysen, A. C. Michael
Modeling the dopaminergic nerve terminal
Journal of Neuroseience Methods, 22 (1988) 239–252

Non-linear stochastic model for dopamine cycle

- **nine-dimensional non-linear diffusion process** satisfying SDE system

$$dx(t) = \mu(x(t))dt + \sigma(x(t))dw(t),$$
$$x(t) = [x_1(t), x_2(t), \ldots, x_9(t)]^T,\ t \in [0, T],$$

with **initial conditions**

$$\begin{cases} x_i(0) = x_i^0,\ x_i^0 > 0, & i \in \{1, 2, \ldots, 9\} \\ E(x_i^0)^2 < \infty, & i \in \{1, 2, \ldots, 9\} \end{cases}$$

- w_i and w_j, $i, j = 1, \ldots, 9$, $i \neq j$, are one-dimensional pairwise independent **standard Brownian motions** on the probability space $(\Omega, \mathcal{F}, P)$
- $\sigma_i \geq 0$, $i = 1, \ldots, 9$ and **all model parameters are positive**

Stochastic model for dopamine cycle

$$dx_1(t) = \left[\frac{V_{mTH}x_3(t)}{x_3(t) + \frac{K_{mTYR}}{TYR}\left(1 + \frac{K_{mCOF}}{COF}\right)\left(x_3(t) + k_{ifDA}\right)} - k_{DC}x_1(t)\right]dt + \sigma_1 x_1(t)dw_1(t) \tag{1}$$

$$dx_2(t) = \left[k_{DC}x_1(t) + \frac{V_{mfb}x_3(t)}{x_3(t) + K_{mfb}} - \frac{V_{mbf}x_2(t)}{x_2(t) + K_{mbf}} - (k_{bi} + k_{br})x_2(t) + k_{ib}x_6(t)\right]dt + \sigma_2 x_2(t)dw_2(t) \tag{2}$$

$$dx_3(t) = \left[\frac{V_{mrf}x_4(t)}{x_4(t) + K_{mrf}} - \frac{V_{mfr}x_3(t)}{x_3(t) + K_{mfr}} + \frac{V_{mbf}x_2(t)}{x_2(t) + K_{mbf}} - \frac{V_{mfb}x_3(t)}{x_3(t) + K_{mfb}} - k_{maof}x_3(t)\right]dt + \sigma_3 x_3(t)dw_3(t) \tag{3}$$

$$dx_4(t) = \left[k_{br}x_2(t) + \frac{V_{mfr}x_3(t)}{x_3(t) + K_{mfr}} - \frac{V_{mrf}x_4(t)}{x_4(t) + K_{mrf}} - \frac{V_{mrg}x_4(t)}{x_4(t) + K_{mrg}} - \frac{V_{mrm}x_4(t)}{x_4(t) + K_{mrm}}\right]dt + \sigma_4 x_4(t)dw_4(t) \tag{4}$$

$$dx_5(t) = \left[\frac{V_{mrg}x_4(t)}{x_4(t) + K_{mrg}} - k_{maog}x_5(t)\right]dt + \sigma_5 x_5(t)dw_5(t) \tag{5}$$

$$dx_6(t) = \left[k_{bi}x_2(t) - k_{ib}x_6(t)\right]dt + \sigma_6 x_6(t)dw_6(t) \tag{6}$$

$$dx_7(t) = \left[\frac{V_{mrm}x_4(t)}{x_4(t) + K_{mrm}} - k_{maom}x_7(t)\right]dt + \sigma_7 x_7(t)dw_7(t) \tag{7}$$

$$dx_8(t) = \left[k_{maof}x_3(t) + k_{maog}x_5(t) - \left(k_{comtd} + k_{cld}\right)x_8(t)\right]dt + \sigma_8 x_8(t)dw_8(t) \tag{8}$$

$$dx_9(t) = \left[k_{comtd}x_8(t) + k_{maom}x_7(t) - k_{clh}x_9(t)\right]dt + \sigma_9 x_9(t)dw_9(t) \tag{9}$$

Stochastic model for dopamine cycle

- **explanation of the model:**
  - $x_1(t)$ - amount of $3,4$-dihyroxyphenylalanine at time t, [DOPA]
  - $x_2(t)$ - amount of releasable bound dopamine, [bDA]
  - $x_3(t)$ - amount of free cytosolic dopamine, [fDA]
  - $x_4(t)$ - amount of extracellular dopamine, [rDA]
  - $x_5(t)$ - amount of glial dopamine, [gDA]
  - $x_6(t)$ - amount of inactive bound dopamine, [iDA]
  - $x_7(t)$ - amount of 3-methoxytyramine, [3–MT]
  - $x_8(t)$ - amount of $3,4$-dihydroxyphenylacetic acid, [DOPAC]
  - $x_9(t)$ - amount of homovanillic acid, [HVA]
- more details, as well as interpretation of parameters of the model, could be found in **Justice et al. (1988)**

Stochastic model for dopamine cycle

Theorem

There exists a unique positive global solution of the system (1)–(9).

- proof can be found in recent paper

J. Đorđević, M. Milošević, N. Šuvak
Non-linear stochastic model for dopamine cycle, 2023
(Manuscript submitted for publication)

Lower and upper bounds for specific moments of coordinate processes

assumptions

- **expected value** of solution $\{x(t),\, 0 \le t \le T\}$,

$$x(t) = [x_1(t), x_2(t), \ldots, x_9(t)]^\tau,$$

  of system (1)-(9) has **referent lower and upper bounds**, i.e. there exist some $0 < a_i < b_i$ such that

$$a_i \le E[x_i(t)] \le b_i, \quad i \in \{1, \ldots, 9\},$$

- $E[x_i(0)]$ **can be from or outside the referent interval** $[a_i, b_i]$

Problem formulation

(1) **determination of bounds for the noise parameter σ_i^2 ensuring that $a_i \leq E[x_i(t)] \leq b_i$ up to specific time $t \in \langle 0, T]$**

- if $a_i \leq E[x_i(0)] \leq b_i$, we determine the bounds for the noise parameter σ_i^2 for which $E[x_i(t)]$ remains in the referent interval $[a_i, b_i]$ up to specific time $t \in \langle 0, T]$

Problems observed

(2) **determination of minimal length of the time-interval in which $E[x_i(t)]$ stays in the same interval as $E[x_i(0)]$, without controlling the noise parameter σ_i^2**

- by assuming that $E[x_i(0)]$ is either in or outside the referent interval $[a_i, b_i]$, we determine the minimal length of the time-interval in which the expected value $E[x_i(t)]$ of the process spends in the same interval as $E[x_i(0)]$

Technique for deriving moment bounds

- to derive these results, first we obtain **component-wise upper bounds** of some moments of process $\{x(t),\, 0 \leq t \leq T\}$ for which we do not claim the optimality in any sense:

$$E[1/x_i(t)], E[x_i(t)], E[x_i^2(t)], \quad i \in \{1, \dots, 9\}$$

- regarding classical techniques used, beside classical **Itô's formula** and a simple inequality

$$xy \leq \frac{x^2}{2} + \frac{y^2}{2}, \quad \forall x, y \in \mathbb{R},$$

other technical results used for calculation of bounds for moments $E[1/x_i(t)]$, $E[x_i(t)]$ and $E[x_i^2(t)]$ are given in following theorems

Technique for deriving moment bounds

Theorem (Gronwall-Bellman's inequality)

Let u and f be continuous and non-negative functions defined on $I = [a, b]$ and let n be a continuous, positive and non-decreasing function defined on I satisfying the integral inequality

$$u(t) \leq n(t) + \int_a^t f(s)u(s)\, ds, \quad t \in I.$$

Then

$$u(t) \leq n(t) \exp\left(\int_a^t f(s)\, ds\right), \quad t \in I. \tag{10}$$

Technique for deriving moment bounds

Theorem (Pachpatte's inequality)

Let u, f *and* g *be non-negative continuous functions on* $\mathbb{R}_+ = [0, \infty\rangle$ *and* $n(t)$ *be a positive and non-decreasing continuous function defined on* $\mathbb{R}_+$ *for which the inequality*

$$u(t) \leq n(t) + \int_0^t f(s) \left(u(s) + \int_0^s g(z)u(z)\,dz \right) ds, \quad t \in \mathbb{R}_+$$

holds for $t \in \mathbb{R}_+$. *Then*

$$u(t) \leq n(t) \left(1 + \int_0^t f(s) \exp\left(\int_0^s \left(f(z) + g(z) \right) dz \right) ds \right), \quad t \in \mathbb{R}_+. \tag{11}$$

Bounds for moments of $x_1(t)$

- **from equation** (1)**, by applying Itô's formula and taking the expectation**, we obtain the upper bounds for $E[1/x_1(t)]$, $E[x_1(t)]$ and $E[x_1^2(t)]$ that are **further simplified by using Gronwall-Bellman's inequality** (Theorem 2, expression (10))

- **the upper bound for** $E[1/x_1(t)]$:

$$E[1/x_1(t)] \leq E[1/x_1(0)]e^{\left(\sigma_1^2+k_{DC}\right)t} \tag{12}$$

Bounds for moments of $x_1(t)$

- **the upper bound for $E[x_1(t)]$:**

$$E[x_1(t)] \leq E[x_1(0)] + \int_0^t K_{x_1}\, ds = E[x_1(0)] + K_{x_1} t := U^{x_1}(t), \tag{13}$$

where

$$K_{x_1} = \frac{V_{mTH} \cdot TYR \cdot COF}{TYR \cdot COF + K_{mTYR}\,(COF + K_{mCOF})} \tag{14}$$

- **lower bound for $E[x_1(t)]$** (Jensen's inequality + (12)):

$$E[x_1(t)] \geq \left(E[1/x_1(0)]e^{\left(\sigma_1^2 + k_{DC}\right)t}\right)^{-1} := L_{x_1}(t) \tag{15}$$

Bounds for noise parameter σ_1^2

- in order to obtain **lower and upper bounds for intensity** σ_1^2 of the Brownian motion w_1, for which the expected value of the process x_1 remains in the referent interval $[a_1, b_1]$, we assume that $a_1 \leq E[x_1(0)] \leq b_1$ and that there exists some $t^{b_1} \in \langle 0, T]$ such that

$$a_1 \leq \frac{1}{E\left[\frac{1}{x_1(0)}\right] e^{\left(\sigma_1^2 + k_{DC}\right)t}} \leq E[x_1(t)] \leq E[x_1(0)] + K_{x_1} t \leq b_1, \qquad (16)$$

for all $t \in \langle 0, t^{b_1}]$, and where the lower and the upper bounds for $E[x_1(t)]$ are given by (15) and (13)

Bounds for noise parameter σ_1^2

- from (16) it follows that $E[x_1(t)]$ **remains in the referent interval** $[a_1, b_1]$ **at least up to the time**

$$t^{b_1} = \frac{b_1 - E[x_1(0)]}{K_{x_1}},$$

for σ_1^2 satisfying the following condition:

$$0 \leq \sigma_1^2 \leq \ln\left(a_1 E[1/x_1(0)]\right)^{-1/t^{b_1}} - k_{DC}$$

- **non-negativity of** σ_1 is ensured by assumption

$$a_1 \leq E[x_1(0)] \leq b_1$$

Upper bounds for time for which $E[x_1(t)]$ remains in the same interval as $E[x_1(0)]$

- **according to assumption on value of $E[x_1(0)]$ regarding the referent bounds a_1 and b_1** we obtain the **lower bound for the time** that the expected value $E[x_1(t)]$ spends in the same interval as the expected starting value of the process x_1
  - if $a_1 \leq E[x_1(0)] \leq b_1$, from the first and the last inequality in (16) it follows that $E[x_1(t)]$ stays in the referent interval $[a_1, b_1]$ at least up to the time $t_{a_1}^{b_1}$ given by

$$t_{a_1}^{b_1} = \min \left\{ \frac{b_1 - E[x_1(0)]}{K_{x_1}}, \frac{1}{\sigma_1^2 + k_{DC}} \ln \left(\frac{1}{a_1 E\left[1/x_1(0)\right]} \right) \right\}$$

Upper bounds for time for which $E[x_1(t)]$ remains in the same interval as $E[x_1(0)]$

- if $E[x_1(0)] < a_1$, we determine the **lower bound** t^{a_1} **such that** $E[x_1(t)] \leq a_1$ **at least up to time** t^{a_1}

- it can be obtained by imposing the following assumption to the upper bound (13) of $E[x_1(t)]$:

$$E[x_1(0)] + K_{x_1} t \leq a_1$$

- it follows that $E[x_1(t)] \leq a_1$ at least up to the time

$$t^{a_1} = \frac{a_1 - E[x_1(0)]}{K_{x_1}}$$

Upper bounds for time for which $E[x_1(t)]$ remains in the same interval as $E[x_1(0)]$

- if $E[x_1(0)] > b_1$, we determine the **lower bound** t_{b_1} **such that** $E[x_1(t)] \geq b_1$ **at least up to time** t_{b_1}
- it can be obtained by imposing the following assumption to the lower bound (15) of $E[x_1(t)]$:

$$b_1 \leq \left(E[1/x_1(0)]e^{\left(\sigma_1^2 + k_{DC}\right)t}\right)^{-1}$$

- it follows that $E[x_1(t)] \geq b_1$ at least up to the time

$$t_{b_1} = \frac{1}{\sigma_1^2 + k_{DC}} \ln\left(\frac{1}{b_1 E[1/x_1(0)]}\right)$$

Simulation technique

- we introduce the **approximate solution corresponding to the solution of the system (1)–(9)**
- approximate solution is based on **standard Euler-Maruyama approximation scheme and Balanced Implicit Method (BIM)** for d-dimensional SDEs of the form

$$dX_t = a(t, X_t)dt + \sum_{j=1}^{m} b_j(t, X_t)dW_t^j, \quad t \geq 0$$

- here $E(X_0)^2 < \infty$, where $a, b^1, \ldots, b^m$ are d-dimensional Lipschitz continuous vector-valued function fulfilling linear growth condition

Simulation technique

- BIM method is of the following form

$$Y_{n+1} = Y_n + a(\tau_n, Y_n)\Delta + \sum_{j=1}^{m} b^j(\tau_n, Y_n)W_n^j + C_n(Y_n - Y_{n+1}),$$

where

$$C_n = c_0(\tau_n, Y_n)\Delta + \sum_{j=1}^{m} c^j(\tau_n, Y_n)|\Delta W_n^j|,$$

and $\Delta W_n^j = W_{\tau_{n+1}}^j - W_{\tau_n}^j, \Delta = \tau_{n+1} - \tau_n, n = 0, 1, \ldots, N-1,$ and $c^0, c^1, \ldots, c^m$ represent $d \times d$-matrix-valued functions

Simulation technique

- let $\Delta \in (0,1)$ be the step-size and let

$$k\Delta, \quad k \in \{0, 1, \ldots, N\},$$

be the equidistant partition of the time interval $[0, T]$, where $N = \left\lfloor \frac{T}{\Delta} \right\rfloor$, while $\lfloor \cdot \rfloor$ is the integer part function

- for $k = 0, 1, \ldots N - 1$ we define the **discrete-time approximate solution of the system (1)–(9)** in accordance with BIM as follows:

Simulation technique

$$x_1^{k+1}$$
$$= (1+C_1^k)^{-1}\left[x_1^k + \frac{V_{mTH}x_3^k\Delta}{x_3^k+\frac{K_{mTYR}}{TYR}\left(1+\frac{K_{mCOF}}{COF}\right)(x_3^k+k_{ifDA})} + \sigma_1 x_1^k \Delta w_1^k + \sigma_1 x_1^k |\Delta w_1^k|\right]$$

$$x_2^{k+1}$$
$$= (1+C_2^k)^{-1}\left[x_2^k + \left(k_{DC}x_1^k + \frac{V_{mfb}x_3^k}{x_3^k+K_{mfb}} + k_{ib}x_6^k\right)\Delta + \sigma_2 x_2^k \Delta w_2^k + \sigma_2 x_2^k |\Delta w_2^k|\right]$$

$$x_3^{k+1} = (1+C_3^k)^{-1}\left[x_3^k + \left(\frac{V_{mrf}x_4^k}{x_4^k+K_{mrf}} + \frac{V_{mbf}x_2^k}{x_2^k+K_{mbf}}\right)\Delta + \sigma_3 x_3^k \Delta w_3^k + \sigma_3 x_3^k |\Delta w_3^k|\right]$$

$$x_4^{k+1} = (1+C_4^k)^{-1}\left[x_4^k + \left(k_{br}x_2^k + \frac{V_{mfr}x_3^k}{x_3^k+K_{mfr}}\right)\Delta + \sigma_4 x_4^k \Delta w_4^k + \sigma_4 x_4^k |\Delta w_4^k|\right]$$

$$x_5^{k+1} = (1+C_5^k)^{-1}\left[x_5^k + \frac{V_{mrg}x_4^k\Delta}{x_4^k+K_{mrg}} + \sigma_5 x_5^k \Delta w_5^k + \sigma_5 x_5^k |\Delta w_5^k|\right]$$

$$x_6^{k+1} = (1+C_6^k)^{-1}\left[x_6^k + k_{bi}x_2^k\Delta + \sigma_6 x_6^k \Delta w_6^k + \sigma_6 x_6^k |\Delta w_6^k|\right]$$

$$x_7^{k+1} = (1+C_7^k)^{-1}\left[x_7^k + \frac{V_{mrm}x_4^k\Delta}{x_4^k+K_{mrm}} + \sigma_7 x_7^k \Delta w_7^k + \sigma_7 x_7^k |\Delta w_7^k|\right]$$

$$x_8^{k+1} = (1+C_8^k)^{-1}\left[x_8^k + \left(k_{maof}x_3^k + k_{maog}x_5^k\right)\Delta + \sigma_8 x_8^k \Delta w_8^k + \sigma_8 x_8^k |\Delta w_8^k|\right]$$

$$x_9^{k+1} = (1+C_9^k)^{-1}\left[x_9^k + \left(k_{comtd}x_8^k + k_{maom}x_7^k\right)\Delta + \sigma_9 x_9^k \Delta w_9^k + \sigma_9 x_9^k |\Delta w_9^k|\right]$$

Simulation results

- **initial conditions and parameter values** for model (1)–(9) are chosen as in the paper **Justice et al. (1988)**

  - initial conditions

$x_1(0) = 0.25$	$x_2(0) = 11.57$	$x_3(0) = 2.5$
$x_4(0) = 0.0017$	$x_5(0) = 3$	$x_6(0) = 64.8$
$x_7(0) = 0.063$	$x_8(0) = 5.9$	$x_9(0) = 3.3$

  - parameters values

$V_{mTH} = 40$	$K_{mTYR} = 55.3$	$TYR = 150$	$k_{ifDA} = 110$
$k_{DC} = 1.38$	$V_{mfb} = 0.439$	$K_{mfb} = 0.459$	$k_{ib} = 0.295$
$k_{bi} = 1.65$	$k_{br} = 0.012$	$V_{mfr} = 7.807$	$K_{mfr} = 25.04$
$k_{maof} = 0.0598$	$V_{mrf} = 12.51$	$K_{mrf} = 0.032$	$V_{mrg} = 31.9$
$K_{mrg} = 0.315$	$V_{mrm} = 0.15$	$K_{mrm} = 0.012$	$k_{maog} = 0.0598$

Simulation results

- to illustrate theoretical findings regarding the **behavior of the first moment of the solution** we consider coordinate processes $\{x_i(t), 0 \leq t \leq T\}$, $i \in \{1, \dots 9\}$
- **we focus here on coordinate process** $(x_1(t),\ 0 \leq t \leq T)$; other coordinate processes can be treated analogously
- **simulation steps for** $(x_1(t),\ 0 \leq t \leq T)$**:**

(1) **simulation of deterministic model**

- solution of deterministic model, corresponding to the approximate solution for $\sigma_i = 0, i \in \{1, 2, \dots, 9\}$, is simulated
- for every coordinate process of deterministic model minimal and maximal values of simulated trajectories are taken as initial values for referent boundaries a_i^{det} and b_i^{det}

Simulation results

(2) **determination of the referent interval** for the first moment of $(x_1(t), 0 \leq t \leq T)$

- for simulation of stochastic model for x_1 **new initial value** $x_1(0)$ is chosen from $\mathcal{U}(a_1^{det}, b_1^{det})$, with fixed initial values for $i = 2, \ldots, 9$
- 100 **values for** σ_1 **are chosen from uniform distribution on interval (16)**, with $\sigma_i = 0.05$, $i = 2, \ldots, 9$, replacing a_1 from that relation by a_1^{det}
- **for each** σ_1, i.e. for each stochastic model for x_1, the **minimal value of simulated trajectory** is taken and a_1 is set to be the minimum of that sequence
- analogously, for each σ_1 the **maximal value of simulated trajectory** is taken and b_1 is set to be the maximum of that sequence

Simulation results

(3) **simulation of stochastic model** for $(x_1(t), 0 \leq t \leq T)$

- x_1 **starts from** $\mathcal{U}(a_1, b_1)$ and other coordinate processes start from the initial values of the deterministic model
- **value of** σ_1 **is arbitrarily chosen** from the interval determined by the relation (16), while $\sigma_i = 0.05$, $i = 2, \ldots, 9$
- $E[x_1(t)]$ **is approximated by sample average of** 100 **trajectories**

Simulation results - $(x_1(t),\, 0 \leq t \leq T)$

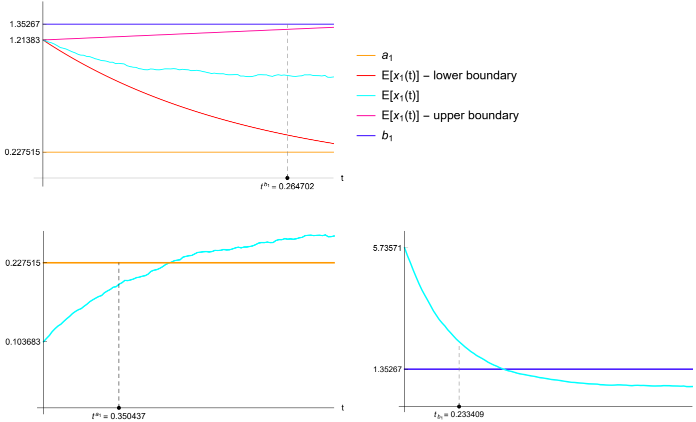

Figure 1: Cases when (a) $E[x_1(0)] \in [a_1, b_1]$, (b) $E[x_1(0)] < a_1$ and (c) $E[x_1(0)] > b_1$, respectively

Simulation results - $(x_2(t),\, 0 \le t \le T)$

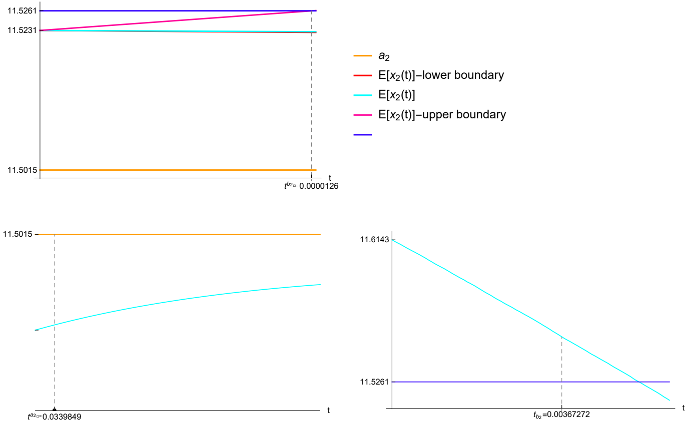

Figure 2: Cases when (a) $E[x_2(0)] \in [a_2, b_2]$, (b) $E[x_2(0)] < a_2$ and (c) $E[x_2(0)] > b_2$, respectively

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