Internship at EPFL Blue Brain Project

Clementine Domine
Blue Brain Project

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This Internship was realised under the supervision of *Rajnish Ranjan*

Abstract

Internship at the EPFL Blue Brain Project with Dr. Rajnish Ranjan, Section Manager of the Membrane Systems Group in the Simulation Neuroscience Division (Lausanne, Switzerland). My main duties consist of redesigning and upgrading the existing ion channel model fitting with Hodgkin-Huxley and Markov model formulation. Other duties include implementing results of the fitting to a neuron model and helping with the documentation of ion channels literature for the research group.

1 Introduction

1.1 The Blue Brain Project

EPFLs Blue Brain Project is a Swiss brain research initiative which aims at building biologically detailed digital reconstructions and simulations of the rodent and human brains. This project led by the Founder and Director Professor Henry Markram tackles one of the largest Big Data challenges we have today: Understanding the brain. After years of theory and experimentation, simulation is the evolved phase of many of the sciences and engineering fields. Simulation neuroscience is fundamental to understanding the brain as a complex multi-scale system. Therefore, the supercomputer-based simulations and reconstructions built by Blue Brain offer a radically new approach for understanding the multi-level structure and function of the brain [1].

1.2 The Membrane Systems Group

The Membrane Systems Group aims at identifying the distribution and biophysical properties of different ion channels expressed across the membrane of neurons. The electrical activity of neurons is governed by more than 300 types of ion channels. To model the diversity of electrical behaviors in neurons, it is necessary to characterize the biophysical properties of individual ion channels in standardized and controlled conditions. The analysis of existing literature on ion channel characterization revealed that previous efforts are at best, anecdotal and in many cases insufficient to properly build models from experimental data. The team has developed a workflow to systematically characterize ion channel biophysics. The workflow consists of cloning individual ion channels from rat brain to generate a cell line library and making use of automated patch-clamp technique to screen the biophysics of each ion channel. The team has also developed a web-based wiki-like resource Channelpedia (www.channelpedia.net) to share experimental and modeling data with the neuroscience community [2] [3].

2 Hodgkin-Huxley Model

In 1963, Hodgkin-Huxley (HH) won the Nobel prize for their work on the development of the kinetic model of the ion channel that gives rise to the spiking behavior of the neuron described in part in the paper "A QUANTITATIVE DESCRIPTION OF MEMBRANE CURRENT AND ITS APPLICATION TO CONDUCTION AND EXCITATION IN NERVE" . [4]. The study has been realized on the squid giant axon, a gargantuan axon, up to 1 mm in diameter which provided a technically convenient preparation. The mathematical model made by Hodgkin and Huxley which incorporates the voltage-dependent properties of the potassium channel conductance was reproduced. This model is well implemented in computational neurosciences to mimic the behavior of the ion channels giving rise to the action potential seen in neurons. [5].

2.1 Theory

The HH model relies on the idea that the electrical properties of a segment of nerve membrane can be modeled by an equivalent circuit of the form shown in Figure 4. The total ionic current of the membrane is built by three different current sources: a sodium current I_{Na}, a potassium current I_K, and a small leakage current I_L that is primarily carried by chloride ions.

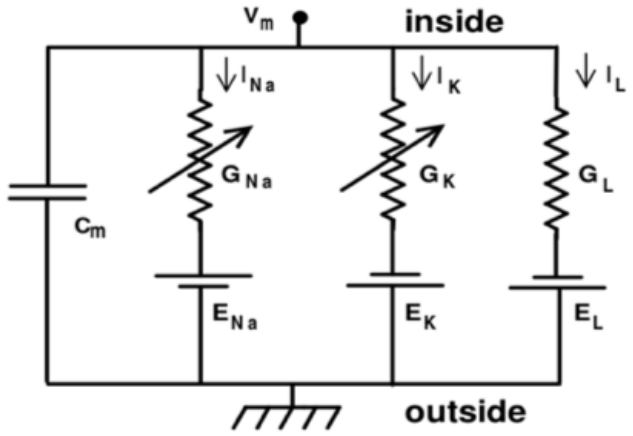


Figure 1: Electrical equivalent circuit proposed by Hodgkin and Huxley for a short segment of squid giant axon. The variable resistances represent voltage-dependent conductance (Hodgkin and Huxley 1952d).

$$I_{ext} = C_m \frac{dV_m}{dt} + I_{ion}. \tag{1}$$

The above equation describes the behavior of the electrical equivalent circuit of the membrane where C_m is the membrane capacitance, V_m is the membrane potential, I_{ion} is the total ionic current and I_{ext} is an externally applied current. I_{ion} is defined as the algebraic sum of the individual contributions from all ion types flowing across the membrane.

$$I_{ion} = \sum G_k(V_m - E_k). \tag{2}$$

where Gk is the associated conductance value.

Conductance is defined as the reciprocal of resistance, $G_k = \frac{1}{R_k}$. The equilibrium potential E_k is defined as the potential for which the net ionic current flowing across the membrane is null. [6]

The conductance of the HH model arises from contributions from the numerous microscopic ion channels in the membrane. The permittivity of the channel is characterized by the fraction of

gates that are in the permissive state p_i. The conductivity of the ion channel k can be defined as

$$G_k = g_k \prod p_i, \tag{3}$$

with g_k the normalization constant.
For instance, the Hodgkin and Huxley modeled macroscopic conductance G_{Na} due to channels of type Na, with constituent gates of types m and h, is given by the following equation

$$G_{Na} = gm^3h. \tag{4}$$

The potassium channel conductance using four identical n gates yields:

$$G_K = gn^4. \tag{5}$$

Transitions between permissive and non-permissive states in the HH model are assumed to obey first-order kinetics:

$$\frac{dp_i}{dt} = \alpha_i(V)(1 - p_i) - \beta_i(V)p_i, \tag{6}$$

where $\alpha_i(V)$ and $\beta_i(V)$ are voltage-dependent constants describing the non-permissive to permissive and permissive to non-permissive transition rates, respectively.

$$P_{i,t->\infty}(V) = \frac{\alpha_i(V)}{\alpha_i(V) + \beta_i(V)}, \tag{7}$$

$$\tau_i(V) = \frac{1}{\alpha_i(V) + \beta_i(V)}, \tag{8}$$

Equation 7 gives the steady-state value of the permittivity when the membrane is clamped at a fixed voltage value V as time tends to infinity. A simple exponential with a time constant $\tau_i(V)$ defined in equation 8 describes the time course for approaching this equilibrium value.

If the membrane potential starts in the resting state ($V_m = 0$) and is then instantaneously stepped to a new clamp voltage V_c, the time course of the state variable is given by the following equation

$$p(t) = p_\infty(V_c) - (p_\infty(V_c) - p_\infty(0)e^{-\frac{t}{\tau_p}}. \tag{9}$$

Once the values for $p_\infty(V_c)$ and $\tau_i(Vc)$ have been determined by fitting the conductance data, values for $\alpha_i(V)$and $\beta_i(V)$ can be determined by the following relationships:

$$\alpha_i(V) = \frac{p_\infty(V)}{\tau_i(V)}, \tag{10}$$

$$\beta_i(V) = \frac{1 - p_\infty(V)}{\tau_i(V)}. \tag{11}$$

2.2 Ion channel model fitting with Hodgkin-Huxley

The aim of my project was to reproduce computationally the behavior of the ion channel with the hope to build a model of the neuron and subsequently the brain. The model was written with MATLAB, a fourth-generation programming language and numerical analysis environment. In the current document, I present the model formulation that fits potassium K_v channel current curves recorded by the Blue Brain Project Membrane Systems group. The algorithm uses optimization function, $fminsearch$, to estimate the eight parameters, A_{1-8}, of the function given in equations 12, 13,14 and 15.

$$\alpha_m(V) = \frac{A_1 * (-V + A_2)}{e^{\frac{-V+A_2}{A_3-1}}} \tag{12}$$

$$\beta_m(V) = A_4 * e^{\frac{-V}{A_5}} \tag{13}$$

$$\alpha_h(V) = A_6 * e^{\frac{-V}{A_7}} \tag{14}$$

$$\beta_h(V) = \frac{1}{1 + e^{\frac{-V+A_8}{A_9}}} \tag{15}$$

These equations can be used to retrieve the current curve as described by the HH model theory in section 2.1 where V is the voltage applied to the cell. The model was firstly validated using external representative data.

The user has determined the threshold of the parameters of a good fit. The sum of the squared differences between each observation and its group's mean (SSE) gives an indication of the goodness of the fit. Another important indicator is the graphical plot of the fitted curve on top of the data curve. If the equation form is defined to perform the best possible fit, it is important to note that the fitting is more accurate with the increasing number of parameters. However, It could be the case that too many parameters were used and the data is hence overfitted using. Therefore, one must put some thoughts on the significance of these variables for a chosen equation form. The accuracy of the fitting process also greatly relies on the starting values of the parameters in the optimization function. The current traces are variable within different ion channel types and subtypes as well as at different temperatures of the recording. As a result, each data curve has a singular set of the above parameters that gives the best possible fit.

This multivariate aspect of the fitting process motivated further development of the fitting model. The aim is to fit with accuracy any type of data curve given to the program. A study of the starting value was performed on $K_v1.1$ at 35 C.

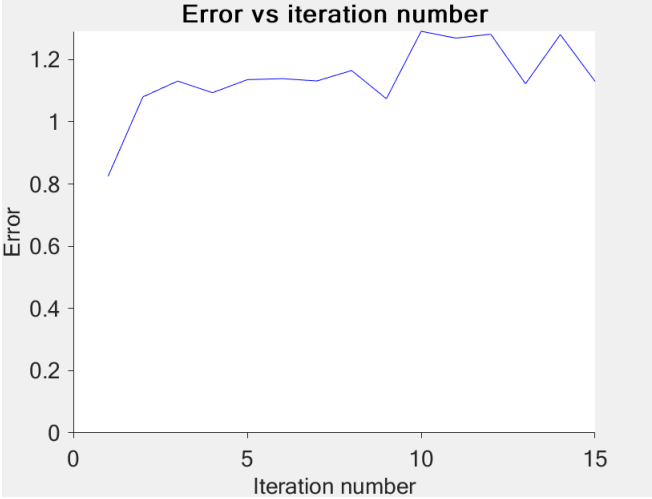


Figure 2:

The primary approach used the random values given by the function *rand* which returns a number from a uniform distribution of values between 0 and 1 as the starting values. A good fit was defined to be below 0.3 SSE. This method was not conclusive, producing fits with random SSE values ranging between 0.8 and 1.3 as shown in Figure 2.

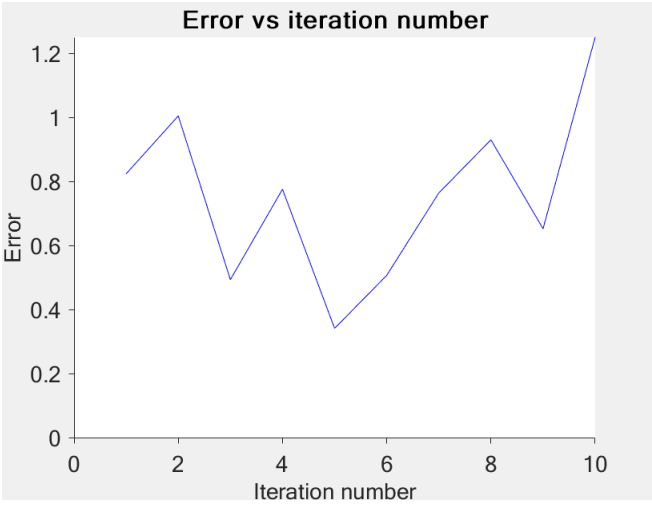


Figure 3:

In a second time, the function *randi* was used to give random starting values. $Randi(imax, sz)$ returns an array of pseudo-random scalars with size vector Sz and maximum value $imax$. With

$imax = 30$ and $sz = 10$ the same randomness in the produced SSE can observed in Figure 3. The SSE values range between 0.4 and 1.2. This is still not considered a good fit but we observe an improvement in the SSE values with the increase in range of possible random starting values.

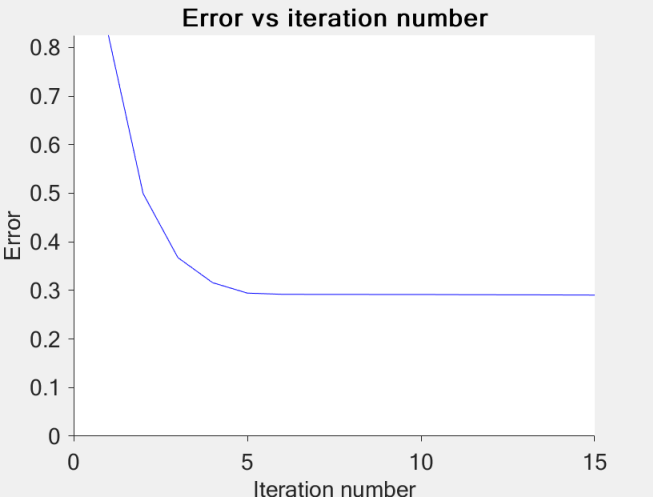


Figure 4:

Finally, an iteration loop was implemented on the random seed produced by the function rand, using the previously estimated value as the new starting value. The fitting seemed to improve with the iteration process giving SSE values ranging between 0.8 and 0.2 as shown in Figure 4. Hence, with the iteration method, a good fit was obtained.

In conclusion, even though the iteration method always reaches a conversion point, it seems to be the most appropriate method to lower the SSE value and obtain a better fit. The random starting values methods were not convincing. Further research should be carried using the known starting value of the fitting program previously built by Dr. Ranjan for the K_v channels to be used for other types of ion channels. During the investigation, limitations of the code were uncovered. For instance, when trying to implement a conditional parameter linked to the convergence of the SSE to the number of iteration, it was found that the value was stored as strings with limited significant digits. Another improvement of the model would be to investigate how the equation form would affect the goodness of the fit.

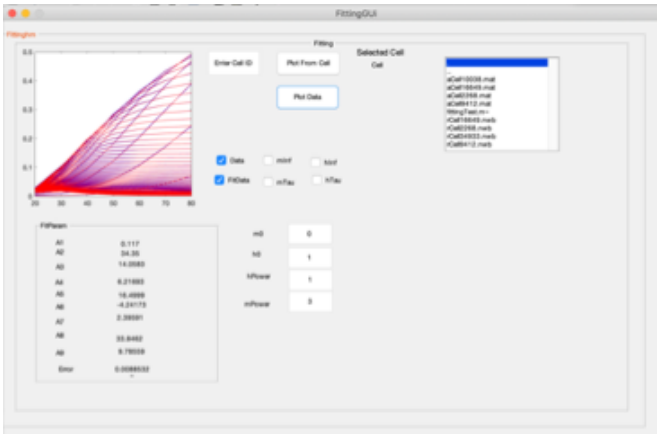


Figure 5: Picture of the Graphical User Interface (GUI) for the fitting model-based of the HH model of both N_a and K channels.

Graphical User Interface (GUI) is a visual and simplified interface between the user and a computer. Multiple graphical items such as windows, icons, and menus enable the user to interact with most modern operating systems. The GUI shown in Figure 5 provides the following functions

- Visualize the data available for fitting.
- Type in the Cell ID of the recorded data that the user wants to work with.
- Plot the recorded data and build-in curves.
- Plot the function of interest ($mInf$, $hTau$,etc...) from the Hodgkin-Huxley model.
- Visualize the fit parameters and error of the fit (SSE).
- Modify the fitting parameters (m_0, h_0, $mPower$, $hPower$).

3 NEURON at Yale

The NEURON simulation environment is used in laboratories and classrooms around the world for building and using computational models of neurons and networks of neurons. The neuron is a complex system made of multiple types of ion channel giving rise to various spiking behaviors. The different types of neurons are characterized by their morphology and their ion channel composition. Other parameters such as the timing of the stimulation, amplitude of the stimuli and conductance of the ion channel affect the spiking response of a neuron. All these parameters can be implemented in the NEURON simulation environment in order to gain further insight into the behavior of neurons and neural networks. [7] [8] [9]

From the three tutorials built by Dr. Ranjan, I was able to simulate a neuron and simple

neural networks to observe and understand their spiking behavior. An example exercise from one of the tutorial is shown in Figure 6.
I also further investigated the influence of the conductance of each ion channel on a neuron model built by Dr.Ranjan. The exact role of each ion channel conductance in the brain is hard to determine from the multivariate nature of this complex system. A few major effects were noticed. The increase in conductance of the potassium channel creates a diminution of the frequency or elimination of spikes. This observation is consistent with the expected result and observed result of an increasing flow of potassium ion during the re-polarizing phase of the action potential explained in the literature. The increase of the conductance of the sodium channel leads to an increase in the frequency of spikes. This is also consistent with the expected result and observed an increase of sodium ion through the channel during the polarizing phase of the action potential described in the literature.

A model of the neuron was built using the parameter found with the developed fitting model with Hodgkin-Huxley described in section 2. The spiking behavior observed was consistent with the known behavior of the neuron.

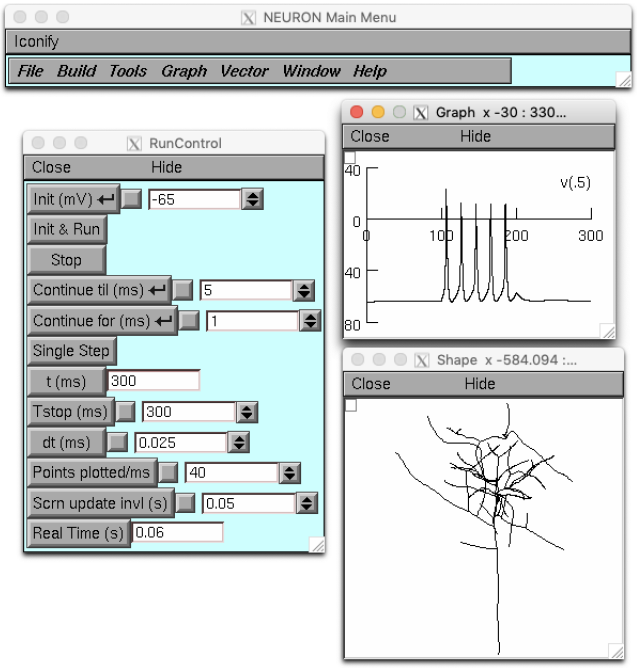
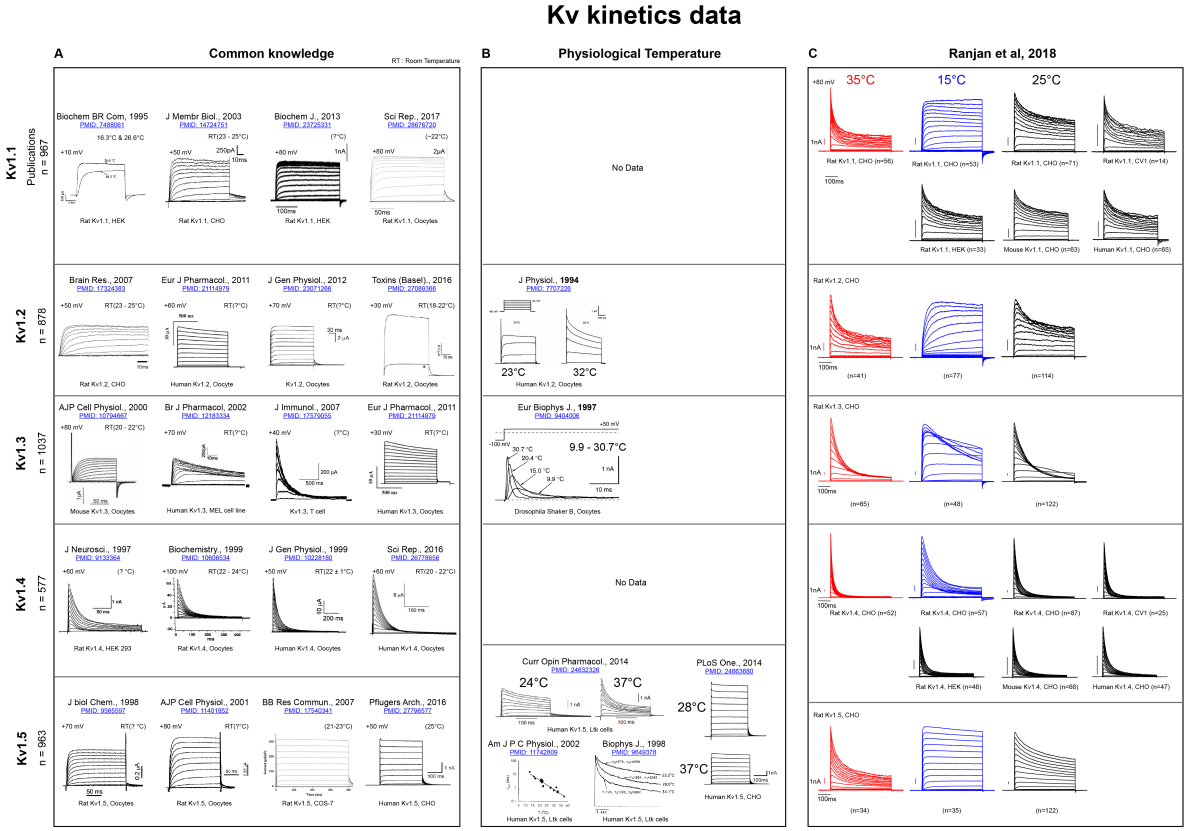


Figure 6: Picture of a neuron build with the HH model formulism in the Neuron simulation environment and simulated with a current described by the following parameters $tstop = 300$, $stim.amp = 0.2$, $stim.dur = 100$, $stim.del = 100$

4 Documentation of the existing litterature

On August 15^{th} 2019 the Membrane Systems Group published 'A Kinetic Map of the Homomeric Voltage-Gated Potassium Channel K_v Family' paper in the journal Frontiers. In addition to giving an unprecedented amount of data on the kinetic of the K_v ion channel, the paper outlines the variability in the current traces behavior of the ion channels with temperatures. The ionic current of each channel type has been recorded at 15, 25 and 35 °C by the research group as shown in Figure 7 [10]. To communicate efficiently this feature, a figure comparing the data from literature at room temperature to the recorded data at 25 and 35 °C was created. The published paper and respective figures are protected by copyright laws which vary depending on the publishing journal. Therefore,the permission policies and permission request procedures of the different journals of interest were searched and documented.



Annex 2. Summary of reported kinetics of Kv1.1-Kv1.5 ion channels. **Left,** "Publication n = x" indicates the total number of publications found for a given Kv channel (searched with gene OR protein name) in PubMed by January 2019. **A) Exemplar data** representative of channel kinetics reported at room temperature (RT). **B) All data** found on channel kinetics reported near physiological temperature. **C)** Experimental data reported in our manuscript. One example is shown for each condition, n is the total number of cells reported for each condition. **(A-C)** The species, cell line and temperature are indicated for each study.

Figure 7: [10]

The collaboration also needed help with the documentation and classification of paper on the ten different types of sodium ion channel kinetic for their future experiment. The documentation of the literature is an important aspect of the research to avoid the duplication of results. This

task has taught me to quickly read and retrieve key information from biological scientific papers. Moreover, I further learned about the techniques such as the patch-clamp or transfection procedures that enable the group to record the current traces.

5 Conclusion

The project being outside of my area of study (physics) was a very motivating challenge. I gained valuable insights into neuroscience research both from an experimental and theoretical standpoint. I further developed my programming and public speaking skills. I also had the opportunity to expand my knowledge in the domain of neurosciences. I particularly enjoyed the multidisciplinary aspect of the internship. This experience has confirmed my will to embark on a career as a Neurophysicist. Hence, I am currently searching for a Ph.D. position in the field of computational neurosciences.

6 Acknowledgement

I would like to express my special thanks of gratitude to my supervisor Dr. Rajnish Ranjan who gave me the opportunity to do this wonderful project on the ion channel model fitting with Hodgkin-Huxley and Markov model formulation, and who also helped me in the research. I would like also to thank all the members of the Membrane Systems Group in the Simulation Neuroscience Division for welcoming me so kindly in their team.

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