Mathematical model of epileptic discharge propagation

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Abstract. Mathematical modelling of epileptic activity of a nervous tissue is an open problem. The previously developed biophysical model Epileptor-2 which describes the excitability of the neural network and the ionic dynamics reproduces ictal (convulsive) and interictal (usually pre-convulsive) discharges as a spatially homogeneous activity. To describe the spatial propagation of the discharges across the cerebral cortex a generalization of the model is proposed, based on an elliptical equation that takes into account the propagation of neuronal impulses via axodendritic trees. Simulated spatio-temporal patterns of extracellular potassium concentration as of the main characteristic of spatial excitability reflect the wave-like nature of the discharge propagation and are comparable with experimental observations. The propagation of neural impulses via axo-dendritic trees may play the main role in the mechanism of propagation of ictal discharges.

1. Introduction

According to the World Health Organization, the epilepsy is a chronic neurological disease of the human brain, characterized by repeated epileptic seizures that associated with abnormal intense electrical neural discharges.

Despite ongoing studies, the mechanisms of generation and propagation of these discharges are not yet fully understood. These discharges are of interest for mathematical modeling because they reflect the regime of strong synchronization of neuronal activity, which is simpler than the regime of normal functioning. On the other hand, epileptic discharges affect the mechanisms of dynamic changes in ionic concentrations which requires a more complete mathematical description. Thus, the consideration of spatial propagation of epilepsy requires a reduced but biophysically detailed model able to reproduce repeating discharges.

Experimentally registered discharges are of two types – ictal and interictal. Ictal discharges refer to the seizure, each lasting several tens of seconds. Interictal discharges pass between seizures or precede them, lasting about a second [1]. In this paper, the previously proposed biophysical model of Epileptor-2 [2] is extended with an equation that allows testing one of the hypotheses about a mechanism of the spatial propagation of the discharges across the cerebral cortex.

The first hypothesis is based on the diffusion propagation of potassium ions in extracellular space and the excitation effect of an increased concentration of these ions. In this case, discharges that occur in a focus of activity increase the concentration of potassium locally, and the diffusion increases the concentration on the periphery of the focus, thereby increasing the excitability of the nervous tissue and
leading to the spread of the discharges. Although, in the framework of this hypothesis the speed of activity propagation turns to be low [3].

The second hypothesis is based on the spread of epileptic neural activity via axonal and dendritic trees of the cortical neurons without a contribution of the diffusive propagation of the potassium. This hypothesis is considered in the present work.

2. Model

2.1. Governing equations of the Epileptor-2

Model Epileptor-2 describes the excitability of the neural network and ion dynamics [2]. This model is alternative to the previous more abstract model “Epileptor” [4], in contrast to which the model Epileptor-2 is expressed in terms of variables that have physical meaning. Such a biophysical interpretation allows experimental verification of the model. The basic equations of the model are ordinary differential equations for four variables: extracellular potassium concentration $[K]\_o$, intraneuronal sodium concentration $[Na]_i$, membrane depolarization $V(t)$ and synaptic resource $x^D(t)$. These equations are as follows (see Table 1 for parameter notations):

$$\frac{d[K]_o}{dt} = \frac{[K]_{bath} - [K]_o}{\tau_K} - 2\gamma I_{pump} + \delta [K]_o v(t)$$

$$\frac{d[Na]_i}{dt} = \frac{[Na]_i^0 - [Na]_i}{\tau_{Na}} - 3I_{pump} + \delta [Na]_i v(t)$$

$$C \frac{dv}{dt} = -g_L V(t) + u(t)$$

$$\frac{dx^D}{dt} = \frac{1-x^D}{\tau_D} - \delta x^D x^D v(t)$$

The dynamics described by these equations is driven by $v(t)$, the firing rate of an excitatory population. The inhibitory population firing rate is supposed to be proportional to the firing rate of the excitatory population. The firing rate is calculated with a sigmoidal input-output function:

$$v(V(t)) = v_{max} \left[ \frac{2}{1+\exp(-2(V(t)-V_{th})/\kappa_v)} - 1 \right]_+$$

where $[x]_+$ is equal to $x$ for the positive argument and 0 otherwise.

$I_{pump}$ is the $Na^+ / K^+$ pump current taken from Cressman et al. [5] in the form:

$$I_{pump} = \rho/(1 + \exp((3.5 - [K]_o)(1 + \exp((25 - [Na]_i)/3)))$$

$u(t)$ is the input current, which includes the potassium depolarizing current $g_{K,\text{leak}}$, the synaptic drive $g_{\text{syn}}$ and the noise $\xi(t)$. The equation for the input current reads

$$u(t) = g_{K,\text{leak}}(V_K(t) - V_K^0) + g_{\text{syn}}v(t)(x^D(t) - 0.5) + \sigma \xi(t)$$

$V_K$ is the potassium reversal potential. It depends on the ion concentrations via the Nernst equation in the form:

$$V_K = 26.6 \text{ mV } \ln \left( \frac{[K]_o}{130 \text{ mM}} \right)$$

$$V_K^0 = 26.6 \text{ mV } \ln \left( \frac{[K]_o^0}{130 \text{ mM}} \right)$$

The Gaussian white noise $\xi(t)$ has zero mean and unity dispersion, $\langle \xi(t)\xi(t') \rangle = \tau_m \delta(t - t')$

The parameters are given in Table 1.

The above equations (1-9) fully describe the population activity. In order to visualize the activity of a representative neuron, such neuron is modeled as an adaptive quadratic integrate-and-fire neuron [6].
that receives the population input \( u(t) \). The equations for the membrane potential \( U(t) \) and the adaptation current \( w(t) \) are as follows:

\[
C \frac{du}{dt} = g_u(U - U_1)(U - U_2) - w + u + I_a \quad (10)
\]

\[
\tau_w \frac{dw}{dt} = -w \quad (11)
\]

\[
\text{if } U > V^T \text{ then } U = V_{\text{reset}}, \ w = w + \delta w \quad (12)
\]

\( U = -70 \text{ mV} \) is the initial conditions and \( I_a = 116 \text{ pA} \) is the tonic current. The representative neuron does not affect the population dynamics.

### Table 1. The system parameters.

| Parameter | Value | Name |
|-----------|-------|------|
| \( \tau_K \) | 100 s | time constant for potassium ionic dynamics |
| \( \tau_{Na} \) | 20 s | time constant for sodium ionic dynamics |
| \( \tau_m = C/g_L \) | 10 m\( s \) | time constant for membrane polarization |
| \( \tau_D \) | 2 s | time constant for synaptic depression |
| \( \delta[K]_0 \) | 0.02 mM | potassium concentration increments at spike |
| \( \delta[Na]_i \) | 0.03 mM | sodium concentration increments at spike |
| \( \delta x_b \) | 0.01 | synaptic resource increments at spike |
| \( \sigma / g_L \) | 25 mV | noise amplitude |
| \( \rho \) | 0.2 mM/s | maximum pump flux |
| \( \gamma \) | 10 | volume ratio |
| \( G_{syn} / g_L \) | 5 mV \( \cdot s \) | postsynaptic charge |
| \( g_{K,\text{leak}} / g_L \) | 0.5 | potassium leak conductance |
| \( [K]_0 \) | 3 mM | initial extracellular potassium concentration |
| \( [K]_{\text{bath}} \) | 8.5 mM | bath potassium concentration |
| \( [Na]_i \) | 10 mM | resting intracellular sodium concentration |
| \( \nu_{\text{max}} \) | 100 Hz | maximal rate |
| \( V_{th} \) | 25 mV | threshold potential |
| \( k_y \) | 20 mV | gain |

### Table 2. The parameters of the representative neuron model.

| Parameter | Value |
|-----------|-------|
| \( g_u \) | 1.5 nS/mV |
| \( C \) | 1 nF |
| \( \tau_w \) | 200 ms |
| \( V^T \) | 25 mV |
| \( V_{\text{reset}} \) | -40 mV |
| \( \delta w \) | 100 pA |
| \( U_1 \) | -60 mV |
| \( U_2 \) | -40 mV |
| \( I_a \) | 116 pA |
2.2. The equation for spatial distribution

The Epileptor-2 model has been generalized by adding the equation of spatial propagation of firing along the cortex, introducing a relationship between the presynaptic firing rate \( \phi(t, x, y) \) and the somatic firing rate \( \nu(t, x, y) \) [7]:

\[
\frac{\partial^2 \phi}{\partial t^2} + 2\gamma \frac{\partial \phi}{\partial t} + \gamma^2 \phi - c^2 \left( \frac{\partial^2 \phi}{\partial x^2} + \frac{\partial^2 \phi}{\partial y^2} \right) = \left( \gamma^2 + \gamma \frac{\partial}{\partial t} \right) \nu(t, x, y)
\] (13)

where \( \gamma = c/\lambda; \ c \) is the average spike propagation velocity along the cortical tissue; \( \lambda \) is the characteristic length of the axo-dendritic connections.

Because the delays of spike propagation on the distance \( \lambda \) are small compared to the fastest time scale in equations (1-4), which is the membrane time constant \( \tau_m \), i.e. \( \lambda/c < \tau_m \), we assume that \( \gamma \to \infty \) and \( c \to \infty \). It simplifies the equation (13) to the following second-order elliptic equation:

\[
\frac{\partial^2 \phi}{\partial x^2} + \frac{\partial^2 \phi}{\partial y^2} = \frac{\phi - \nu(t, x, y)}{a^2}
\] (14)

This equation as a part of the system of ordinary differential equations of the Epileptor-2 model was integrated using the implicit numerical scheme based on the spatial variables factorization and the Thompson’s algorithm. The system of ordinary differential equations (1-12 and 14) was integrated by the Euler’s method with the time step \( dt = 0.5 \) ms. Solutions with a smaller time step did not change the solution significantly.

3. Results

Our simulations have reproduced the spatial-temporal patterns of activity of the cortical neural tissue during the generation of epileptic ictal discharges. Since one of the key roles in the mechanisms of the discharge generation belongs to the dynamics of the extracellular potassium concentration, one of the main experimental observations is the optical imaging of potassium distribution along the surface of the mouse brain cortex at different time moments after local application of the proepileptic agent 4-AP [8]. This experiment shows the wave-like pattern of the spread of a zone of elevated potassium and allows estimations of the average potassium concentration at various points of the cortical area.

In the model, we considered a square-shaped domain of nervous tissue with a small circular central zone with increased excitability \( G_{syn}/G_L = 5 \) mV \( \cdot \) s in the center and \( G_{syn}/G_L = 1 \) mV \( \cdot \) s at the periphery. Characteristics of the simulated activity were recorded at two points: in the center and at the periphery.

3.1. Central point

The membrane potential of the neuron (Figure 1A) and the concentrations of potassium and sodium (Figure 1B, D, solid lines) reflect the spontaneous occurrence of discharges. As seen, when the potassium concentration reaches a certain threshold level, short spontaneous, interictal-like discharges begin to occur, which are united in an one cluster constituting an ictal discharge. Sodium concentration increases during and ID. When a certain high level of the intracellular sodium concentration is reached, the potassium-sodium pump activates (Figure 1C) and the burst terminates. The observed activity is similar to that reproduced with the original Epileptor-2 model [2]. Thus, the proposed here extended model clearly visualizes the characteristic features of epileptic discharges. As shown [2], IDs discharges are quasiperiodic oscillations (Figure 1A), which consist of clusters – short bursts (SBs) similar to interictal discharges (IID) (Figure 1B) [1].

3.2. Point close to the periphery

The population of neurons on the periphery, involved in seizure generation, behave similar to the populations in the center. That is why, for a representative peripheral point S2 only graphs for concentrations are shown in Figure 1C, D (dashed lines). The signals at the site S2 are delayed relative to those at the site S1.
Figure 1. Simulation of ictal discharges (IDs). A, The membrane depolarization during a series of IDs. B, Zoomed plot for the membrane depolarization, showing one ID consisting of interictal-like bursts. C, The intracellular sodium concentration (solid line is at site S1 shown in panel E; dotted line is at site S2) and the activity of the potassium-sodium pump (grey line). D, The extracellular potassium concentration (solid line at S1; dotted line at S2). E, 2D-patterns of the potassium distribution. Simulated domain is a square with a side of 10 mm.
3.3. Spatio-temporal patterns of activity
The main characteristic of spatial aspects of excitability is the distribution of the extracellular potassium concentration. The obtained solutions reflect the wave-like nature of the discharge propagation (Figure 1E), with a spherical, uniform wavefront clearly visible in the figure. The wave velocity during propagation remains almost constant, minor deviations are due to residual errors of the integration solution of the system (1-9, 14).

4. Discussion
The IDs simulated with the proposed model are similar to those registered in slices of the rat entorhinal cortex and in vivo [1,2]. The computer model has helped to analyze the propagation of the ictal discharge wave and assess the factors affecting its speed. For a given value of the connection length \( d = 0.175 \text{ mm} \) the speed is about \( 0.26 \text{ mm/s} \). The speed of the wavefront is comparable with the experimental estimations, which are of order of tenths of millimeters per second.

Wenzel et al. [9] reported the data of fast two-photon calcium imaging combined with local field potential (LFP) recordings of the spread of locally induced (with 4-AP or picrotoxin) seizures in anesthetized and awake mice. The propagation velocity of the seizure front measured in anesthetized mice was \( 0.64 \text{ mm/s} \).

Ma et al. [10] simultaneously recorded voltage-sensitive and intrinsic optical signals to measure neurovascular coupling between membrane potential changes and cerebral blood flow in vivo in a rat model of partial onset neocortical ictal events using focal injection of 4-aminopyridine (4-AP). This was done to precisely characterize and understand the spatiotemporal dynamics of the coupling between the neuronal activity and the hemodynamic response as seizures evolve. The propagation velocity in response to the onset of the seizure was \( 0.45 \pm 0.12 \text{ mm/s} \), that is, the orders also coincide.

As a result, the propagation of neural impulses via axo-dendritic trees may play the main role in the mechanism of propagation of ictal discharges. This hypothesis seems to be more feasible in comparison with that based on the potassium diffusion.

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