**FACULITY OF ENGINEERING**

**A PURKINJE CELL MODEL THAT SIMULATES COMPLEX SPIKES**

**BY**

**STEFANOS CHARAKIDIS**

**Supervised by**

**Conor Houghton**

A dissertation submitted to the University of Bristol in accordance with the requirements of the degree of [Bachelor/Master] of [Computer Science/Mathematics and Computer Science] by advanced study in [computer science/mathematics with computer science] in the Faculty of Engineering. School of Computer Science, Electrical and Electronic Engineering, and Engineering Maths (SCEEM), [insert submission date here].

Word count: N/A

Declaration and statements of student in respect of their submitted work

I declare that the work in this dissertation was carried out in accordance with the 1requirements of the University’s Regulations and Code of Practice for Taught Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, this work is my own work. Work done in collaboration with, or with the assistance of others, is indicated as such. I have identified all material in this dissertation which is not my own work through appropriate referencing and acknowledgement. Where I have quoted or otherwise incorporated material, which is the work of others, I have included the source in the references. Any views expressed in the dissertation, other than referenced material, are those of the author.

SIGNED: ..................................................................... DATE: ...............

“This project did not require ethical review, as determined by my supervisor, Conor Houghton”

***Acknowledgements***

Throughout this dissertation thesis, I have received a lot of support and assistance both mentally and physically. I would like to personally thank my supervisor, Professor Conor Houghton, whose expertise was critical in and methodology. By having a great collaboration, you helped me set ambitious goals and pay attention to details, always guiding me to the points I should dedicate my time and effort to. Along with Conor I would like to thank Amelia Burroughs, Nadia L. Cerminara and Richard Apps from School of Physiology, Pharmacology and Neuroscience, University of Bristol for their contributions in the original research paper [1]. I may not have met you, but I would like to express my gratitude for conducting research on this topic and as a result allowing me to take another look from the computer science viewpoint.

**Abstract**

Purkinje cells are the principal neurons of the cerebellar cortex. One of their distinguishing features is that they fire two distinct types of action potential, called simple and complex spikes, which interact with one another. Simple spikes are stereotypical action potentials that are elicited at high, but variable, rates (0 − 100 Hz) and have a consistent waveform. Complex spikes are composed of an initial action potential followed by a burst of lower amplitude spikelets. Complex spikes occur at comparatively low rates (∼ 1 Hz) and have a variable waveform. Although, they are critical to all motor coordination in the cerebellar cortex, a simple model that describes the complex spike waveform is lacking. ++

**Keywords: Purkinje cells, neurons, mathematical model, complex spikes, simulation**

**TABLE OF CONTENTS**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |  |  |  |  | Page |
| Declarations |  |  |  |  |  |  |  |  |  | 1 |
| Acknowledgements |  |  |  |  |  |  |  |  |  | N/A |
| Abstract |  |  |  |  |  |  |  |  |  | N/A |
| Contents |  |  |  |  |  |  |  |  |  | N/A |
| Chapter 1 |  |  | *Introduction* |  |  |  |  |  |  | N/A |
| CHAPTER 2 |  |  | *Methods* |  |  |  |  |  |  | N/A |
| Chapter 3 |  |  | *Implementation and fitting* |  |  |  |  |  |  | N/A |
| CHAPTER 4 |  |  | *Results* |  |  |  |  |  |  | N/A |
| CHAPTER 5 |  |  | *Discussion* |  |  |  |  |  |  | N/A |
| References |  |  |  |  |  |  |  |  |  | N/A |

1. ***Introduction***

Located in the cerebellum and being amongst the largest neurons in the central nervous system [1], Purkinje cells(PCs) are extraordinary and instantly distinguishable from other brain neurons for their complex planar dendritic trees and for their ability to fire to distinct types of action potential, namely simplex and complex spikes. With over 150,000 input synapses, far most than most other cell types [2] PCs have gathered the interest of many neuroscientists of their potential and capabilities. The mossy fibre activates the granule cell which connects to the parallel fibre exciting simple spikes (see Figure 1), ranging from 0 – 100 Hz . On the other hand, the climbing fibre “entangles” the PC where it directly triggers complex spikes (CSs) at a remarkably low frequency (~1 Hz) [3] with one climbing fibre per PC (see Figure 1). CSs can induce long-term depression at parallel fibre synapses on PCs, which may be involved in cerebellum-dependent learning and motor coordination [4] [5]. Purkinje cells are GABAergic neuron and are the only neurons that send output Diagram

Description automatically generatedfrom the cerebellar cortex to nuclear neurons [6].

Figure 1: Purkinje cell layout. Climbing fibres receive input from motor system where they are thought to code error signals [7] and connecting directly to the parallel fibres. In contrast mossy fibre connects to parallel fibres via the Granular cell having received input from multiple sources(spinal cord, cerebellar cortex, vestibular system ).

Despite the existence of a range of computational models to address various features of Purkinje cells, a simple model that captures the complex spike behaviour is lacking . An extensive attempt to create a necessary model to address the issue has been done by Amelia Burroughs, Nadia L. Cerminara , Richard Apps , and Conor Houghton [8]. Here, this paper seeks to review and rework the modelling from the computer science perspective in order to provide an efficient, optimized, and simplistic solution without losing the resolution of the original paper. This paper’s aim is via simulation, to prove the hypothesis that a restricted number of channel-dynamics can explain the complex spike waveform. The model that is presented is a three-current model that shows that three channels, a leak channel and two active channels, are sufficient to simulate the complex spike waveform. This model attempts to provide an adequate description of the essential ion-channel dynamics that support the complex spike production, behaviour and enable further analysis of complex spiking.

1. ***Methods***

In this paper a model of the Purkinje cell somatic voltage dynamics is presented with a three-current model, which has a leak channel and two voltage-gated channels:

( 1 )

where Cm = 1 μF / cm2 is the membrane capacitance, is a leak current,

( 2 )

with = 0.3 mS / cm2 and = 10.613 mV. INa and IK stand for the sodium current and the potassium current.stands for the external input current. This is described below and is made up of a background current and a synaptic current entering the soma from the dendrites The most commonly used sign convention in neural modeling is that ionic current flowing out of the cell is positive and ionic current flowing into the cell is negative [8].

* 1. **Ion channels**

The current through the sodium channel was modelled using a Markovian scheme developed by Raman and Bean [9] , as seen in Table 1. This scheme models the dynamics of both the transient and resurgent gate. The sodium current is:

( 3 )

Where *o* is the fraction of gates in the open state O, = 120.0 mScm−2 and VNa = 115 mV

Diagram, schematic

Description automatically generated with medium confidence

Table 1: Sodium channel current described using a Markovian Scheme. “C1-C5 describe sequential closed configurations; I1-I6 describe sequential inactivated states; O represents the open channel configuration where sodium ions only pass through the channel when it is in this state. B describes a second inactivated state where the channel is likened to being in an open-but-blocked configuration that is non-conducting. Return from this state back to the closed, or inactivated, states must occur through the open (O) configuration” [10].

Where

( 4 )

( 5 )

( 6 )

and γ = 150 ms−1 , δ = 40 ms−1 , ε = 1.75 ms−1 , D = 0.005 ms−1 , U = 0.5 ms−1 , N = 0.75 ms−1 , F = 0.005 ms−1 with

( 7 )

The potassium current is:

( 8 )

Where , = 36.0 mScm−2 and VK = -12 mV. *n* is described with the usual Hodgkin-Huxley channel equations(Eq 17, Eq 18) described in 2.2.

* 1. **Hodgkin-Huxley model**

The **Hodgkin–Huxley model**, or **conductance-based model**, is a mathematical model that describes how action potentials in neurons are initiated and propagated. It is a set of nonlinear differential equations that approximates the electrical characteristics of excitable cells such as neurons. It is a continuous-time dynamical system.

The typical Hodgkin–Huxley model treats each component of an excitable cell in this case a Purkinje cell as an electrical element. The lipid bilayer is represented as a capacitance (Cm). Voltage-gated ion channels are represented by electrical conductances (, for the potassium channel and for the sodium channel) that depend explicitly on voltage. Leak channels are represented by linear conductances (). Finally, the membrane potential is denoted by *Vm,* and it is time dependent.

Thus, for a cell with sodium and potassium channels, the total current through the membrane is given by:

( 9 )

The Hodgkin and Huxley developed a model in which the properties of an excitable cell are described by a set of four ordinary differential equations. Together with the equation for the total current mentioned above, these are:

( 10 )

( 11 )

( 12 )

( 13 )

where *I* is the current per unit area, and α{\displaystyle \alpha \_{i}} and {\displaystyle \beta \_{i}}β are rate constants for the each ion channel, which depend on voltage but not time. There are three gating variables: n for the Potassium channel activation, m for the Sodium channel activation (opening) and h for the Sodium channel inactivation (closing). The value of a gating variables is dimensionless and will vary between 0 and 1; 0 indicates that the channel is closed, whereas 1 indicates that the channel is open. The gating variable fraction is an indication of the conductance of a certain ion at a given time and membrane voltage

( 14 )

( 15 )

( 16 )

(n,m,h)∞ are the steady state values for activation and are usually represented as a function of Vm.

Chart, histogram

Description automatically generated

Figure 2: Potassium and Sodium channels as function of time{\displaystyle V\_{m}}

A system of four ordinary differential equations is used to represent the Hodgkin-Huxley model as seen in Eq 10, Eq 11, Eq 12, Eq 13. As a nonlinear system it is difficult for the model to be studied as it cannot be solved analytically However, certain properties and general behaviors, such as limit cycles(closed trajectories), can be proven to exist using numerical methods. A picture containing chart

Description automatically generated

Figure 3: Limit cycles of the gating variables as a function of Voltage

Channel kinetics are described with the original Hodgkin-Huxley channel equations [11] and constants with, α, β being the forward and backwards rate in ms-1, respectively.

( 17 )

( 18 )

( 19 )

( 20 )

( 21 )

( 22 )

One other technical note is that certain function forms can become indeterminate at certain voltage values(Nelson05-ElectrophysModels). Given a specific voltage, an(Vm) and am (Vm) may evaluate to the indeterminate form 0/0. The solution to this problem is to apply L’Hospital’s rule [12], which states that if f(x) and g(x) approach zero as x approaches a, and f ‘(x)/ g’(x) approaches L as x approaches a, then the ratio f (x)/ g(x) approaches L as well. Using this rule, it can be shown that an(10) = 0.1 and am(25) = 0.430825375 . Also, the limits for every case are hand-tuned for simplicity and efficiency.

All the input parameters listed in Table 2, are defined in Python.

|  |  |  |
| --- | --- | --- |
| ***Parameters*** | ***Chosen Value*** | ***Reference*** |
| Cm (μF/cm2) | 1.0 | [11] |
| (mS/cm­­2) | 120.0 | [11] |
| (mS/cm­­2) | 36.0 | [11] |
| (mS/cm­­2) | 0.3 | [11] |
| Vm (mV) | 0.0 | [11] |
| VNa (mV) | 115.0 | \* [11] |
| VK (mV) | -12.0 | \* [11] |
| Vl (mV) | 10.613 | \* [11] |
| VThreshold (mV) | 55.0 | \* [11] |
| Iinj (μA/cm2) | 10.0 |  |
| Tmax (ms) | 35.0 |  |

Table 2: Experimental Constants for the Hodgkin and Huxley model. The parameters with a star (\*) have been hand-tuned to have their signs follow the sign convention see Section 3.1.

Chart, line chart

Description automatically generated

Figure 4: Neuron potential as a function of time

1. ***Implementation and fitting***

Simulations were run in Python 3.9.10, OS on a CPU. Models were simulated as ordinary differential equations and integration was performed explicitly using the scipy.integrate.solve\_ivp package suitable for stiff problems or non-stiff problems of first order ode-s. One second of Purkinje cell activity can be simulated in N/A minute N/A seconds.--++

* 1. **Sign Convention**

One issue while implementing the Hodgkin-Huxley model was the voltage sign convention. The modern convention is that depolarization makes the membrane potential Vm more positive [13]. However, Hodgkin and Huxley [11] used the opposite sign convention (depolarization negative) in their paper. Figures and parameters in this paper follow the modern convention that depolarization is positive. The modern convention is chosen in order to display a more modern example of the Hodgkin-Huxley model. To achieve this, the rate constants and the voltage values have been adjusted accordingly.+

* 1. **Error minimization**

Error function Markov and HH model

Optimization was performed using a mixture of error minimization and hand-tuning techniques.++

1. ***Results***
2. ***Discussion***

**Code Availability Statement:**

The Python source code used to create the figures and the modelling is available at github.com/PurkinjeCell.

# **References**

|  |  |
| --- | --- |
| [1] | C.-P. V. Palay S.L., The Purkinje Cell. In: Cerebellar Cortex., Berlin, Heidelberg., 1974. |
| [2] | H. T., "Purkinje Neurons: Development, Morphology, and Function.," *Cerebellum,* vol. 17, no. 6, pp. 699-700, 2018. |
| [3] | I. S. J. P. W. a. R. L. J. Lang, "Patterns of spontaneous Purkinje cell complex," *Journal of Neuroscience ,* vol. 19, no. 7, pp. 2728-2739, 1999. |
| [4] | M. Ito, "Cerebellar long-term depression: characterization, signal transduction and functional roles.," *Physiol. Rev.,* no. 81, pp. 1143-1195, 2001. |
| [5] | V. M. W. H. F. E. S. R. A. D. Z. C. I. H. M. e. a. Steuber, "Cerebellar LTD and Pattern Recognition by Purkinje Cells.," *Neuron,* vol. 54, no. 1, pp. 121-136, 2007. |
| [6] | K. S.-y. Hirano Tomoo, "Regulation and functional roles of rebound potentiation at cerebellar stellate cell—Purkinje cell synapses," *Frontiers in Cellular Neuroscience,* vol. 8, 2014. |
| [7] | K. a. S. J. I. Maekawa, "Climbing fiber responses evoked in vestibulocerebellum of rabbit from visual pathway.," *J. Neurophysiol. ,* no. 36, pp. 649-666, 1973. |
| [8] | M. Nelson, Electrophysiological Models In: Databasing the Brain: From Data to Knowledge., New York., 2004. |
| [9] | R. a. B. P. Bean., "Inactivation and recovery of sodium currents in cerebellar Purkinje neurons: evidence for two mechanisms.," *Biophysical Journal,* pp. 729-737, 2001. |
| [10] | N. L. C. R. A. C. H. Amelia Burroughs, "A Purkinje cell model that simulates complex spikes," *bioRxiv,* 2020. |
| [11] | H. A. Hodgkin AL, ""A quantitative description of membrane current and its application to conduction and excitation in nerve".," *The Journal of Physiology,* vol. 117, no. 4, pp. 500-544, 1952. |
| [12] | G. d. l'Hôpital, Analyse des Infiniment Petits pour l'Intelligence des Lignes Courbes, 1724, p. 145–146.. |
| [13] | C. C.D., "Unified theory on the basic mechanism of normal mitotic control and oncogenesis.," *Journal of Theoretical Biology,* vol. 30, pp. 151-181, 1971. |

**References(old)**

1. *Nelson05 ElectrophysModels | Action Potential | Membrane ...,* *https://www.scribd.com/document/259508572/Nelson05-ElectrophysModels.*
2. *Paul MS, Limaiem F. Histology, Purkinje Cells. [Updated 2021 Nov 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from:* [*https://www.ncbi.nlm.nih.gov/books/NBK545154/*](https://www.ncbi.nlm.nih.gov/books/NBK545154/)*.*
3. Raman IM & Bean BP (1997). Resurgent sodium current and action potential formation in dissociated cerebellar Purkinje neurons. J Neurosci 12, 4517–4526.
4. Hausser M & Clark BA (1997). Tonic synaptic inhibition ¨ modulates neuronal output pattern and spatiotemporal synaptic integration. Neuron 19, 665–678
5. Eccles JC, Ito M & Szentagothai J (1967). The Cerebellum as a Neuronal Machine. Springer, Berlin.