Epilepsy etiology

A study on the principles leading to seizure events

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1. Introduction

For our project we wanted to study how a epileptic seizure-like event occurs both in the microscale and the mesoscale. Our main objective is to model seizures using a biological approach, focusing on the ion channels dynamics of a single neuron and moving to population dynamics for hippocampal and neocortical networks.
Our goal is to show that, by manipulating parameters, we can simulate the anomalous behaviour seen in the above mentioned event.
The final goal was to determine which of the considered parameters is the main cause of the considered disease, and verify that it reflects the already established biological knowledge.

2. Methods

We decided to divide our work into two separate segments to better highlight the differences in the two considered scales.

Part 1: *Microscale*

For the first simulation we opted for the Hodgkin-Huxley model, in order to leverage the way in which it models the conductances - in particular Na+ and K+.
In the context of single neurons, epileptic activity arises from the dysfunction of the channels involved in the generation of action potentials: some Na^+ channels fail to fully inactivate, leading to a persistent Na^+ influx that prolongs depolarisation, making the neuron more likely to fire repetitive action potentials, and therefore increasing excitability; also reduced K^+ outflow leads to a delay in repolarisation, causing prolonged neuronal firing.

After defining the differential equations characterising the chosen model, including the external current and the ionic currents we initialised the parameters using the same values as in in Hodgkin and Huxley, 1952. Following the setting of a time interval of 120 ms and the definition of the parameters initial conditions, we proceeded to the resolution of the ODEs using the Runge-Kutta method, through a dedicated SciPy function.

We first plotted the activity resulting from a normal functioning neuron. The injection of an external current leads to the generation of a sequence of action potentials, where all the spikes show similar amplitude and the rate is constant.

Then a seizure, again for a single neuron , was modelled by defining a dedicated time factor to show a dynamic change in the neuronal activity at 50 ms into the simulation. This factor was incorporated in the sodium and potassium conductances,

so to make them respectively grow and decay at the time indicated. The resulting signal is denoted by a clear increase in both the amplitude and the rate of the spikes after the variation of the conductances, confirming the effect of sustained depolarisation and ineffective repolarisation which is biologically observable.

Please note that all the other parameters were kept fixed through the whole experiment, and therefore the rise of the seizure event was determined only by the variation in the conductances, which reflects the impairment of the ionic channels of a pathologic neuron.

Part 2: *Mesoscale*

This second section has its foundations in the 2002 academic article on this same subject by F. Wendling, F. Bartolomei, J. J. Bellanger and P. Chauvel.

Here a full neuronal population was considered, so the focus was moved from molecular level dynamics to the interaction between large groups of neurons, therefore we transitioned to a model better suited for this task. The **Wendling** model takes into consideration the interaction between three populations of neurons located in the hippocampus and in the cerebral neocortex, specifically:

- excitatory pyramidal cells
- slow inhibitory interneurons
- fast inhibitory interneurons

The inhibitory populations play a crucial role in regulating the firing of the pyramidal cells. In particular the somatic projections from the subset of GABA fast interneurons onto the subset of pyramidal are controlled by the subset of dendritic GABA slow interneurons. These groups are each represented by one main parameter, respectively the excitatory ("A"), slow inhibitory ("B") and fast inhibitory ("G") synaptic gain, which are integrated in feedback loops from interneurons to pyramidal cells and in the control of fast inhibitory interneurons by slow ones. The gains are incorporated in three dedicated impulse response functions $h(t)$ each introducing a second order ordinary differential equation which is represented in the model by a pair of first order ODEs, and are then combined together with a sigmoidal transfer function and 7 parameters representing different synaptic connections to establish 10 differential equations to model the populations.

Following the indications from the paper, we varied the parameters A, B and G to simulate a full epileptic event, starting from the resting state.
At first we set standard values for normal background activity as established by Jansen & Rit (1995) and then we moved to 5 other states, in order: emerging of spikes, discharge of spikes, slow rhythmic activity, low-voltage rapid activity and slow quasi-sinusoidal activity. The output plots are EEG signals describing each of these conditions.

Since the states all represent a part of a full event, we then plotted a comprehensive EEG signal, concatenating the 6 previous configurations and smoothing the transitions between them by setting a time window of 2 seconds around each change, in which the three parameters change of half the difference between the current state

and the following one. Finally we normalised with respect to the baseline to obtain a more realistic EEG.

3. Conclusions

Our model successfully verified the biological impairments that lead to epileptic events.

In the single-neuron case, the Hodgkin–Huxley model confirmed the crucial role of ion channels, with the primary dysfunction being a deficit in sodium channel inactivation coupled with impaired potassium channel activation. In the population model, the predominant issue was a reduction in the activity of dendritic GABAergic slow interneurons, represented by the B parameter. The reduction in B led to a rhythmic discharge—resulting from an increased excitation-to-inhibition ratio—followed by low-voltage rapid activity due to the disinhibition of fast inhibitory interneurons (reflected by the G parameter), which itself is influenced by the decrease in B.