A time-delay nonlinear model of dopamine-modulated prefrontal-limbic interactions in schizophrenia

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Abstract. We present a nonlinear mathematical model of dopamine-modulated prefrontal-limbic interactions in schizophrenia, including discrete time-delays. An extensive stability and bifurcation analysis is undertaken in a neighborhood of the positive equilibrium of the system. The results reveal the importance of time-delays in modulating dopamine reactivity.

Keywords: schizophrenia, mathematical model, time delay, stability, bifurcations

1 Introduction

Schizophrenia is an incurable neuropsychiatric illness, with dramatic personal and social implications [2, 4, 6, 11]. Its diagnosis and treatment are currently based on clinical symptoms rather than on the neurophysiological basis (which remains unknown). The "stress-diathesis model" remains a popular hypothesis that attributes stress vulnerability in schizophrenia to a pre-existing impairment in hippocampal and prefrontal inhibitory control of the limbic arousal response. The subsequent exacerbated fear reaction raises cortisol levels, with toxic effects on the hippocampus, further deepening the pre-existing impairment of the inhibitory unit. This is a possible trigger for the main neurodegenerative cycle in schizophrenia. While empirical work cannot fully explain the complex mechanics of the prefrontal-limbic system, a mathematical model can approach system dysregulation with analytical techniques, quantifying the nonlinear components of a self-interacting network. It can be used to test hypotheses that bridge connectivity with functional dynamics and subsequently with behavior observed empirically.

It has been proposed that schizophrenia symptoms constitute an end-stage of a cyclic and neurodegenerative process [1], in which a hereditary predisposition reduces the individual psychological threshold toward stimuli to the point where even minor daily stresses will directly trigger psychotic experiences. However,

the etiology of this systemic degeneration has been challenging any simple explanation, and current antipsychotic medications are likely treating the outward symptoms rather than their cause.

2 Modeling methods

One of our earlier studies on empirical fMRI time series from human subjects suggested that key dynamic differences between patients with schizophrenia and healthy controls can be captured in the existence and geometry of oscillations in a two dimensional subspace of prefrontal-limbic regions [12]. This inspired us to consider, in our subsequent modeling work [13], a two-dimensional prefrontal-amygdala system, and understand analytically how the coupled dynamics can play the major role that had been demonstrated empirically in regulation of emotional arousal. In the current paper, we refine the model with a focus on the dopamine regulatory aspect, which in previous work was represented mathematically by nonlinear terms. New literature shows that dopamine-modulated mechanisms, unlike those mediated by other neurotransmitters, operate based on a system of actual biophysical delays. It has been suggested that the three different timescales across which dopamine operates [15, 14] (fast, intermediate and low) may underlie the broadness of dopamine's effects on executive, cognitive and motivational function (disrupted in schizophrenia). In particular, at the lowest timescale, "dopamine exerts an almost tonic influence on postsynaptic structures." Deficits in this delayed/tonic dopamine release have been shown to affect post-synaptic function (which cannot be otherwise explained by reductions in phasic dopamine changes) and may further lead to the deficits in movement, attention and cognition – characteristic to pathologies like Parkinson's disease or schizophrenia.

A realistic model of brain function which encompasses the regulatory effect of dopamine must therefore take into consideration delays, which may have crucial, if subtle effects that go beyond the nonlinearities included and discussed in our original framework. The use of nonlinear delayed equations as a distinct and important approach in modeling schizophrenia-like neural patterns have been recently investigated in [15]. In this paper, we improve our previous work to address dopamine delay mechanisms, by introducing a delayed neural response in the target regions of dopamine-mediated pathways.

Our model represents the time activations of the amygdala, the hippocampus and the prefrontal cortex as three distinct variables a, p and h, while a fourth variable δ stands for the activation of the dopamine system, controlled via the nucleus accumbens and the ventral tegmental area.

$$\begin{cases} \dot{a} = -\mu_1 a - k_1 p - \gamma_1 h + I \\ \dot{p} = k_2 a - \mu_2 f(p, \delta_\tau) + \dfrac{\gamma_2}{a_1 C(a) + 1} h \\ \dot{h} = k_3 f(p, \delta_\tau^2) - a_2 C(a) \\ \dot{\delta} = -\xi_1 f(a, \delta) + \xi_2 f(p, \delta) + \xi_3 f(h, \delta) \end{cases} \tag{1}$$

Here, the function f is of the form $f(x, \delta) = xg(\delta)$, where x can be a, p or h, and the function g is increasing, such that $g(0)$=1. The term $\delta_\tau(t) = \delta(t - \tau)$ represents the delay term, where the parameter τ is the delay in the dopamine action. The linear coefficients are positive system parameters, representing the strengths of the connections between the respective brain areas. As in prior works [3, 10, 13], the dependence of cortisol on arousal levels (measured as amygdala activation) is represented as $C(a) = \dfrac{\alpha e^a}{e^a + 1}$.

In prior work [13], we investigated the dependence of the system's temporal dynamics on an larger set of physiological parameters, representing connectivity strengths between the same key brain areas, but also including vulnerability to stress-induced cortisol, dopamine regulation and autoimmunity.

3 Results

We performed stability analyses, we studied the system's sensitivity to parameter perturbations, and we computed bifurcations. We obtained analytical conditions for the existence of a positive stable equilibrium, and for this equilibrium to undergo a supercritical Hopf transition into stable oscillations. Hopf transitions are illustrated in the presence and the absence of delays, with respect to different parameters.

3.1 Nonlinear model

For the system without delays, we focused on locating Hopf bifurcation curves in the parameter plane defined by μ_1 (level of anxiety) and a_2 (vulnerability to stress cortisol). Our results suggest that varying a_2 for fixed μ_1 can readily push the system through qualitative changes in asymptotic dynamics (see Fig.1), while changing μ_1 and keeping a_2 fixed, is more likely to introduce more subtle quantitative/kinetic changes in the convergence to the equilibrium, or in the duty cycle. A small sensitivity to stress cortisol in the system is necessary to stabilize the system to the equilibrium characteristic to a healthy functional (region 2). When this sensitivity is increased past a "vulnerabilty" threshold, the system crosses the Hopf curve and enters oscillations (region 3), exhibiting out of phase swings in the amygdala arousal reaction to the stimulus I, and in the prefrontal activation, attempting to (unsuccessfully) provide appropriate inhibition. When a_2 is increased past a "pathological" value, the system loses the oscillatory stability, and enters unstable oscillations, with escaping trajectories (region 4).

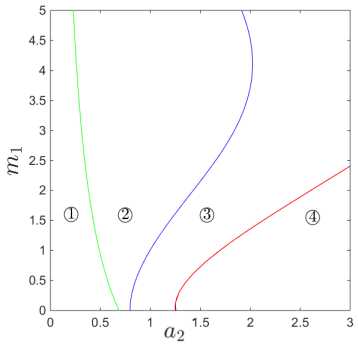

Fig. 1. Transitions in between dynamic regimes in the (a_2, μ_1) parameter plane. The Saddle Node (green), Hopf (blue) and Fold (red) curves delimit the plane into the parameter regions (1)-(4), with different asymptotic behaviors, as explained in the text.

3.2 Delay model

The equilibrium states of the model (1) are the solutions of the following system:

$$\begin{cases} \mu_1 a + k_1 p + \gamma_1 h = I \\ k_2 a - \mu_2 p g(\delta) + C_2(a) h = 0 \\ k_3 p g(\delta^2) - a_2 C(a) = 0 \\ \xi_1 a = \xi_2 p + \xi_3 h \end{cases} \tag{2}$$

with $C_2(a) = \dfrac{\gamma_2}{a_1 C(a) + 1}$.

In the delayed case, the linearization of system (1) at an equilibrium state $E = (a^\star, p^\star, h^\star, \delta^\star)$ has the form:

$$\dot{x}(t) = Ax(t) + Bx(t-\tau),$$

where $x(t) = (a(t) - a^\star, p(t) - p^\star, h(t) - h^\star, \delta(t) - \delta^\star)^T$ and

$$A = \begin{pmatrix} -\mu_1 & -k_1 & -\gamma_1 & 0 \\ k_2 + C_2'(a^\star)h^\star & -\mu_2 g(\delta^\star) & C_2(a^\star) & 0 \\ -a_2 C'(a^\star) & k_3 g((\delta^\star)^2) & 0 & 0 \\ -\xi_1 g(\delta^\star) & \xi_2 g(\delta^\star) & \xi_3 g(\delta^\star) & 0 \end{pmatrix} \text{ and } B = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu_2 p^\star g'(\delta^\star) \\ 0 & 0 & 0 & 2k_3 p^\star \delta^\star g'(\delta^\star) \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

Therefore, the characteristic equation is of the form:

$$\Delta(\lambda, \tau) := \lambda P_3(\lambda) - P_2(\lambda) e^{-\tau\lambda} = 0 \tag{3}$$

where

$$P_3(\lambda) = \lambda^3 + r_2\lambda^2 + r_1\lambda + r_0 = \lambda^{-1} \det(\lambda I_4 - A),$$
$$P_2(\lambda) = s_2\lambda^2 + s_1\lambda + s_0$$

with r_i and s_i expressed in terms of the elements of the matrices A and B.

Proposition 1 (Local asymptotic stability in the non-delayed case)**.** *In the non-delayed case, if the following inequalities are satisfied:*

$$\begin{array}{l} r_2 > 0, \quad r_1 > s_2, \quad r_0 > s_1, \quad s_0 < 0, \\ r_2(r_1 - s_2)(r_0 - s_1) > (r_0 - s_1)^2 - s_0 r_2^2, \end{array} \tag{4}$$

then the equilibrium point E of system (1) is locally asymptotically stable.

Following [5, 7–9], we obtain:

Theorem 1. *Assume that inequalities (4) are satisfied and consider*

$$\tau_0^+ = \frac{1}{\omega_0} \arccos\left(\frac{1}{\omega_0} \cdot \Im\left(\frac{P_2(i\omega_0)}{P_3(i\omega_0)}\right)\right) \tag{5}$$

where $\omega_0 > 0$ is the smallest positive solution of the equation $|P_2(i\omega)| = \omega |P_3(i\omega)|$.

The equilibrium point E is asymptotically stable for $\tau \in [0, \tau_0^+)$. At $\tau = \tau_0^+$, system (1) undergoes a Hopf bifurcation at the equilibrium point E.

Proof. The characteristic equation (3) has a pair of complex conjugate roots $z = \pm i\omega$ (with $\omega > 0$) on the imaginary axis if and only if

$$i\omega P_3(i\omega) = P_2(i\omega) e^{-i\omega\tau}. \tag{6}$$

Taking the absolute value in (6) we obtain $|P_2(i\omega)| = \omega |P_3(i\omega)|$. The roots of this equation are the solutions of the equation $R(\omega) = 1$ where

$$R(\omega) = \left(\frac{|P_2(i\omega)|}{\omega |P_3(i\omega)|}\right)^2.$$

The continous function R satisfies $R(0) = \infty$ and $R(\infty) = 0$, therefore there exists at least one $\omega_0 > 0$ such that $R(\omega_0) = 1$. If ω_0 denotes the smallest such solution, it can easily be seen that $R'(\omega_0) < 0$, i.e.

$$R'(\omega_0) = -\frac{2}{\omega_0}\left(1 + \omega_0 \Im\left[\frac{P_2'(i\omega_0)}{P_2(i\omega_0)} - \frac{P_3'(i\omega_0)}{P_3(i\omega_0)}\right]\right) < 0$$

From equation (6), we obtain the critical value τ_0^+ given by (5). Based on Proposition 1, the equilibrium point E is asymptotically stable when $\tau = 0$, and therefore, due to the continuous dependence of the roots of the characteristic equation on the parameter τ, we have that E is asymptotically stable for any $\tau \in (0, \tau_0^+)$.

Let $\lambda(\tau)$ denote the root of the characteristic equation (3) satisfying $\lambda(\tau_0^+) = i\omega_0$. Therefore:

$$\lambda'(\tau_0^+) = -\frac{\partial \Delta / \partial \tau}{\partial \Delta / \partial \lambda}\Big|_{\tau=\tau_0^+} = -\frac{\lambda P_2(\lambda) e^{-\tau\lambda}}{P_3(\lambda) + \lambda P_3'(\lambda) - P_2'(\lambda) e^{-\tau\lambda} + \tau P_2(\lambda) e^{-\tau\lambda}}\Big|_{\tau=\tau_0^+}$$

and hence, a straightforward computation leads to:

$$\operatorname{sign}\left(\Re\left[\lambda'(\tau_0^+)\right]\right) = \operatorname{sign}\left(1 + \omega_0 \Im\left[\frac{P_2'(i\omega_0)}{P_2(i\omega_0)} - \frac{P_3'(i\omega_0)}{P_3(i\omega_0)}\right]\right) = \operatorname{sign}\left(-R'(\omega_0)\right) = 1.$$

This nondegeneracy condition for the Hopf bifurcation shows that the equilibrium point E is asymptotically stable if $\tau \in [0, \tau_0^+)$ and at $\tau = \tau_0^+$, system (1) undergoes a Hopf bifurcation at the equilibrium point E. □

We conclude that the parameter dependence observed in the nonlinear system is further modulated by the degree of delay, in the sense that: (1) the system will be prompted to cross from a regime of stable equilibrium into a stable oscillation one at lower levels of stress vulnerability a_2 and/or anxiety μ_1 for slower dopamine reactivity τ, and will be more "resilient" for higher dopamine reactivity; (2) for given stress vulnerability and anxiety, the lack of appropriate dopamine reactivity (too large τ) may in and of itself push the system into oscillations.

4 Numerical simulations

For the numerical simulations, we have chosen the following parameter values:

$$\mu_1 = 3, \quad \mu_2 = 1, \quad k_1 = 2, \quad k_2 = 1, \quad \xi = 1,$$

$$\gamma_2 = 1, \quad a_1 = 2, \quad a_2 = 1, \quad \alpha = 0.8, \quad I = 0.83.$$

For these values, we find the positive equilibrium state of system (1):

$$E = (a^\star, p^\star, h^\star, \delta^\star) = (0.2075, 0.146798, 0.0607023, 0.015552).$$

The set of inequalities (4) are satisfied and the equilibrium E is therefore asymptotically stable when there is no delay in system (1), i.e., when $\tau = 0$. Based on Theorem 1, we compute $\omega_0 = 0.209336$ and we obtain the critical value of the time delay for the occurrence of a Hopf bifurcation: $\tau_0^+ = 0.08416$. In Figs. 2 and 3, the trajectories of system (1) are shown for two different values of the time-delay: $\tau = 0$ and $\tau = 0.1$ (after the Hopf bifurcation). The appearance of a stable limit cycle is observed numerically, suggesting a supercritical Hopf bifurcation. A theoretical investigation of the criticality of the Hopf bifurcation and the stability of the resulting limit cycle will be provided in a future paper.

5 Conclusions

Dopamine reactivity is a crucially determinant factor of prefrontal-limbic systemic behavior, and subsequently of emotional regulation. The timing factor involved in dopamine-regulated pathways seems to have in particular a strong effect on the regulation efficiency. This effect could only be captured by a theoretical model incorporating dopamine reactivity as a time delay, and was invisible in a classical nonlinear model of prefrontal-limbic interactions.

For the considered nonlinear mathematical model of dopamine-modulated prefrontal-limbic interactions in schizophrenia with time delay, we performed a thorough local asymptotic stability and bifurcation analysis. The critical value

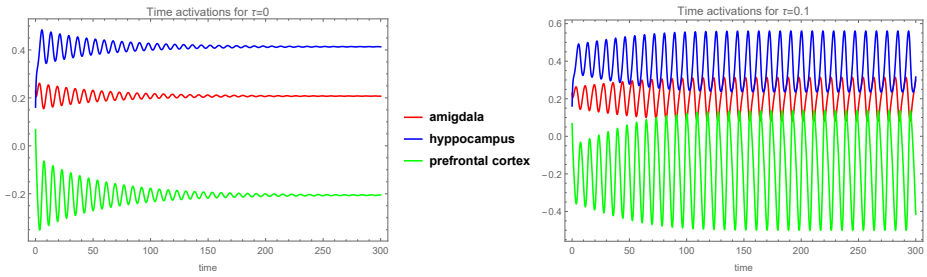

Fig. 2. Trajectories of system (1) when $\tau = 0$ (left) and $\tau = 0.1$ (right). When $\tau = 0$ (shown on the left), the solution of (1) converges to the asymptotically stable equilibrium state E. In the second case, $\tau = 0.1$ (shown on the right), the solution of (1) converges to the stable limit cycle, occurring due to the Hopf bifurcation which takes place at $\tau = \tau_0^+ = 0.08416$.

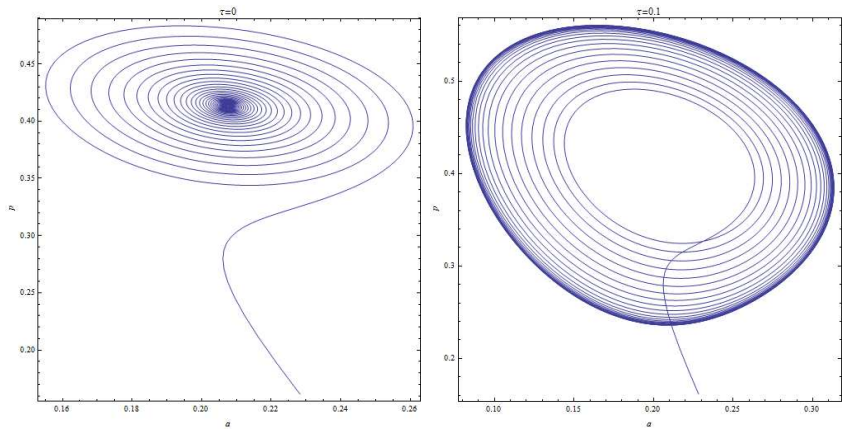

Fig. 3. Evolution of the trajectories of system (1) in the phase-plane (a, p) when $\tau = 0$ (left) and $\tau = 0.1$ (right). When $\tau = 0$ (shown on the left), the solution of (1) converges to the asymptotically stable equilibrium state E. In the second case, $\tau = 0.1$ (shown on the right), the solution of (1) converges to the stable limit cycle, occurring due to the Hopf bifurcation which takes place at $\tau = \tau_0^+ = 0.08416$.

of the time delay corresponding to a Hopf bifurcation in a neighborhood of the equilibrium point has been determined theoretically. Numerical simulations have been presented to substantiate the theoretical results, which show that the resulting limit cycle due to the Hopf bifurcation is asymptotically stable. The theoretical analysis of the stability of this limit cycle will be explored in a future work. Moreover, the effect of different types of distributed time delays on the system's dynamics will also be investigated.

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