Summary and report of "Nonequilibrium thermodynamics of voltage-gated ion channels"

Ada Cottam Allen

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Regularly buoyed from thermodynamic equilibrium by complex and fluctuating environments, living systems must continually respond and adapt to external stimuli. Recent tools from stochastic thermodynamics place concrete energetic and entropic bounds on these processes, for systems arbitrarily far from equilibrium both in and out of steady-state conditions, and thus reveal mechanisms by which these systems absorb and dissipate energy to function. Here, we leverage these tools to simulate and calculate the thermodynamic signatures of several models of sodium and potassium ion channels—channels crucial to propagating action potentials in mammalian neurons—as driven by biologically-realistic action potential spiking protocols. Thus uncovering their detailed energetic responses to such complex environmental conditions, these results enable detailed comparison between the thermodynamic functionality of each channel type with driving one would expect in-vivo. When applied to competing models of the same channel, these tools also provide additional criteria for model selection; to this end, we close by calculating expected ionic currents, directly facilitating comparison with dynamically-driven patch-clamp experiments.

Introduction

Many complex systems, including biological systems, operate far from thermodynamic equilibrium. Such nonequilibrium systems require tools beyond equilibrium thermodynamics to meaningfully describe their energetic behavior. Stochastic thermodynamics provides a set of tools that can break down the otherwise quite challenging energetics of these nonequilibrium systems.

Among many things, stochastic thermodynamics defines two distinct heat quantities: "excess heat," heat dissipated in direct response to environmental conditions; and "housekeeping heat" heat dissipated to maintain nonequilibrium steady states. If we know how a system transitions between states as it is driven by a changing environment, we can calculate these heat quantities.

Neural cell membranes are covered in pores called ion channels. The behavior of these ion channels—how they change between open and closed states—is subject to the voltage the channel experiences. This behavior governs the propagation of electric signals between neurons. Experimentalists study this open-close transition in "patch-clamp" experiments in-vitro and build models for the ion-channel's states and voltage-dependent state transitions. It would be useful to know how the channels store and transfer energy. However, it is difficult if not impossible to meaningfully measure the heat behavior of the channels as they transition.

In simulation, we can leverage the more subtle heat quantities of stochastic thermodynamics to reveal this heat behavior. The insight we can provide into the thermodynamic behavior of various lab-built models of ion channels allows for more detailed comparison between different types of ion channels and can be an additional tuning dial for realistic model construction.

Procedure

We examined two types of ion channels, Na^+ and K^+. The behavior of ion channels can be modeled as a Markov chain Fig 1,2. We rewrite the Markov chains as transition rate matrices as shown in Fig 3. Note that the transition rates between states are functions of the transmembrane voltage α.

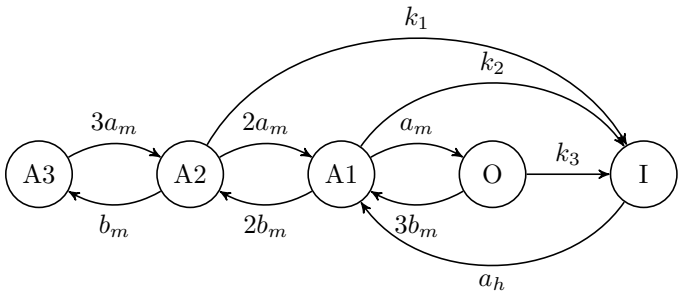


Figure 1: Markov chain model of Na^+ ion channel. Each circle represents a state; O is the open state and the rest are closed. An arrow denotes the rate of transition from one state to another. Each state also has a rate of transition to itself, the rate at which ion channels stay in that same state, which is not marked in the diagram. Note that two pairs of states have an arrow going only one way between them. These transitions are irreversible.

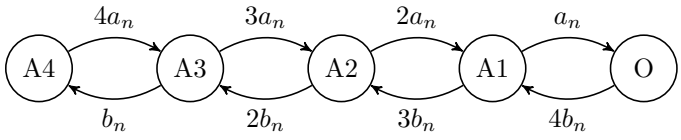


Figure 2: Markov chain model of K^+ ion channel. O is again the open state and all others are closed. Self-transitions are again implied. Notice that, unlike the Na^+ model, every transition in this model is reversible.

$$\mathbf{G}_\alpha^{\mathrm{Na}^+} = \begin{bmatrix} -3a_m & 3a_m & 0 & 0 & 0 \\ b_m & -(b_m + 2a_m + k_1) & 2a_m & 0 & k_1 \\ 0 & 2b_m & -(2b_m + a_m + k_2) & a_m & k_2 \\ 0 & 0 & 3b_m & -(3b_m + k_3) & k_3 \\ 0 & 0 & a_h & 0 & -a_h \end{bmatrix},$$

$$\mathbf{G}_\alpha^{\mathrm{K}^+} = \begin{bmatrix} -4a_n & 4a_n & 0 & 0 & 0 \\ b_n & -(b_n + 3a_m) & 3a_n & 0 & 0 \\ 0 & 2b_n & -(2b_n + 2a_n) & 2a_n & 0 \\ 0 & 0 & 3b_n & -(3b_n + a_n) & a_n \\ 0 & 0 & 0 & 4b_n & -b_n \end{bmatrix}$$

$$a_m(\alpha) = \frac{(\alpha + 40\mathrm{mV}/10\mathrm{mV}}{1 - \exp(-(\alpha + 55\mathrm{mV})/20\mathrm{mV}}, \qquad b_m(\alpha) = 4\exp(-(\alpha + 65\mathrm{mV})/18\mathrm{mV},$$
$$a_h(\alpha) = .07\exp(-(\alpha + 65\mathrm{mV})/20\mathrm{mV}, \quad k_1 = \tfrac{6}{2}5\mathrm{ms}^{-1},\ k_2 = 0.4\mathrm{ms}^{-1},\ k_3 = 1.5\mathrm{ms}^{-1},$$
$$a_n(\alpha) = \frac{(\alpha + 55\mathrm{mV}/100\mathrm{mV}}{1 - \exp(-(\alpha + 55\mathrm{mV})/10\mathrm{mV}}, \qquad b_n(\alpha) = .125\exp(-(\alpha + 65\mathrm{mV})/80\mathrm{mV}$$

Figure 3: The transition rate matrices and equations for each model. Note the dependence on transmembrane voltage α. Each matrix row indicates transition rates *from* a state, and columns indicate transition rates *into* a state: the value at row i and column j is the transition rate from state i to state j. The values on the diagonal are negative; this indicates the total transition rate *out of* the state. Each of these negative values is the sum of all other transition rates on that row, hence, each row sums to 0.

It is useful to note that since the Markov chains describe the probabilistic behavior of a single ion channel, we can simulate a collection of many ion channels with the assumption that their states are distributed based on that probability.

With any one constant voltage α, the state distribution will eventually converge onto a "steady state" π_α such that $\langle \pi_\alpha | \mathbf{G}_\alpha = \langle 0 |$, where the distribution no longer changes (though individual ion channels still transition). However, we do not let the system settle, and instead drive it with a changing voltage parameter.

We chose to use a neural spike pattern as our parameter function, which would be similar to realistic in-vitro action potentials. We used Izhikevich's system of ODEs for neural spikes,[4,5] which can produce several different spike patterns depending on a set of variable inputs. We primarily used the "regular spiking" and "intrinsic bursting" patterns. It is useful to note that while this type of neural spike is more biologically realistic, many publications which evaluate different ion channel models use square functions for simulations. These and any function can be easily input for voltage parameters in the code.

We now progress our simulation forward, step by step, driven by our voltage parameter function α. Note that, because of the construction of the code, the values of the voltage function must be calculated for a discreet time with a time step Δt, the same discreet time on which will run the simulation itself. The discreet evolution of the state distribution μ of the system at a certain time step, governed by the transition rate matrix $\mathbf{G}$, is given:

$$\langle \mu_{n+1} | = \langle \mu_n | e^{\Delta t \mathbf{G}_{\alpha_n}} \tag{1}$$

The result of this progression over the whole length of the voltage function is a long sequence of state distributions for the ion channel patch. From this sequence we can calculate our desired thermodynamic values. To calculate excess heat Q_{ex}, we must define "steady state surprisal" ϕ.

$$\phi_\alpha = -\ln \pi_\alpha$$

We can now define Q_{ex}, which for our N-length sequence of state distributions accumulates thus:[2]

$$-\langle Q_{\text{ex}} \rangle = \sum_{n=0}^{N-1} \langle \mu_{t_{n+1}} - \mu_{t_n} | \phi_{\alpha_n} \rangle \tag{2}$$

With our sequence of state distributions, we also calculate current I, which will be useful when, in the future, we compare our simulations with experimental results observed in-lab. Since each ion channel is binary-open or closed-and current only flows when one is open, the current calculation uses a vector $|\delta_{\text{open}}\rangle$, for which every element is 0 except that which corresponds to the open state of the ion channel, which has a value of 1. The current calculation also uses two physical constants: the conductance of an open channel g_0, and Nerst potential V_0.[3] We've used Nerst potentials $V_{0\text{Na}^+} = 90\text{mV}$ and $V_{0\text{K}^+} = -80\text{mV}$.[1] I couldn't find a value for the conductance of the open channels, so since we are physicists, we shall take $g_0 = 1\Omega^{-1}$.

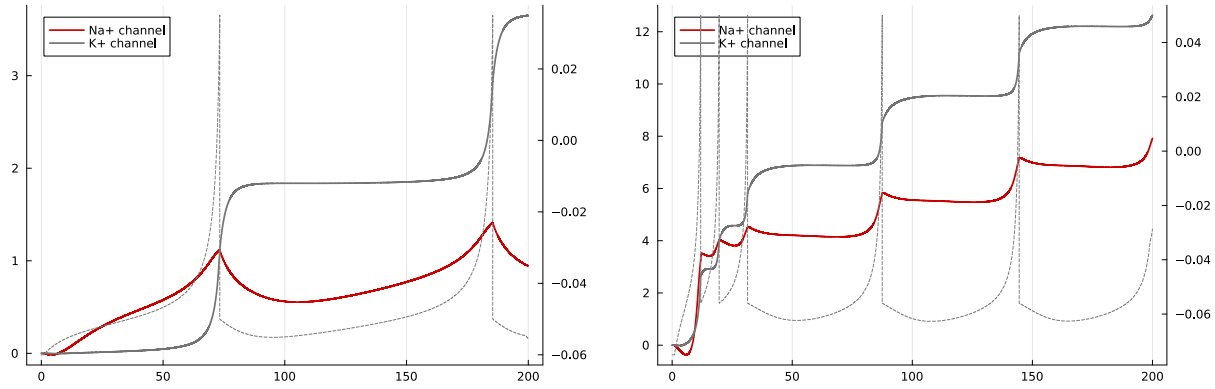
$$\langle I(t) \rangle = g_0[\alpha(t) - V_0]\langle \mu(t) | \delta_{\text{open}} \rangle \tag{3}$$

Results

In Fig 4 is graphed the calculate Q_{ex} for both channels under the two different voltage protocols. Remember, Q_{ex} is the heat that the channel dissipates into its environment as it changes state. The heat behavior of Na^+ and K^+ have very distinct shapes, as clear in both graphs.

Over the full interval, the K^+ channel dissipates significantly more than the Na+ channel, while, as evident early in the RS graph, the Na^+ channel responds more quickly to the environmental change with its dissipation. However, as visible between the first two spikes of the IB graph, on a more rapid timescale, the Na^+ channel's dissipation exceeds that of the K^+ channel. Additionally, while the K^+ channel's dissipation levels off between spikes, the Na^+ channel dissipates negative heat—rather, it absorbs heat from the environment, which is a violation of the irreversible process.

The calculated current through the ion channels is graphed in Fig 5. Notice, like with Q_{ex}, the slower response of the K^+ channel to the change in transmembrane voltage and its sharper peak. Also note how



(a) Regular spiking protocol

(b) Intrinsically bursting protocol

Figure 4: Graphs of Q_{ex} under two different spike protocols. The protocols were constructed with Eugene Izhikevich's system of differential equations for neural spike patterns, using parameters for "regular spiking" (RS) and "intrinsically bursting" (IB) neurons.

Axes bottom: time [ms]; left: $\langle Q_{\text{ex}} \rangle$ [$k_{\text{B}}T$]; right: transmembrane voltage [mV]

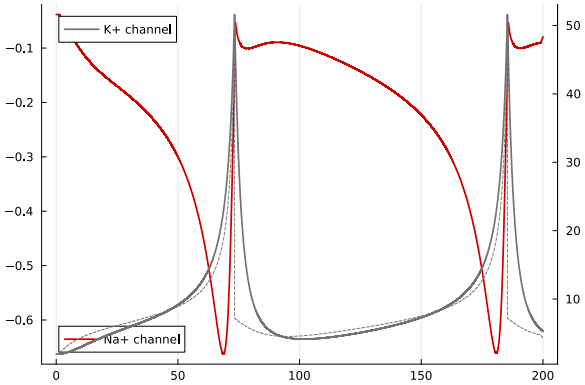


Figure 5: Average current $\langle I(t) \rangle$ through a patch of channels over an RS spike protocol. The values of the transmembrane voltage (dotted line) are identical to those in Fig 4.

Axes bottom: time [ms]; left: Na^+ channel $\langle I(t) \rangle$ [mA]; right: K^+ channel $\langle I(t) \rangle$ [mA]

the current of the Na^+ channel peaks and begins decreasing in magnitude even while the voltage is still increasing, and its sudden drop almost to zero as the voltage reaches its maximum.

The functional difference of the Na^+ and K^+ channels is important to understanding the $I(t)$ results. The video by Neuro Transmissions in the references gives useful context that explains the sign difference between the currents of the two channels.

Directions for the future

I imagine two main options for building on this project.

- **Implementation of more Markov chain models** This thermodynamic insight into the behavior of the ion channel models has potential to be valuable in model construction and comparison. This project used two of the simplest Markov chains for Na^+ and K^+. Many more models exist for both, and the construction of the code allows for straightforward substitution of other transition rate matrices. One could simulate and compare the energetics of different models of the same channel.
- **Comparison with experimental current calculates** This is a very strong option for developing this project that has the possibility of dialogue with other labs. Biophysicists and neuroscientists drive patches of ion channels with various action potential voltages to measure the resulting current. If one calibrated our calculated current from the simulated ion channels against observed values from in-lab patch-clamp experiment, the thermodynamic values we can calculate could possibly be of some interest to the experimental researchers, who are unable to measure those values themselves.

However, there are any number of possibilities which I have not imagined. Ion channel research is a rich and established field of study, and there are certainly more places where this thermodynamic approach could be valuable.

References

[1] Dayan, P. , Abbott, L. F.: Theoretical Neuroscience: Computational and Mathematical Modeling of Neural Systems. Computational Neuroscience Series, revised edn. MIT Press, Boston (2005)
[2] M. T. Semaan and J. P. Crutchfield, Homeostatic and adaptive energetics: Nonequilibrium fluctuations beyond detailed balance in voltage-gated ion channels, Phys. Rev. E 106, 044410 (2022).
[3] P. M. Riechers and J. P. Crutchfield, Fluctuations when driving between nonequilibrium steady states, J. Stat. Phys. 168, 873 (2017).
[4] E. M. Izhikevich, Simple model of spiking neurons, IEEE Trans. Neural Netw. 14, 1569 (2003).
[5] E. M. Izhikevich, Dynamical Systems in Neuroscience: The Geometry of Excitability and Bursting, 1st ed., Computational Neuroscience (The MIT Press, Cambridge, MA, 2006).

Additionally, I found this video a useful explanation of the function of ion channels, including the difference between Na^+ and K^+ channels. It also provides context for where ion channel research fits into understanding neuron behavior.

Neuro Transmitters, "How the Giant Squid Axon Changed Neuroscience." YouTube, 7 July 2019. `https://www.youtube.com/watch?v=dxbffhJWd7M`