Mathematical Modeling of Schizophrenia

Sareh Zendehrouh[1], Fatemeh Bakouie[1], Shahriar Gharibzadeh[1,*],Amin Rostami[2],

[1]Neuromascular Systems Laboratory, Faculty of Biomedical Engineering, Amirkabir University of Technology (Tehran Polytechnich), Tehran, Iran
[2]Clinical Proteomics Research Center, Faculty of Paramedical Sciences, Shahid Beheshti University of medical sciences. Tehran, Iran

*Corresponding author: e-mail address: gharibzadeh@aut.ac.ir (S. Gharibzadeh)

ABSTRACT

Abnormal brain function in schizophrenia involves an extended network of brain structures. In schizophrenia, an abnormal dopamine activity in accordance with altered GABA and glutamate transmission appears to interfere with this process. In this study, we have examined the effect of dopamine hyperactivity on CA3 pyramidal cells using a mathematical model. Our simulation results show that while normal activity of dopamine system causes the membrane potential of pyramidal cell to display a periodic bursting behavior, hyperactivity of this system brings about irregular and aperiodic patterns of activity. In addition, it is suggested that hypo-glutamatergic conditions result in reduced activation of the striatal complex and may induce psychotic symptoms. Thus, we also investigated the role of glutamate level in postsynaptic cell activity. Simulation results indicate that hypo-glutamatergic condition has the same effect on the membrane potential of pyramidal cells, i.e. aperiodic and irregular firing patterns. Based on these results, we hypothesize that glutamate receptor activation may have good therapeutic results in schizophrenia.

Keywords hyper-dopaminergic; glutamate; cortical-striatal-thalamic loop

INTRODUCTION

Despite traditional psychological theories explaining schizophrenia, most current researches on the etiology of the disorder have focused on the role of brain micro-structural abnormalities. Unfortunately, none of these abnormalities are accepted completely to implicate a clear etiology or pathology of schizophrenia.

One of the most famous biochemical theories of schizophrenia is the ‘‘dopamine hypothesis’’, which claims that the disorder results from dopamine (DA) over-activity in the brain.

The excitatory amino acid glutamate, which is the primary transmitter of pyramidal neurons, may also play a role in the neurochemistry of schizophrenia. It has been suggested experimentally that hypoglutaminergic states may induce schizophrenia like symptoms [1]. It seems that this suggestion needs to be proved with more experimental and modeling studies. Modeling the biological systems is a proper of pyramidal cells is studied and showed that changing dopamine concentration forces the system to bifurcate between route of evaluating complex brain behaviors. There are few models for schizophrenia. One of the difficulties in proposing models for this disease is the complexity and heterogeneity of the illness [2]. What is clear from previous researches is that most of the proposed models are descriptive rather than mathematical.

In an attempt to model the cortical-striatal-thalamic loop involved in planning and executive control, the researcher proposed that his computational model produces a better match to the data of schizophrenic patients on a standard cognitive test (the Wisconsin card sorting task (WCST)) [3] and makes different predictions about the possible deficits in schizophrenia, suggesting that basal ganglia deficits may play a role in schizophrenic cognitive performance.

The most important model is presented by [4] which views the disease from the perspective of dynamical systems. In this model, the effect of different levels of dopamine concentration on firing patterns different states (health and disease); however, the effect of glutamate system on disease is neglected in this study. Since the glutamate system is emerging as a promising

and mechanistically relevant novel therapeutic target [5], we present a mathematical model in this study to analyze the role of hyper- and hypo-activity of both dopamine and glutamate neurotransmitters on producing psychosis and simulate the effect of different dopaminergic and glutaminergic drugs on the disease.

Model description

Here, we adopt a mathematical model developed by [6]. Their model is a recurrent inhibitory circuit in the hippocampus, the mossy fibre-CA3 pyramidal cell-basket cell complex. This model considers three populations of neurons: the *presynaptic fibres,* which have excitatory effects on the *postsynaptic cells* and the *inhibitory interneurons.* The interneuronal population is activated by axon collaterals from the postsynaptic cells and, in turn, returns an inhibitory input to the postsynaptic cells (Fig.1).

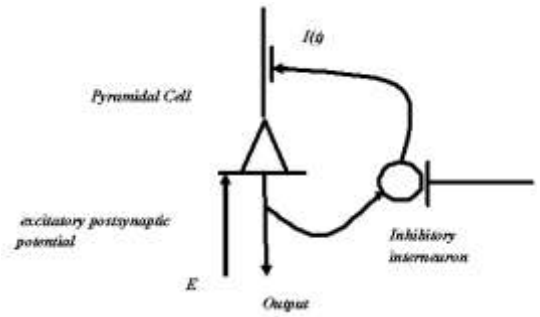

Figure1. The recurrent inhibitory circuit in the hippocampus, as a preliminary basis of cortical-striatal-thalamic circuit.

The postsynaptic cell has an input given by $E(t)-I(t)$, where *E(t)* is the excitatory postsynaptic potential (EPSP) due to activity in the presynaptic cell, and *I(t)* is the inhibitory postsynaptic potential (IPSP) arising from activity in the inhibitory interneuron. Both *E(t)* and *I(t)* are measured in millivolts (mV) relative to the resting potential of the postsynaptic cell. The output of the postsynaptic neuron is in the form of action potentials occurring at frequency of *F(t),* measured in Hertz (Hz). Here we assume that this postsynaptic cell output is given simply by:

$$F(t) = x\ \vartheta(E(t)-I(t)-\theta) \qquad (1)$$

Where

$$\vartheta(x) = \begin{cases} 0 & x \le 0 \\ x & x \ge 0 \end{cases}$$

In Eq. (1), the constant x (Hz/mV) is the slope of the "firing frequency versus postsynaptic cell input" curve, and θ is the threshold measured in mV relative to the postsynaptic cell resting potential. Activity in the postsynaptic cells activates the inhibitory interneurons, causing action potentials to be conducted along their axons which arrive at the synaptic terminals at a frequency $\tilde{F}(t)$.

The arrival of an action potential at the inhibitory interneuron synaptic terminals leads to the generation of the IPSP, *I(t).* Due to the resistive-capacitive properties of the postsynaptic cell membrane, this inhibitory potential will decay at a characteristic rate of γ (msec^{-1}). The dynamics of the IPSP will be determined by:

$$\frac{dI}{dt} = -\gamma\ I + \eta\tilde{F} \qquad (2)$$

η (mV) is a time-dependent inhibitory interaction coefficient given by:

$$\eta(t) = TV_m G(\tilde{F}(t)) \qquad (3)$$

where

T is The average number of inhibitory postsynaptic receptors per cell, V_m (mv) is the inhibitory potential resulting from activation of one receptor, and $G(\tilde{F})$ is the fraction of inhibitory receptors available for activation by transmitter.

To determine $G(\tilde{F})$, it is necessary to consider the stoichiometry of the transmitter-receptor interaction. It is assumed that the receptor-transmitter interaction is governed by:

$$M + nC \leftrightarrow L$$

Where

n is the number of molecules of transmitter (C) required to activate one receptor, L is the number of active receptors (combined with transmitter) of total receptor population T, and M is the number of inactive receptors.

Therefore, the fraction of receptors available for activation is

$$\frac{K}{K+[C]^n}$$

Where *K* is the equilibrium constant for the transmitter-receptor reaction, and [*C*] is the concentration of transmitter.

Taking the assumption that the pool of inhibitory transmitter is sufficiently large not to be depleted by interneuronal activity, the relation between released transmitter levels and interneuron firing frequency will be:

$$[C] = m\tilde{F}$$

where *m* is a constant. Thus, the function $G(\tilde{F})$ is given by:

$$G(\tilde{F}) = \frac{K}{K + (m\tilde{F})^n} \qquad (4)$$

To relate the frequency of arrival of action potentials at the interneuron axon terminal ($\tilde{F}$) to the frequency of generation of action potential in the postsynaptic cell (*F*), we assumed that activity in the postsynaptic cell at a frequency *F(t)* requires a finite time τ to be translated into activity at the axon terminal of the inhibitory interneuron. Thus we take:

$$\tilde{F}(t) = \alpha\ F(t-\tau) \qquad (5)$$

where α is to be interpreted as the reciprocal of the number of action potentials in the postsynaptic cell required to elicit one interneuronal action potential. Equations (1) through (5) may be combined to give:

$$\frac{dI(t)}{dt} = -\gamma\ I(t) + \alpha\ T\ V_m\ F(t-\tau)\frac{K}{K+(m\alpha F(t-\tau))^n} \qquad (6)$$

and

$$F(t) = x\ \vartheta(E(t) - I(t) - \theta) \qquad (7)$$

Equations (6) and (7), in conjunction with an initial condition $I(t) = I_o(t)\ \ -\tau \le t \le 0$, and a specific amount of *E(t)*, form a complete description of the simplified recurrent inhibitory feedback neuronal network. Rewriting the equations in dimensionless form, the following notation is introduced:

$$\begin{aligned}
&\bar{t} = t/\tau && \psi^n = K\left(\frac{\tau}{m\alpha}\right)^n \\
&e(\bar{t}) = E(t)/\theta && \Gamma = \gamma\ \tau \\
&i(\bar{t}) = I(t)/\theta && \beta = \alpha T \psi V_m/\theta \\
&f(\bar{t}) = \tau F(t)/\psi && H = \tau x \theta/\psi
\end{aligned} \qquad (8)$$

Using (8), Equations (6) and (7) may be written as

$$\frac{di(\bar{t})}{d\bar{t}} = -\Gamma\, i(\bar{t}) + \beta\ g(f(\bar{t}-1)) \qquad (9)$$

$$f(\bar{t}) = H\ \vartheta(e(\bar{t}) - i(\bar{t}) - 1) \qquad (10)$$

in which

$$g(f) = \frac{f}{1+f^n} \qquad (11)$$

Physiological plausibility of the model

In this section, we are going to match the abovementioned model to a recurrent inhibitory circuit in cortical-striatal-thalamic loop which is known to be involved in schizophrenia.

There is a direct loop and an indirect loop projecting to the thalamus. Most corticostriatal projections have contacts with striatal GABA neurons which project to the thalamus. These convergent pathways have two or three inhibitory GABAergic interneurons before giving feedback to cortex via thalamic glutamatergic neurons [1]. This is illustrated in Fig. 2.a.

The direct pathway in cortico-striato-thalamocortical loop has two gabaergic interneurons, which result in disinhibition of the thalamus. In combination with the D1 recoptor-coupled dopamine pathways projecting from the substantia nigra, this pathway generates activation of the cortico-striato-cortical loop and in the case of dopamine hyperactivity, a disinhibition of thalamus occurs. The inhibiting indirect pathway in the level of the striatal complex has three GABAergic interneurons, which results in general inhabitation of the thalamus activity. The dopamine system is also coupled with this pathway, but the inhibitory D2 receptors are involved here and in the case of dopamine system hyperactivity, disinhibition of the thalamus will arise.

Since these two pathways result in disihibitaion (activation) of thalamus, we replace these inhibitory interneurons with

one interneuron which projects from striatum to thalamus. As a result, the *T* parameter of the equation (6) is related to receptor densities of GABA transmitter. Neurons in the thalamus receive excitatory inputs from sensory organs and inhibitory inputs from GABAergic interneourns in striatum. The activities in the presynaptic cells results in the net input of $e-i$ to the postsynaptic cell (thalamic cell). It is well understood that the thalamus is a sensory processing/relay center for all sensory afferents, with the exception of some olfactory inputs [7]. Using this fact, we assumed that the postsynaptic potential $e-i$ will generate an input in relevant postsynaptic cell in the cortex that is proportional to $e-i$. Therefore, we have three populations of neurons (Fig 2.b) each corresponding to a specific brain area (the striatum, thalamus, and cortex).

The subtantia nigra (SN) has two sub-structures, the Subtantia Nigra Pars compacta (SNPc) which provides dopaminergic input to the straitum (excitatory or inhibitory depending on receptor type) and the Substantia Nigra Pars reticula (SNPr) [3]. Since the activity of both D1 and D2 receptors produce the same effect on thalamic neurons, we have simplified the direct and indirect pathways and replaced them by a simple pathway projecting from striatum to thalamus (Fig 2.b). In our simplified circuit, dopamine activity has an indirect relation with GABA activity. Here, we assumed that this relationship obeys the function $y=1/x$.

We have also modeled the effect of glutamate concentration on firing frequency of inhibitory interneuron using the α parameter of the equation (5). As mentioned, α is the reciprocal of the number of action potentials in the postsynaptic cell required to elicit one interneuronal action potential. In this context, α may also be considered inversely proportional to glutamate concentration. Considering the effect of glutamate in our model may be a valuable part of the simulation which will be discussed in detail later.

The block diagram of our model is depicted in Figure 3.

Parameters of the model

The parameters of equations (1) through (5) are chosen from (Mackey and an der Heiden, 1984) and are:

$\theta = 4mV$, $\gamma^{-1} = 10m\sec$,
$x = 2.25Hz/mV$, $\tau = 100m\sec$,
$V_m = 24mV$, $n = 3$
$\sqrt[3]{K} = 5\mu M$, $m = 50\ \mu M.\sec$, $e = 1.6$.

The above data give $\Gamma = 10$, $H = 90\times\alpha$, and $\beta = 0.06\times T$.

Simulations were done with Simulink package in Matlab, version 7.2, using ode4 (4th order Runge-Kutta) solver, using an integration step size of 0.01 (corresponding to 1 msec integration steps, since $\tau = 100m\sec$), an initial condition of $i_0(\bar{t}) = 0.1 \quad -1 \le \bar{t} \le 0$ and a variety of GABA receptor densities *T* which have an inverse relationship with dopamine activity, and different values of α which has direct relationship to glutamate activity. For normal state (health) α and *T* equal to 0.1 and 1900, respectively; but depending on the hypoactivity or hyperactivity of the glutamatergic and dopaminerigc systems, they give different values.

RESULTS

In order to test the effect of dopamine and glutamate concentrations on model behavior, we run the model for different values of *T* and α which correspond to different levels of dopamine and glutamate activities. In Figure 4, we can see the effect of dopamine on the model output which corresponds to the pyramidal cell electrical activity. In this figure, the pyramidal cell activity is depicted in three different dopamine concentrations. Figure 4.a shows the normal state, whereas in Figure 4.b dopamine is increased moderately and in Figure 4.c. it is increased severely. It must be noted that in the abovementioned formula, increased T corresponds to hypo-activity of dopamine and decreased T is equivalent to hyper-activity of it. In the same manner, increased α corresponds to hypo-activity of glutamate and decreased α means its hyper-activity.

In Figure 5 the model output for different values of glutamate activities is depicted. Figure 5.a shows the normal state, whereas in Figure 5.b glutamate is decreased moderately and in Figure 5.c it is decreased severely.

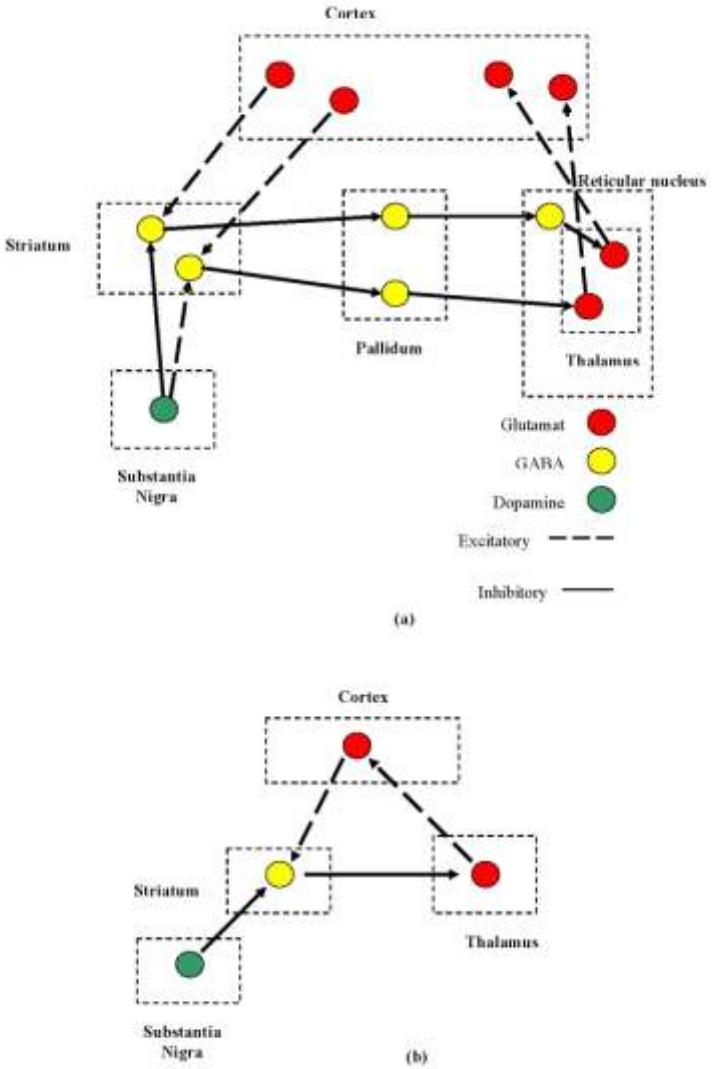

Figure 2. The neuronal circuitry of the brain which is prone to defect in schizophrenia (a) complete circuit (b) simplified circuit.

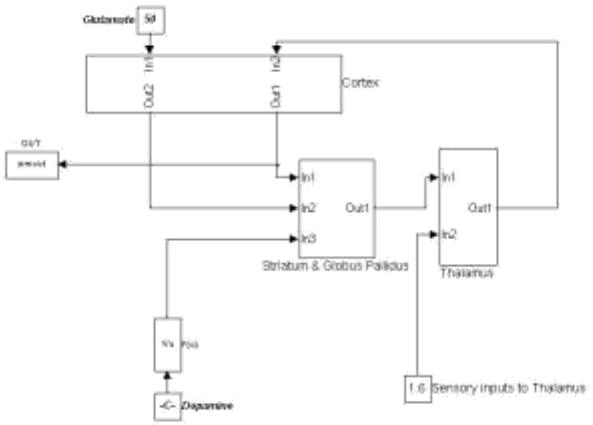

Figure 3. Block diagram of our proposed model.

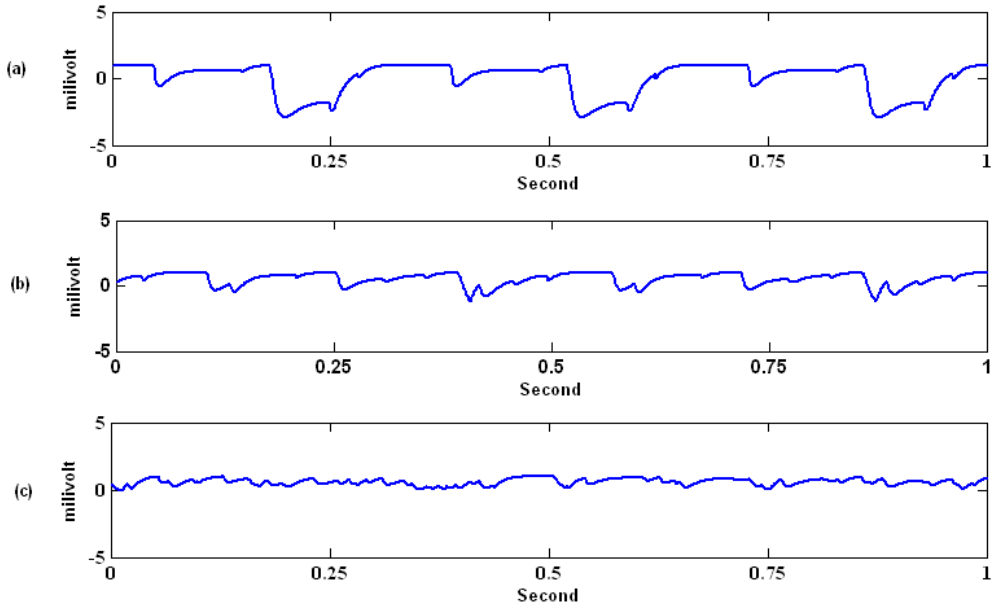

Figure 4. The effect of different amounts of dopamine on the mathematical model of pyramidal cell activity. a) normal state, b) moderately increased dopamine, and c)severely increased dopamine.

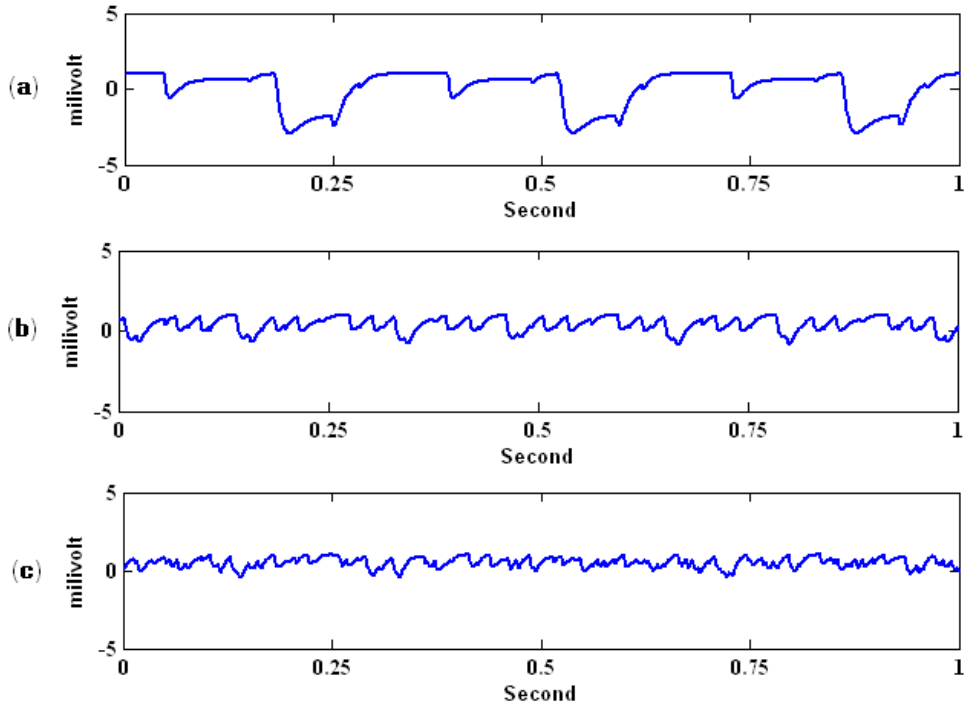

Figure 5. The effect of different amounts of glutamate on the mathematical model of pyramidal cell activity. a) normal state, b) moderately decreased glutamate, and c) severely decreased glutamate.

DISCUSSION

There is general agreement that abnormal brain function in schizophrenia involves an extended network of brain structures including the frontal, temporal and parietal cortices, the basal ganglia, the cerebellum, the hippocampus and the thalamus [5].

Hypo-functional dopamine states underlie Parkinson's disease and attention deficit hyperactivity disorder, and there is increasing evidence for dopamine hyperactivity in schizophrenia [8]. Dopamine is crucial in optimizing signal-to-noise ratio of local cortical microcircuits. This action of dopamine is achieved principally by dopamine effects on pyramidal and local

circuit neurons, which mediate neuronal excitability and recurrent inhibition. In schizophrenia, an abnormal dopamine activity appears to interfere with this process [9].

In this study we have examined the effect of dopamine hyperactivity on pyramidal cells using a mathematical model. Our simulation results show that while normal

activity of dopamine system causes the membrane potential of pyramidal cell to display a periodic bursting behavior, hyperactivity of this system brings about irregular and aperiodic patterns of activity. These patterns can be interpreted as a disturbance in information processing in local neuronal circuits in striatum and thalamus (Figure 4)

Moreover, it is proposed that hypo-glutamatergic conditions result in reduced activation of the striatal complex and may induce psychotic symptoms [1]. Thus, we also investigated the role of glutamate activity in postsynaptic cell activity. Simulation results (Figure 5) indicate that hypo-glutamatergic conditions have the same effect on the membrane potential of pyramidal cells, i.e. aperiodic and irregular firing patterns. Although some hypotheses have been proposed about the role of glutamate in pathogenesis and treatment of schizophrenia, still this issue is in debate. Based on our mathematical modeling, we proposed that glutamate receptor activation may have good therapeutic results in schizophrenic patients. Surely, our hypothesis must be evaluated in the light of future mathematical modeling and experimental studies on animal models or clinical trials.

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