Low-Frequency Electrical Stimulation in Epilepsy: a Biophysical and Mathematical Representation

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Abstract:

The biological mechanisms underlying the recurring seizures in the epileptic brain remain poorly understood. As a consequence of that, a substantial proportion of epilepsy patients cannot be sufficiently treated by currently available treatment options. Newly developed brain stimulation protocols have been shown to successfully reduce the seizure rate (1,2). However, their success critically depends on chosen stimulation parameters, such as the time point, amplitude and frequency of stimulation. This study focuses on the seizure delaying effect of 1 Hz stimulation in an animal model of epilepsy. We study this effect using a computational model, a modified version of the so-called Epileptor-2 model (3), in close comparison with a real dataset of local field potential recordings from four hippocampal rat brain slices under high potassium condition. The Epileptor-2 model describes the dynamics of population potential, synaptic resources, potassium and sodium ions.

First, we study the parameters that control the duration of seizures and inter-seizure intervals. These parameters are then optimized to fit the model to the data. In the experiments, potassium was added to the extracellular bath until spontaneous seizures appeared. We study

this phenomenon through bifurcation analysis, based on the potassium bath parameter Kbath, and a slow ramp up of Kbath (Kbath = ε, with $0 < \varepsilon \ll 1$) in order to reproduce the transition between the different dynamical states. Thus, different thresholds (appearance of seizure, passage to status epilepticus) can be defined. In addition, corresponding to experimental observations, we show that seizures can be induced by external stimulations, from the moment when a certain potassium concentration is exceeded. Next, we reproduce the experimental stimulation protocol and the seizure delay in the model. For instance, we demonstrate that it is possible to delay seizures indefinitely in the model for as long as it is stimulated, which can be explained by the emergence of a new stable attractor. Here, the effect of the stimulation is balanced by the activity of the Na-K pumps, which counteracts the accumulation of potassium in the extra-cellular medium, and therefore prevents seizures. We will also show that this phenomenon is preserved even in the presence of noise. Beyond confirming that the model can produce the delay effect, we establish the presence of a critical value for the amplitude of the stimulation, and the,moment at which to stimulate. Finally, we ensure that the stimulation itself does not cause small-scale seizures: based on slow-fast theory, we produce a 3D-bifurcation diagram to break down the bifurcation diagram into the different components of the epileptic phenomenon (seizure and interseizure domain), and we show that the attractor induced by stimulation lies outside the seizure domain.

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