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Multilevel mathematical model of epileptic seizures

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Motivation and Aim: There are three approaches to brain modeling: nanoscopic (cellular), focusing on individual neurons; microscopic (population), simulating interactions among neuron populations; and mesoscopic (regional), examining entire brain regions.

The microscopic approach's applicability is limited by the high computational complexity of its models. Mesoscopic models, using methods akin to statistical physics, reduce micro-level complexity to achieve macro-organization. These models simulate neuronal fields instead of individual neurons, generating accurate electroencephalogram (EEG) and local field potential (LFP) signals. However, they often lack biological interpretation, which significantly complicates result validation. Nanoscopic models simulate biophysical processes within individual neurons, providing strong biological significance but failing to reproduce brain signals like EEG, limiting their clinical applicability.

The Virtual Brain (TVB) project, which uses mesoscopic models to forecast surgical outcomes, has made significant progress and is now undergoing clinical trials [1]. However, TVB models do not consider the nanoscopic factors influencing seizures, such as receptor dynamics, gene and metabolic networks, signal transmission pathways within neuron, etc. Our team is developing the BioUML (Biological Universal Modeling Language) platform, which is well-suited for describing the nanoscopic level [2].

Thus, we aim to recreate a series of existing epilepsy models in BioUML that qualitatively reproduce seizure phenomena and then link the mesoscopic and nanoscopic levels, bypassing the microscopic. This will allow the generation of model electrophysiological signals and comparison with experimental recordings, while drug therapy modeling will be conducted at the nanoscopic level.

Methods and Algorithms: We developed a multilevel model using a modular approach in the BioUML platform, decomposing complex systems into modules. This enables the integration of multiple biological system levels within a single model, facilitating the exploration of interactions within subsystems and between different organizational levels.

Numerical calculations used patient-specific connectivity and delay matrices to determine signal transmission strength and time delays due to limited speed of nerve impulse propagation.

The model's equations include stochastic terms to describe natural brain network noise. We integrated a solver for stochastic differential equations based on the Euler–Maruyama method in BioUML.

Results: The multilevel model includes one regional submodel that models interactions between brain regions, with each region corresponds to a cellular submodel calculating

ion concentration dynamics, and a receptor submodel determining the dynamics of AMPA receptor trafficking in dendritic spine (Fig. 1). The receptor submodel regulates synaptic transmission efficiency, while the cellular submodel serves as the excitation source for the corresponding brain region.

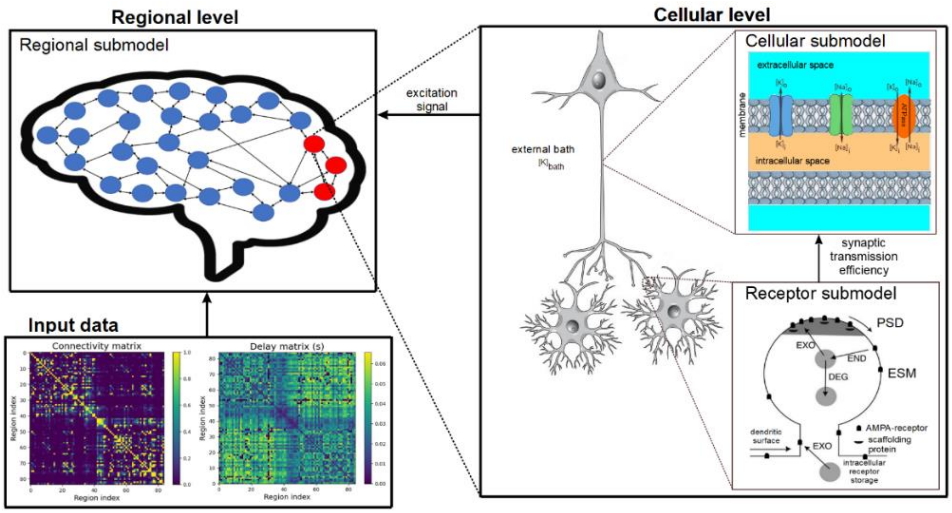

Fig. 1. Multilevel model structure

Simulations were performed for a system of 84 regions, with the epileptic focus set in region 64, corresponding to the right parahippocampal gyrus. All other regions were considered healthy, incapable of autonomous epileptiform activity.

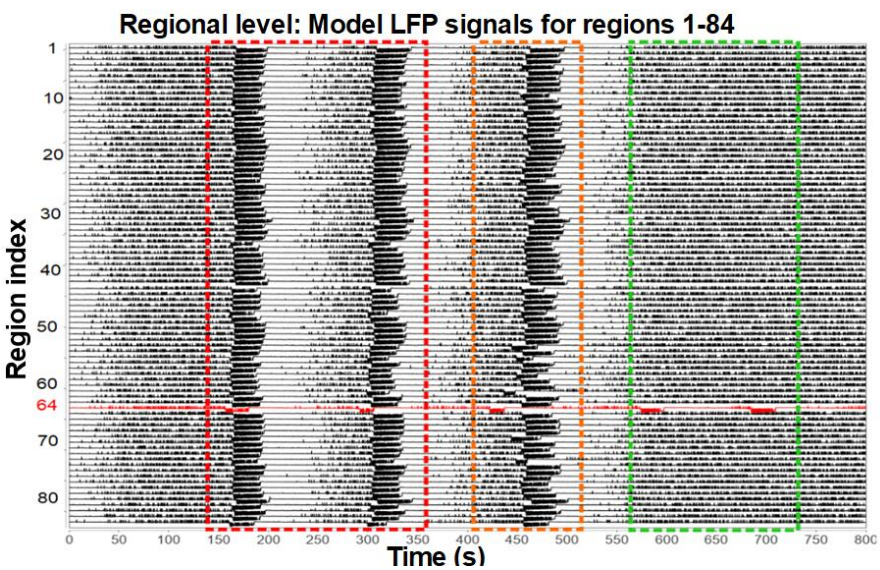

Fig. 2. Dynamics of the regional submodel. The epileptogenic region signal is red, healthy region signals are black. Red dashed frame highlights seizure spread throughout all brain regions, orange dashed frame indicates delayed propagation, and green dashed frame shows localized seizures

Figure 2 depicts the dynamics of model local field potentials for all considered brain regions. The seizure first emerges in the epileptogenic region. It then propagates to

healthy regions, and epileptiform activity is concurrently observed across all brain zones. The system's excitation gradually diminishes, leading to subsequent ictal periods where either the recruitment of healthy regions occurs with a significantly greater delay compared to the initial period, or the seizure is entirely localized in the epileptogenic region.

In Figure 3, the dynamics of the cellular submodel associated with the epileptogenic region is presented. During each seizure event, there is an increase in extracellular potassium concentration, leading to membrane depolarization, and the generation of action potentials by the cell.

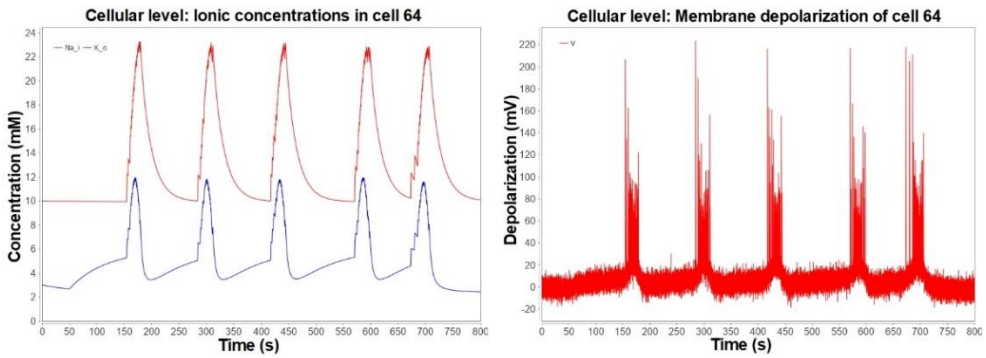

Fig. 3. Dynamics of the cellular submodel. Left: ion concentrations (red – intracellular sodium, blue – extracellular potassium). Right: membrane depolarization

It is demonstrated that the dynamics of individual submodels used in the structure of the multilevel model corresponds to the dynamics of the original models, validated by comparison with experimental data conducted by their authors. Theoretical justification of the connections uniting submodels into a unified structure is provided.

Conclusion: This study presents a novel developed multilevel mathematical model of epileptic seizures, describing interactions between brain regions while considering the biophysical processes occurring within individual neurons.

The constructed model for the first time makes it possible to simulate the dynamics of seizure onset, propagation and termination simultaneously at the cellular and regional levels of brain organization.

Analysis of numerical simulation results of the model demonstrated a qualitative reproduction of the main processes observed during seizures. Thus, the constructed multilevel model can be reasonably used in epilepsy research.

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