Mouse hippocampal dendritic spine dynamics over the estrous cycle as stochastic system

EEMB 247/IQB 247 - Quant. Methods in Biology
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Abstract

example text

1 Introduction

1.1 Neural plasticity and dendritic spine dynamics

1.2 The rodent estrous cycle

1.3 Modulation of spine dynamics by sex hormones

Figure 1: Neural plasticity, hippocampal dendritic spines, and the rodent estrous cycle. **a.** Neural plasticity....

2 Experimental methods

Here, we use the publicly available dataset of [**?**], which provides more detailed methodological details. A brief summary is provided here for context.

2.1 Estrous cycle staging

2.2 Surgical procedures

2.3 Structural two-photon calcium imaging of dendritic spines

2.4 Spine classification

Figure 2: Overall title. **a.** estrousnet (adapted from [**?**]), **b.** Schematic of hippocampal prisms implanted into mice. **c.** Strucural imaging of HP dendridic spines, segmentation, etc.. **d.** Spine classification schematic.

3 Modeling results

3.1 State variables and population flow

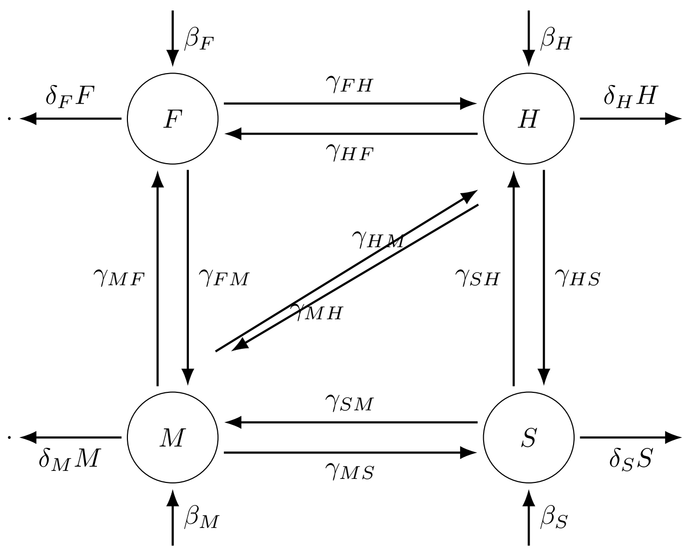

Figure 3: Arrows stop at circle edges; opposing transitions are offset for clarity.

3.2 Estradiol concentration over the estrus cycle

The four-harmonic Fourier series for estradiol concentration over the estrus cycle can be expressed as

$$f(t) = a_0 + \sum_{n=1}^{4} a_n sin\frac{2\pi nt}{p} + b_n cos\frac{2\pi nt}{p} \tag{1}$$

where the values of parameters are $a_0 = 65.07, a_1 = -35.94, b_1 = 68.53, a_2 = -71.13, b_2 = -2.5, a_3 = -43.44, b_3 - 66.03, a_4 = 11.67, b_4 = -55.08$.

Here, $f(t)$ predicts the endogenous concentration of E2 estradiol in units of pg/mL as a function of time, with time in units of days aligned to diestrus ($0 \leq t < 1$), proestrus ($1 \leq t < 2$), estrus ($2 \leq t < 3$), and metestrus ($3 \leq t < 4$) stages. In these timesteps, ovulation occurs at $t = 2.25$ and given a period of $p = 4$ in equation (**??**), $t = 0$ and $t = 4$ are of equivalent value.

Figure 4: Overall title. **a.**

3.3 Spine class transition probabilities

Let β_x be the spontaneous growth rate new spines, for $x \in \{F, H, S, M\}$, δ_x the per-individual death rate, and $\gamma_{x \to y}$ the per-individual transition rate from state x to y, for all distinct $x, y \in \{F, H, S, M\}$. The growth rates β_x are treated as independent from the current population size.

Each entry in the transition matrix $Q \in \mathbb{R}^{5x5}$ gives the frequency of transition from the current state x to the next state y as $Q_{x \to y}$. The set of possible states is defined as $\mathcal{S} = \{NS, F, H, S, M\}$

where NS indicates no spine to allow for growth and pruning terms. Rows of Q are the current state and columns of Q are the target state. The zeroth row represents outgoing transitions from the NS state, i.e., new growth, while the zeroth column represents incoming transitions to the NS state, i.e., existing spines being pruned away. The diagonal entries, λ_x represent the total rate of leaving state x, where

$$\lambda_x = \delta_x + \sum_{y \neq x} \gamma_{x \to y}$$

The complete transition matrix takes the form of

$$Q = \begin{bmatrix} \delta_M & \gamma_{M\to F} & \gamma_{M\to H} & \gamma_{M\to S} & -\lambda_M \\ \delta_S & \gamma_{S\to F} & \gamma_{S\to H} & -\lambda_S & \gamma_{S\to M} \\ \delta_H & \gamma_{H\to F} & -\lambda_H & \gamma_{H\to S} & \gamma_{H\to M} \\ \delta_F & -\lambda_F & \gamma_{F\to H} & \gamma_{F\to S} & \gamma_{F\to M} \\ 0 & \beta_F & \beta_H & \beta_S & \beta_M \end{bmatrix}$$

However, Q must be calculated for all four of the estrous cycle stage transitions, i.e., Q_x for $x \in \{D, P, E, M\}$ Following the approach in equations ??? and ???, the following transition probabilities were computed:

Figure 5: Overall title. **a.**

3.4 Spine dynamics as a continuous-time system

The expression for the four continuous-time state equations is

$$\begin{aligned} \frac{dF}{dt} =& \beta_F - \delta_F F + \gamma_{HF} H + \gamma_{SF} S + \gamma_{MF} M - F(\gamma_{FH} + \gamma_{FS} + \gamma_{FM}) \\ \frac{dH}{dt} =& \beta_H - \delta_H H + \gamma_{FH} F + \gamma_{SH} S + \gamma_{MH} M - H(\gamma_{HF} + \gamma_{HS} + \gamma_{HM}) \\ \frac{dS}{dt} =& \beta_S - \delta_S S + \gamma_{FS} F + \gamma_{HS} H + \gamma_{MS} M - S(\gamma_{SF} + \gamma_{SH} + \gamma_{SM}) \\ \frac{dM}{dt} =& \beta_M - \delta_M M + \gamma_{FM} F + \gamma_{HM} H + \gamma_{SM} S - M(\gamma_{MF} + \gamma_{MH} + \gamma_{MS}) \end{aligned} \tag{2}$$

However, this can be expressed as a stochastic system of discrete events, where $F, H, S, M \in \mathbb{Z}_{\geq 0}$.

The system described by these equations involve 20 possible events affecting the state vector

$$X(t) = \begin{bmatrix} F(t) \\ H(t) \\ S(t) \\ M(t) \end{bmatrix}$$

Using these event definitions, we can reformulate the state equations as a stochastic birth-death-transition process where the probability of having n spines of type F at time t is given by $p_n^F(t)$.

#	Event	Definition	Vector	#	Event	Definition	Vector
1	New F grown	$k_1 = \beta_F$	$v_1 = \begin{bmatrix}1\\0\\0\\0\end{bmatrix}$	11	M transitions to F	$k_{11} = \gamma_{MF} M$	$v_{11} = \begin{bmatrix}1\\0\\0\\-1\end{bmatrix}$
2	New H grown	$k_2 = \beta_H$	$v_2 = \begin{bmatrix}0\\1\\0\\0\end{bmatrix}$	12	F transitions to H	$k_{12} = \gamma_{FH} F$	$v_{12} = \begin{bmatrix}-1\\1\\0\\0\end{bmatrix}$
3	New S grown	$k_3 = \beta_S$	$v_3 = \begin{bmatrix}0\\0\\1\\0\end{bmatrix}$	13	F transitions to S	$k_{13} = \gamma_{FS} F$	$v_{13} = \begin{bmatrix}-1\\0\\1\\0\end{bmatrix}$
4	New M grown	$k_4 = \beta_M$	$v_4 = \begin{bmatrix}0\\0\\0\\1\end{bmatrix}$	14	F transitions to M	$k_{14} = \gamma_{FM} F$	$v_{14} = \begin{bmatrix}-1\\0\\0\\1\end{bmatrix}$
5	Existing F pruned	$k_5 = \delta_F F$	$v_5 = \begin{bmatrix}-1\\0\\0\\0\end{bmatrix}$	15	S transitions to H	$k_{15} = \gamma_{SH} S$	$v_{15} = \begin{bmatrix}0\\1\\-1\\0\end{bmatrix}$
6	Existing H pruned	$k_6 = \delta_H H$	$v_6 = \begin{bmatrix}0\\-1\\0\\0\end{bmatrix}$	16	M transitions to H	$k_{16} = \gamma_{MH} M$	$v_{16} = \begin{bmatrix}0\\1\\0\\-1\end{bmatrix}$
7	Existing S pruned	$k_7 = \delta_S S$	$v_7 = \begin{bmatrix}0\\0\\-1\\0\end{bmatrix}$	17	H transitions to S	$k_{17} = \gamma_{HS} H$	$v_{17} = \begin{bmatrix}0\\-1\\1\\0\end{bmatrix}$
8	Existing M pruned	$k_8 = \delta_M M$	$v_8 = \begin{bmatrix}0\\0\\0\\-1\end{bmatrix}$	18	M transitions to S	$k_{18} = \gamma_{MS} M$	$v_{18} = \begin{bmatrix}0\\0\\1\\-1\end{bmatrix}$
9	H transitions to F	$k_9 = \gamma_{HF} H$	$v_9 = \begin{bmatrix}1\\-1\\0\\0\end{bmatrix}$	19	H transitions to M	$k_{19} = \gamma_{HM} H$	$v_{19} = \begin{bmatrix}0\\-1\\0\\1\end{bmatrix}$
10	S transitions to F	$k_{10} = \gamma_{SF} S$	$v_{10} = \begin{bmatrix}1\\0\\-1\\0\end{bmatrix}$	20	S transitions to M	$k_{20} = \gamma_{SM} S$	$v_20 = \begin{bmatrix}0\\0\\-1\\1\end{bmatrix}$

$$
\begin{aligned}
\frac{dp_n^F}{dt} &= k_1 p_{n-1}^F + k_9 p_{n-1}^F + k_{10} p_{n-1}^F + k_{11} p_{n-1}^F - (k_5 + k_{12} + k_{13} + k_{14}) p_n^F \\
\frac{dp_n^H}{dt} &= k_2 p_{n-1}^H + k_{12} p_{n-1}^H + k_{15} p_{n-1}^H + k_{16} p_{n-1}^H - (k_6 + k_9 + k_{17} + k_{19}) p_n^H \\
\frac{dp_n^S}{dt} &= k_3 p_{n-1}^S + k_{13} p_{n-1}^S + k_{17} p_{n-1}^S + k_{18} p_{n-1}^S - (k_7 + k_{10} + k_{15} + k_{20}) p_n^S \\
\frac{dp_n^M}{dt} &= k_4 p_{n-1}^M + k_{14} p_{n-1}^M + k_{19} p_{n-1}^M + k_{20} p_{n-1}^M - (k_8 + k_{11} + k_{16} + k_{18}) p_n^M
\end{aligned} \tag{3}
$$

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