2MDS

Multiscale Modeling of Dravet Syndrome

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The *Inria Exploratory Action 2MDS* is being co-directed by Fabien Campillo (MathNeuro), and Pierre Del Moral (Astral). Mathieu Desroches, head of MathNeuro project, and Serafim Rodrigues, head of the "Mathematical, Computational and Experimental Neuroscience" MCEN research group at BCAM are also participating in this project.

The aim of 2MDS is to develop a multiscale modeling framework for channelopathies, a group of diseases caused by the dysfunction of ion channels or their interacting proteins. These pathologies include the *Dravet Syndrome* (DS), a severe form of child epilepsy. This project will also have a substantial experimental component, conducted by our collaborator Serafim Rodrigues in his experimental laboratory[1], also in collaboration with Juan Manuel Encinas of the Basque center for neuroscience, an expert in DS [4].

1 Biological context

Dravet Syndrome is a severe form of epilepsy that affect children; it is estimated to affect 1 in 40,000 worldwide [8]. It typically appears in babies within a year after birth, and it is characterised by the occurrence of recurrent seizures and a marked sensitivity to temperature. It also manifests itself by causing delays in development, signs of autism spectrum disorder, and even brings an elevated risk of sudden unexplained death in epilepsy (SUDEP).

A majority of the children suffering from DS have a mutation on a specific gene, *SCN1A*, which codes for the voltage-gated sodium channel α-subunit $Na_V1.1$, which are highly expressed in GABAergic (inhibitory) neurons. More precisely, this particular mutation causes a loss of function of the channel on such inhibitory neurons. As a results, they inhibit less the pyramidal (PY) cells, which are the main players underpinning the electrical activity of the brain. This results in an overactivity of the PY cells, i.e. a stronger propensity to fire action potential, also referred to as *hyperexcitability*. The elevated firing of PY cells is a key element of epileptic seizures.

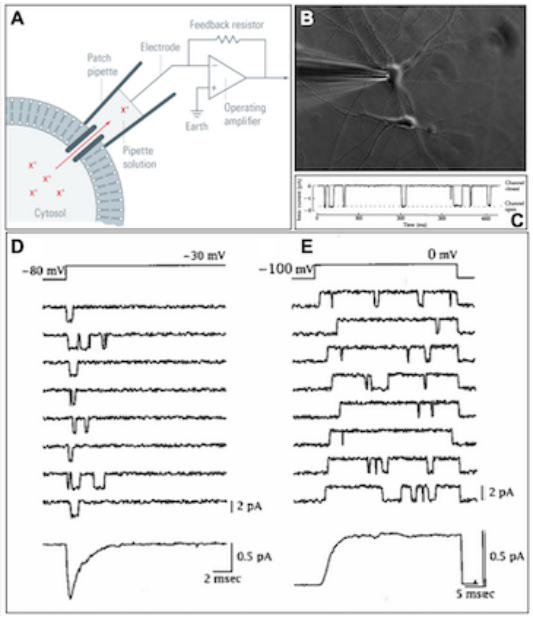

Fig. 1. *Multiscale experiments on ionic channels.*

Several models of DS exist, either based upon standard Hodgkin-Huxley conductance formalism, or considering the neuronal population level and using Wilson-Cowan type neural mass models. In previous work done within MathNeuro through the PhD thesis of Louisiane Lemaire [5], we have modeled SCN1A mutations, both loss and gain of function, using the former,

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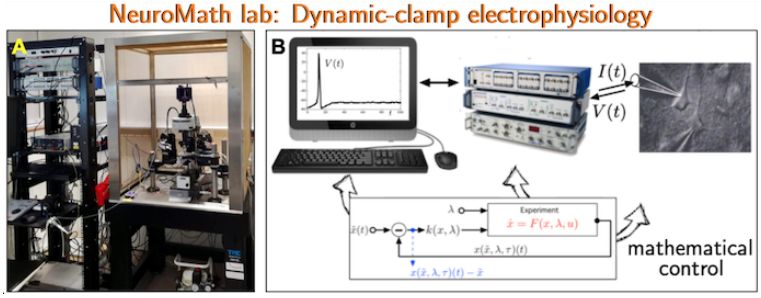

Fig. 2. *Dynamic-clamp electrophysiology in the NeuroMath laboratory (S. Rodrigues, BCAM).*

acting macroscopically on the activation curve of the sodium channel model in order to simulate both types of mutations.

In the 2MDS project, we will go beyond our previous work by developing a truly biophysical multiscale model targeted for DS, starting with a Markov model of $\mathrm{Na_V}1.1$ with specific states affected by the mutation and temperature sensitivity based upon thermodynamical principles. We will then consider both the microscopic, the mesoscopic and the macroscopic scales, *in link with experiments. So what we are proposing is not incremental but a genuinely substantial step in the multiscale modeling of such pathological neuronal states.*

This project will also have a substantial experimental component, conducted by our collaborators Serafim Rodrigues and Juan Manuel Encinas. We will perform single-channel patch-clamp recording to observe the behavior of one $\mathrm{Na_V}1.1$ channel and compare it with our model (Fig. 1). We will also use the dynamic-clamp technique in order to apply closed-loop control to this experimental setup and control the behavior of neurons from DS mice model (Fig. 2).

2 Mathematical framework

The central model will be a detailed model of interacting neurons, where the voltage activity of each neuron is itself in interaction with the activity of families of ion channels, sodium and potassium, present along its axon. The neurons are divided into two classes, inhibitory and excitatory neurons. This model will be presented in the form of **interacting particles**, each particle evolving according to a piecewise-deterministic Markov process (PDMP). We will first focus on the dynamics of a single neuron, then on the dynamics of a neuron network of limited size where the randomness might not be averaged out. The considered mutation will be modeled at the level of the PDMP dynamics of ion channels.

Hence we consider two families of neurons: the set $\mathcal{N}^{\mathrm{i}}$ of inhibitory neurons and a set $\mathcal{N}^{\mathrm{e}}$ of excitatory neurons. Let $\mathcal{N} = \mathcal{N}^{\mathrm{i}} \cup \mathcal{N}^{\mathrm{e}}$. The mutation studied, in link with DS, will affect only inhibitory neurons $\mathcal{N}^{\mathrm{i}}$. The dynamics of the membrane potential V^q of neuron $q \in \mathcal{N}$ will be described by:

$$C_m \dot{V}^q(t) = I - \overbrace{\kappa^q_{\mathrm{Na}}(t)\,(V^q(t) - \mathbf{v}_{\mathrm{Na}})}^{\text{sodium current}} - \overbrace{\kappa^q_{\mathrm{K}}(t)\,(V^q(t) - \mathbf{v}_{\mathrm{K}})}^{\text{potassium current}} - \underbrace{\kappa_{\mathrm{L}}\,(V^q(t) - \mathbf{v}_{\mathrm{L}})}_{\text{leakage current}} - \underbrace{\kappa^q_{\mathrm{I}}(t)\,(V^q(t) - \mathbf{v}_{\mathrm{I}})}_{\text{interaction current}} \tag{1}$$

(κ_{L} constant). In the classical Hodgkin–Huxley model with no interaction ($\kappa^q_{\mathrm{I}} = 0$) we have:

$$\kappa^q_{\mathrm{Na}}(t) = g_{\mathrm{Na}}\,[m^q(t)]^3\,h^q(t) \qquad \dot{m}^q(t) = \alpha_m(V^q(t))\,(1 - m^q(t)) - \beta_m(V^q(t))\,m^q(t) \tag{2a}$$

$$\dot{h}^q(t) = \alpha_h(V^q(t))\,(1 - h^q(t)) - \beta_h(V^q(t))\,h^q(t) \tag{2b}$$

$$\kappa^q_{\mathrm{K}}(t) = g_{\mathrm{K}}\,[n^q(t)]^4 \qquad \dot{n}^q(t) = \alpha_n(V^q(t))\,(1 - n^q(t)) - \beta_n(V^q(t))\,n^q(t) \tag{2c}$$

and the voltage-dependent rate functions α's and β's are identified empirically.

Another possibility, which we want to explore, is to assume that the coefficients of the voltage equation (1) depend on the state of **continuous time Markov chains** (CTMCs), each of the sodium or potassium ion channels being modelized by a CTMC:

$$S^{q,\ell}_t \text{ (resp. } P^{q,\ell}_t) = \text{ state of the sodium (resp. potassium) gate } \ell \in \{1, \dots, L\}$$

whose rate matrices, also called Q-matrices, depend on $V^q(t)$ [1]. The mutation of the gene SCN1A can be directly modeled at the level of the state space of CTMCs and/or their transition matrices, extending for example the work of Lemaire *et al* [6, 7].

Then we take $\kappa^q_{\mathrm{Na}}(t)$ (resp. $\kappa^q_{\mathrm{K}}(t)$) as a function of the state of all the sodium (resp. potassium) channels. For example we can take $\kappa^q_{\mathrm{K}}(t) = g_{\mathrm{K}}\,[N^q_t]^4$ where N^q_t is the proportion of potassium gates that are opened. The rate matrices can be compared to the rate functions α's and β's of (2). We also wish to investigate different rate functions than the ones empirically identified in the classical Hodgkin–Huxley model; in particular, we wish to use a *free energy* approach proposing a more constructive vision of these rates functions [3].

Finally, the interaction term $\kappa^q_{\mathrm{I}}(t)$ may be present on excitatory neurons $q \in \mathcal{N}^{\mathrm{e}}$ as a functional of the voltage state of all inhibitory neurons $q \in \mathcal{N}^{\mathrm{i}}$.

The detailed stochastic model:

$$\left\{ V^q(t)\,,\, (S^{q,\ell}_t\,,\, P^{q,\ell}_t)_{\ell=1\cdots L} \right\}_{q\in\mathcal{N}, t\geq 0}$$

can be viewed as a set of **interacting PDMP particles**. A simpler model would be to adopt a more population dynamics view where CTMCs would represent population sizes (healthy neurons/mutated neurons).

Under the classical assumptions of channel independence and large channel population sizes, the stochastic model converges to the classical Hodgkin-Huxley model.

It is therefore relevant to explore two tracks: on the one hand, how do these models behave in the presence of a channel population size that does not allow to wipe-out the randomness ? On the other hand, how do these models behave in the presence of correlation between the state of the channels ?

This will allow us to simplify, at a meso-scale, the detailed stochastic model by proposing by diffusion approximation more practical stochastic differential equation models.

For large size neuron populations, the interaction term in the voltage equation for excitatory neurons can also be simplified using a mean-field approximation [2]. In the case of smaller populations, stochastic deviations from this mean-field approximation should also be considered.

3 Objectives

The objective of this research project is to develop a multiscale computational framework that integrates micro-, meso-, and macro-scale models with new methods of Monte Carlo simulation to study the dynamics of neuronal systems in the context of Dravet syndrome, and to compare our multiscale model with multiscale electrophysiological experiments. Specifically, the project aims to investigate how the biophysical properties of certain sodium ion channels affect the behavior of individual neurons and the emergent dynamics of neural networks in the presence of SCN1A mutations.

CTMCs can model the behavior of the ion gates in the voltage-gated sodium channels. In CTMCs, the state of the system changes stochastically over time, with the transitions between the different states governed by transition rates. The Hodgkin-Huxley conductance formalism can be used to model the voltage-dependent conductance of the sodium channels.

By coupling the CTMC models of the ion gates to the Hodgkin-Huxley conductance formalism, it is possible to simulate the behavior of the voltage-gated sodium channels in the presence of SCN1A mutations. CTMCs can capture the stochastic behavior of the ion gates, while the Hodgkin-Huxley formalism can capture the voltage-dependent conductance of the channels.

By simulating the behavior of the voltage-gated sodium channels in the presence of SCN1A mutations using the coupled CTMC and Hodgkin-Huxley models, it is possible to investigate how the mutations affect the behavior of the channels and the excitability of neurons. This can provide insights into the mechanisms underlying Dravet syndrome and can inform the development of new treatments for the disorder.

Methodology

1. Microscopic scale. Develop a stochastic model of ion channels on axons that incorporates the biophysical properties of ion channels and the effect of SCN1A mutations on channel function. The model will be based on Hodgkin-Huxley formalism and will be extended to include stochasticity in the gating of ion channels. The model will also take into account the effects of mutations on ion channel kinetics and conductance. Use Monte Carlo simulation with a novel adaptive algorithm that efficiently captures the effects of ion channel stochasticity to simulate the behavior of individual ion channels and their interaction with the surrounding membrane.

2. Mesoscopic scale. Develop a compartmental model of the neuron that includes the soma, dendrites, and axon. Incorporate the stochastic ion channel model developed in step 1 with Monte Carlo simulation to simulate the behavior of the neuron at the meso-scale. The model will include the dynamics of ion channels, ion concentrations, and membrane potential. Study the effects of SCN1A mutations on the neuronal firing patterns and action potential propagation.

3. Macroscopic scale. Develop a network model of neurons that includes populations of excitatory and inhibitory neurons. Incorporate the meso-scale neuronal model developed in step 2 with Monte Carlo simulation to simulate the behavior of the neural network. The model will include synaptic transmission, plasticity, and the dynamics of ion concentrations. Study the emergent dynamics of the network, such as synchronization and oscillations, and investigate how SCN1A mutations affect these dynamics.

4. Multiscale integration. Integrate the micro/meso/macro-scale models with the novel adaptive Monte Carlo simulation algorithm into a cohesive computational framework. Use the framework to simulate the behavior of neuronal systems at different scales in the presence of SCN1A mutations. Investigate how the properties of ion channels at the micro-scale affect the dynamics of neuronal networks at the macro-scale and how SCN1A mutations alter these dynamics.

5. Analysis. Analyze the simulations to identify the effects of SCN1A mutations on ion channel function, neuronal firing patterns, and network dynamics. Use statistical analysis and data visualization tools to quantify the effects of mutations and to identify key factors that contribute to the development of epileptic seizures in Dravet syndrome.

Expected Results

The proposed research project is expected to yield several important results, including:

- A novel multiscale computational framework that integrates micro-, meso-, and macro-scale models with a novel adaptive Monte Carlo simulation algorithm to simulate the behavior of neuronal systems in the presence of SCN1A mutations.
- Compare the model at every scale (micro, meso, macro) with electrophysiological experiments from our partner in Bilbao.

Our aim is to contribute to a better understanding of how SCN1A mutations affect the behavior of individual neurons and the emergent dynamics of neural networks, from the micro- to the macro-scale, and to get insights into the mechanisms underlying Dravet syndrome and the impact of SCN1A mutations on neuronal function. Also in a speculative perspective, it could help to identify key factors that contribute to the development of epileptic seizures in Dravet syndrome, which could inform the development of new treatments.

4 How the project is exploratory ?

This project aims to initiate a collaboration between two MathNeuro (F. Campillo & M. Desroches) and Astral (P. Del Moral) Inria teams, in close partnership with the Mathematical, Computational

and Experimental Neuroscience research group (S. Rodrigues) at BCAM Bilbao and in collabotation with the Basque Center for Neuroscience (Juan Manuel Encinas).

The exploratory aspect of the project comes in two components. First, in the mathematical and computational framework to be developed. Indeed, we will model DS at three separate scales (micro-, meso- and macroscopic, respectively), with three different mathematical frameworks (Markov chains, PDMPs, stochastic differential equations, McKean–Vlasov process, and deterministic mean-field limits, respectively) while respecting free energy principles from thermodynamics, which is more grounded biophysically. The second exploratory component of the project is the link with experiments to validate the modeling approach at multiple scales. First, at the microscopic level, by performing single-channel patch-clamp experiments, and then at the meso-/macroscopic scale, using recording of large parts of neuronal membrane in order to capture a growing number of channels. We will also use dynamic-clamp protocoles at every scale to control the behaviour of neuronal micro-circuits involved in DS.

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