**A Purkinje cell model that simulates complex spikes**

***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. ++

1. ***Introduction***

Purkinje cells are a class of [GABAergic](https://en.wikipedia.org/wiki/GABAergic) inhibitory [neurons](https://en.wikipedia.org/wiki/Neuron) located in the cerebellum. They are named after their discoverer, [Czech](https://en.wikipedia.org/wiki/Czech_people) [anatomist](https://en.wikipedia.org/wiki/Anatomist) [Jan Evangelista Purkyně](https://en.wikipedia.org/wiki/Jan_Evangelista_Purkyn%C4%9B), who characterized the cells in 1839. Purkinje cells are aligned like [dominos](https://en.wikipedia.org/wiki/Domino) stacked one in front of the other. Their large dendritic arbors form nearly [two-dimensional](https://en.wikipedia.org/wiki/Two-dimensional) layers through which [parallel fibers](https://en.wikipedia.org/wiki/Parallel_fiber) from the deeper-layers pass. These parallel fibers make relatively weaker [excitatory](https://en.wikipedia.org/wiki/Excitatory_synapse) ([glutamatergic](https://en.wikipedia.org/wiki/Glutamatergic)) synapses to spines in the Purkinje cell dendrite, whereas [climbing fibers](https://en.wikipedia.org/wiki/Climbing_fibers) originating from the [inferior olivary nucleus](https://en.wikipedia.org/wiki/Inferior_olivary_nucleus) in the [medulla](https://en.wikipedia.org/wiki/Medulla_oblongata) provide very powerful excitatory input to the proximal dendrites and cell soma. Parallel fibers pass [orthogonally](https://en.wikipedia.org/wiki/Orthogonal) through the Purkinje neuron's dendritic arbor, with up to 200,000 parallel fibers[[4]](https://en.wikipedia.org/wiki/Purkinje_cell#cite_note-4) forming a [Granule-cell-Purkinje-cell synapse](https://en.wikipedia.org/wiki/Granule-cell-Purkinje-cell_synapse) with a single Purkinje cell. Each Purkinje cell receives approximately 500 climbing fiber synapses, all originating from a single climbing fiber.[[5]](https://en.wikipedia.org/wiki/Purkinje_cell#cite_note-5) Both basket and stellate cells (found in the cerebellar [molecular layer](https://en.wikipedia.org/wiki/Cerebellum#Molecular_Layer)) provide [inhibitory](https://en.wikipedia.org/wiki/Inhibitory) (GABAergic) input to the Purkinje cell, with basket cells synapsing on the Purkinje cell axon initial segment and stellate cells onto the dendrites.

Purkinje cells send inhibitory projections to the deep cerebellar nuclei, and constitute the sole output of all [motor coordination](https://en.wikipedia.org/wiki/Motor_coordination) in the cerebellar cortex. Purkinje cells show two distinct forms of electrophysiological activity:

* Simple spikes occur at rates of 17 – 150 Hz (Raman and Bean, 1999), either spontaneously or when Purkinje cells are activated synaptically by the parallel fibers, the axons of the granule cells.
* Complex spikes are slow, 1–3 Hz spikes, characterized by an initial prolonged large-amplitude spike, followed by a high-frequency burst of smaller-amplitude action potentials. They are caused by climbing fiber activation and can involve the generation of calcium-mediated action potentials in the dendrites. Following complex spike activity, simple spikes can be suppressed by the powerful complex spike input.[[21]](https://en.wikipedia.org/wiki/Purkinje_cell#cite_note-21)

Purkinje cells show spontaneous electrophysiological activity in the form of trains of spikes both sodium-dependent and calcium-dependent. -- ++

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

( 2 )

with = and = 10.613mV

* 1. **Input current**
  2. **Ion channels**

The current through the sodium channel was modelled using a Markovian scheme Raman and Bean (2001). This scheme models the dynamics of both the transient and resurgent gate.

Diagram, schematic

Description automatically generated with medium confidence

Where

( )

( )

( )

* 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 and cardiac myocytes. 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 (*gn*, where *n* is the specific ion channel) that depend on both voltage and time. Leak channels are represented by linear conductances (*gL*). Finally, the membrane potential is denoted by *Vm*.

( 6 )

where *I* is the total membrane current per unit area, *Cm* is the membrane capacitance per unit area, *gK* and *gNa* are the potassium and sodium conductances per unit area, respectively, *VK*and *VNa* are the potassium and sodium reversal potentials, respectively, and *gl* and *Vl* are the leak conductance per unit area and leak reversal potential, respectively. The time dependent elements of this equation are *Vm*, *gNa*, and *gK*, where the last two conductances depend explicitly on voltage as well.

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:

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( 8 )

( 9 )

( 10 )

where *I* is the current per unit area, and α{\displaystyle \alpha \_{i}} and {\displaystyle \beta \_{i}}β are rate constants for the *i*-th 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

( 11 )

( 12 )

( 13 )

(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 1: Potassium and Sodium channels as function of time

{\displaystyle V\_{m}}

One representation of the Hodgkin–Huxley model can be thought of as a differential equation system with four state variables, {\displaystyle V\_{m}(t),n(t),m(t)}V(t), n(t), m(t) and h(t){\displaystyle h(t)}, that change with respect to time{\displaystyle t}. The system is difficult to study because it is a nonlinear system and cannot be solved analytically. However, there are many numerical methods available to analyze the system. Certain properties and general behaviors, such as limit cycles, can be proven to exist. A picture containing chart

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Figure 2: Limit cycles of the gating variables as a function of Voltage

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

( 14 )

( 15 )

( 16 )

( 17 )

( 18 )

( 19 )

One other technical note is that certain function forms can become indeterminate at certain voltage values. 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 rule2, 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 . Hence, the limits for every case are hand-tuned for simplicity and efficiency.

All of the constants listed in Table 1, are defined in Python.

|  |  |
| --- | --- |
| ***Constant*** | ***Chosen Value*** |
| Cm (μF/cm2) | 1.0 |
| GNa (mmhos/cm­­2) | 120.0 |
| GK (mmhos/cm­­2) | 36.0 |
| Gl (mmhos/cm­­2) | 0.3 |
| Vm (mV) | 0.0 |
| VNa (mV) | 115.0 |
| VK (mV) | -12.0 |
| Vl (mV) | 10.613 |
| VThresh (mV) | 55.0 |
| Iinj (μA/cm2) | 10.0 |
| Tmin (ms) | 0.0 |
| Tmax (ms) | 35.0 |

Table 1: Experimental Constants for the Hodgkin and Huxley model

Chart, line chart

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Figure 3: Neuron potential as a function of time

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.odeint package suitable for stiff problems or non-stiff problems of first order ode-s.

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

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

***References***

1. Hodgkin AL, Huxley AF (August 1952). [*"A quantitative description of membrane current and its application to conduction and excitation in nerve"*](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1392413). The Journal of Physiology. **117** (4): 500–44. [*doi*](https://en.wikipedia.org/wiki/Doi_(identifier)):[*10.1113/jphysiol.1952.sp004764*](https://doi.org/10.1113%2Fjphysiol.1952.sp004764). [*PMC*](https://en.wikipedia.org/wiki/PMC_(identifier)) [*1392413*](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1392413). [*PMID*](https://en.wikipedia.org/wiki/PMID_(identifier)) [*12991237*](https://pubmed.ncbi.nlm.nih.gov/12991237).
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