MATH3888 Group 9: The Connor-Stevens model for excitable neurons

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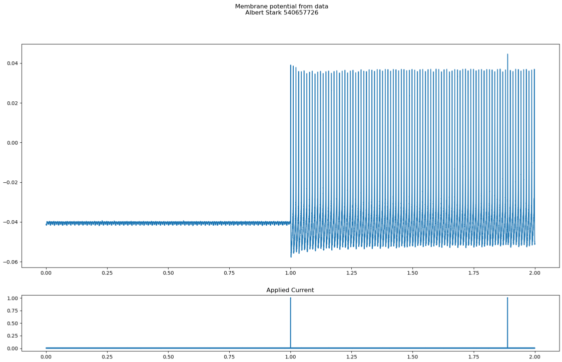
Biological Setting

Ion channels are channels on neuron's membrane that control the flow of ions and allow neurons to exhibit excitability by establishing the resting membrane potential and generate action potentials. To better understand how excitability is desirable for physiological and biological purposes, we focused on studying the different openness of various ion channels on the surface of a given neuron, with respect to the applied current / Nernst potential.



Data from the dataset [3] from the paper of Paydafar et al [2]. Top plot: voltage vs time; Botton plot: applied current vs time.

The Connor-Stevens Model

The Connor-Stevens model [1] is
a system of 9 ODEs, with a voltage equation:

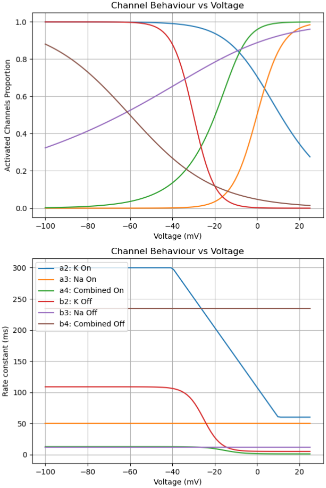
$$I(t) = C_m \frac{dv}{dt} + \sum_{j \in \{1,2,3,4\}} \overline{g}_j (A_j(V,t))^j B_j(V,t)(V - V_j)$$

and a series of channel openness equations:

$$\tau_{Aj} \frac{dA_j(V,t)}{dt} + A_j(V,t) = A_j(V,\infty)$$

$$\tau_{Bj} \frac{dB_j(V,t)}{dt} + B_j(V,t) = B_j(V,\infty)$$

for the index $j \in \{1, 2, 3, 4\}$.
Each channel has timescales defined by τ_{Aj} and τ_{Bj}, and steady state behaviour defined by $A_j(V,\infty)$ and $B_j(V,\infty)$.
The j index also corresponds to the quantity of each channel in a cluster within the cell: two leaky channels, trimeric K^+, tetrameric Na^+ and pentameric combined channel.



The channels of the model and their rate constants and voltage gating.

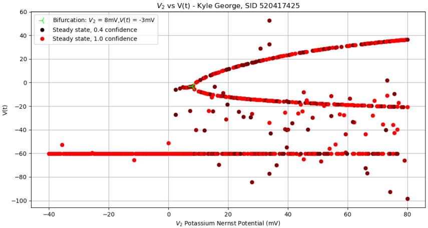
Connecting Biology and Mathematics

The Connor-Stevens model [1], in its standard presentation, models the open / closedness of 4 channels ($c \in [0, 1]$), along with the membrane potential of the cell being modelled, creating a 9 dimensional system.

$$
\begin{aligned}
I(t) = &C_m \frac{dv}{dt} \\
+ \sum_{j \in \{1,2,3,4\}} &\overline{g}_j (A_j(V,t))^j B_j(V,t)(V - V_j)
\end{aligned}
$$

$$\Downarrow$$

$$
\begin{aligned}
I(t) = &C_m \frac{dv}{dt} \\
+ \sum_{j \in \{2,3,4\}} &\overline{g}_j (A_j(V,t))^j B_j(V,t)(V - V_j)
\end{aligned}
$$



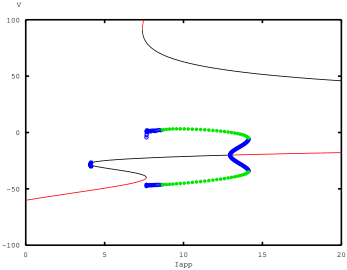
Example of a plot generated stochastically by our python model, note the bifurcation, which is part of a codimension 3 pitchfork bifurcation.

The channels are a Potassium, Sodium, a combined, and a leaky channel. We removed the leaky channel in our computation given its insignificance.
Throughout we utilised a (to our knowledge novel) stochastic method to search the parameter space to find various steady states and bifurcations. We performed some basic value culling in this search, terminating if channel values went outside $[0, 1]$, and if the cell membrane potential was predicted as $|v| > 500mV$.

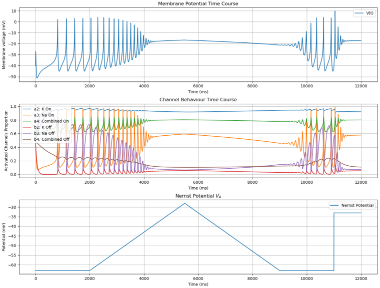
The Mathematical Results

Animated Bifurcation Diagrams: Codimension 3 Pitchfork bifurcation

- Potassium potential (-80 to 80)
- Sodium potential (-10 to 27)
- Triple diagram



(a) Bifurcation diagram (XPP-Auto)



(b) Time series (Python)

Figure: Repeatedly entering (in V_4) and leaving the Andronov-Hopf region (left) creates oscillations and breaks in a simulation (right).

Coordinates of codimension 3 bifurcation: $(V_2, V_3, V_4) = (11.0, 0.00, -42)$,
$(v, a_2, a_3, a_4, b_2, b_3, b_4) = (-10, 0.8, 0.9, 0.9, 0.2, 0.1, 0.1)$

Biological Interpretation & Conclusions

What matched

- DC input ⇒ stable oscillations; waveform shape matches (with a small voltage offset from the dataset).

What did not match

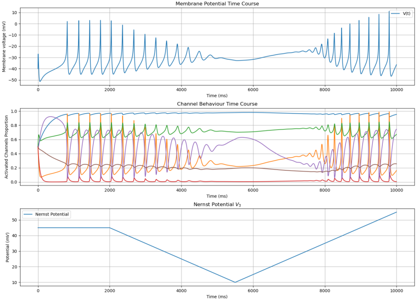
- Millisecond constant pulses in data ⇒ oscillations; our model *does not* sustain oscillations from brief pulses.
- Voltage-style injection did not fix this.

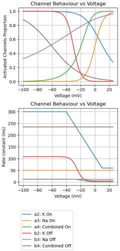
Why (model view)

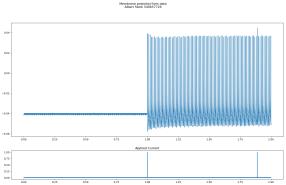
- Variables too independent; no single "switch" variable.
- Oscillation onset via **Hopf in I_{app}**; needs sustained drive, not a 1 ms kick.

Interpretation / Implication

- DC-driven regime resembles hyperexcitability (TBI/epileptiform).
- Hypothesis: direct-current stimulation could shift dynamics back across Hopf and suppress oscillations.[4]







Data: pulse at ∼1.0 s ⇒ sustained spiking.

Conclusion and bibliography

[1] John A. Connor and Charles F. Stevens. "Prediction of repetitive firing behaviour from voltage-clamp data on an isolated neurone soma". In: *The Journal of Physiology* 213.1 (1971), pp. 31–53. DOI: 10.1113/jphysiol.1971.sp009366.

[2] D Paydafar, DB Forger, and JC Clay. "Noisy Inputs and the Induction of On–Off Switching Behavior in a Neuronal Pacemaker". In: *Journal of Neurophysiology* 96 (2006), pp. 3338–3348. URL: https://doi.org/10.1152/jn.00486.2006.

[3] D Paydafar, DB Forger, and JC Clay. *Squid Giant Axon Membrane Potential*. 2016. URL: https://doi.org/10.13026/C25C73.

[4] Ana Luiza Zaninotto et al. "Transcranial direct current stimulation (tDCS) effects on traumatic brain injury (TBI) recovery: A systematic review". In: *Dementia & Neuropsychologia* 13.2 (2019), 172–179. ISSN: 1980-5764. DOI: 10.1590/1980-57642018dn13-020005. URL: https://doi.org/10.1590/1980-57642018dn13-020005.