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

Eva Kaslik[*,**], **Mihaela Neamţu**[*,**] and Anca Rădulescu [***]
[*] *West University of Timişoara, Romania*
[**] *Academy of Romanian Scientists, Splaiul Independenţei 54, 050094, Bucharest, Romania*
[***] *Department of Mathematics, SUNY New Paltz, NY 12561, USA*

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.

Introduction

Schizophrenia is an incurable neuropsychiatric illness, with dramatic personal and social implications. 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.

Modeling methods

In previous modeling work [1], we have considered a network of components whose coupled dynamics was shown empirically to have a major role 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 [2, 3] (fast, intermediate and low) may underlie the broadness of dopamine's effects on executive, cognitive and motivational function (disrupted in 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 which go beyond the nonlinearities included and discussed in our original framework.
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.

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

Here, the function $f(p, \delta_\tau) = p(t)g(\delta(t-\tau))$ represents the delay term, and 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.

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.

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), with 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).

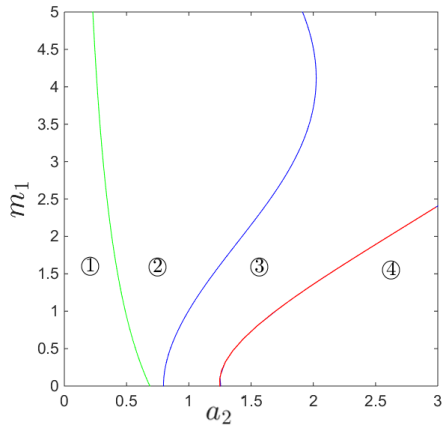

Figure 1: **Transitions in between dynamic regimes in the** (a_2, m_1) **parameter plane**. The Saddle Node (green), Hopf (blue) and Fold (red) curves delimit the plane into the parameter regions (1)-(4), with different asymptotic behaviors, as explained in the text.

Delay model. In the delay case, the characteristic equation is: $\lambda P(\lambda) - Q(\lambda)e^{-\tau\lambda} = 0$, where $P(\lambda) = \lambda^3 + r_2\lambda^2 + r_1\lambda + r_0$, and $Q(\lambda) = s_2\lambda^2 + s_1\lambda + s_0$ are polynomials whose coefficients depend on the system's connectivity strengths. We found conditions for these coefficients so that the time-delay system has a locally stable positive equilibrium. Moreover, under these conditions, we proved that this stable equilibrium transitions into stable oscillations at a critical delay value

$$\tau_0^+ = \frac{1}{\omega_0}\arccos\left(\frac{1}{\omega_0}\cdot\Im\left(\frac{Q(i\omega_0)}{P(i\omega_0)}\right)\right)$$

where $\omega_0 > 0$ is the positive solution of the equation $|Q(i\omega)| = \omega|P(i\omega)|$.
We concluded 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.

Conclusions

Dopamine reactivity is a crucially determinant factor of prefrontal-limbic systemic behavior, and subsequently of emotional regulation. 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.

References

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