Nonequilibrium Thermodynamics of Voltage-Gated Ion Channels

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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 an appropriate suite of tools. Among many things, it 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.

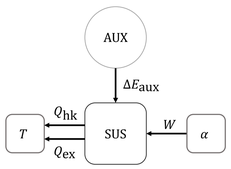

Figure 1 — A thermal system and its interactions. The reservoirs of heat (temperature T) and work (parameter α) are assumed to be ideal, while an “auxiliary” reservoir, of which we assume nothing, contributes a generic ΔE_{aux}. We allow total heat to be split into excess (Q_{ex}) and housekeeping (Q_{hk}) heats.

We leverage stochastic thermodynamics to study the energetics of voltage-gated sodium and potassium ion channels as they respond to realistic environmental stimuli—neuronal action potential spikes. We also calculate the expected current as a function of time, providing a testable prediction of transients in dynamically-driven patch-clamp experiments.

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Methods

The Markov chain models of Na^+ and K^+ channels (Fig. 1, 2) can each be formulated as a transition rate matrix $\mathbf{G}_\alpha$ parameterized by a transmembrane voltage α.

We simulated the behavior of the two channel models by discretizing two spike protocols (indicated in Fig. 4, 5, and 6 as dotted lines) with time steps $\Delta t = 0.001\text{ms}$ over an interval of 200ms and then directly calculating the resulting sequence of state distributions. Using equation (4), from the state distributions and hypothetical steady-state distributions, we calculate the average excess heat $\langle Q_{\text{ex}} \rangle$. Finally, we calculate expected current using equation (5) with Nernst potentials $V_{0\text{Na}^+} = 90\text{mV}$ and $V_{0\text{K}^+} = -80\text{mV}$ [1] and an open conductance $g_0 = 1\Omega^{-1}$.

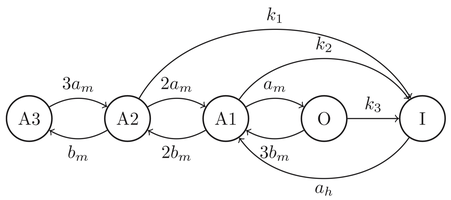


Figure 2 — Markov chain model of the Na^+ channel. Self-transitions are implied. States A_n are closed, state O is the channel’s open state, and state I is an inactivation gate, which is considered closed for the calculation of current. The rate parameters a_h, a_m, b_m are functions of voltage, the equations for which are known but here omitted for space. The rate transition constants $k_{1,2,3}$ are also known.

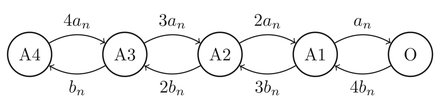


Figure 3 — Markov chain model of the K^+ channel. Self-transitions are implied. States A_n are closed, with state O being the channel’s open state. The rate parameters a_n and b_n are functions of voltage, omitted for space.

Figures 4, 5 (right) — 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, above) and “intrinsically bursting” (IB) neurons.[4,5] 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, in violation of the irreversible process.

A discrete-time evolution for state distribution μ governed by transition rate matrix $\mathbf{G}$ can be defined:

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

From the definition of the transition rate matrix, a steady state distribution π can be defined as

$$\langle \pi_\alpha | \mathbf{G}_\alpha = \langle 0 | \tag{2}$$

Steady state surprisal is then defined:

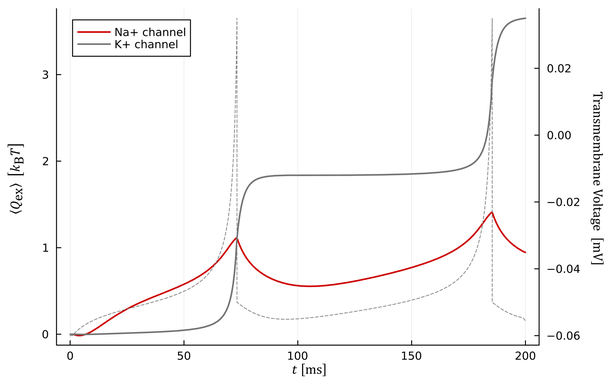
$$\phi_\alpha = -\ln \pi_\alpha \tag{3}$$

For a sequence of N state distributions μ and steady state surprisal ϕ for each present value of α, the average excess heat accumulates:[2]

$$-\langle Q_{\text{ex}} \rangle = \textstyle\sum_{n=0}^{N-1} \langle \mu(t_{n+1}) - \mu(t_n) | \phi_{\alpha_n} \rangle \tag{4}$$

Using the conductance of the open channel and its Nernst potential (g_0 and V_0), both physical constants, and with δ_{open} being defined as a vector denoting the open state, current can be calculated:[3]

$$\langle I\langle t \rangle \rangle = g_0 [\alpha(t) - V_0] \langle \mu(t) | \delta_{\text{open}} \rangle \tag{5}$$



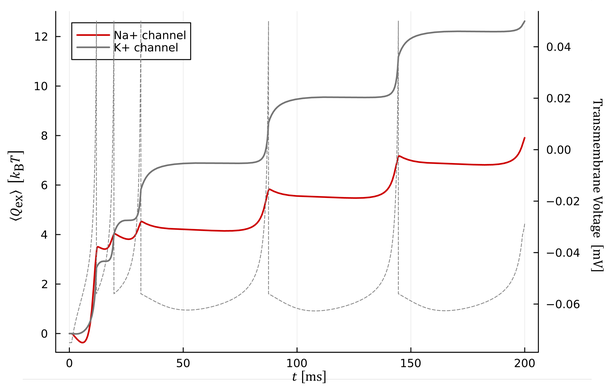
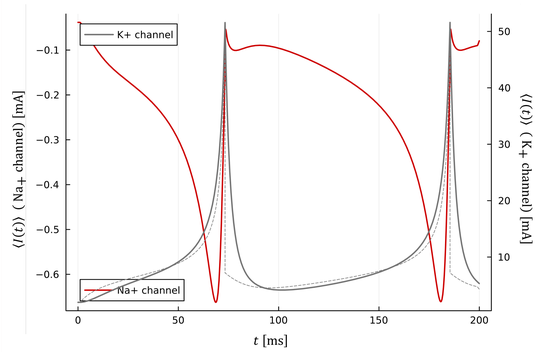


Figure 6 — Average current $\langle I(t) \rangle$ through a patch of channels over an RS spike protocol. The values of the transmembrane voltage (dotted line) have been omitted for readability but are identical to those in Fig. 4. Notice, like with Q_{ex}, the slower response of the K^+ channel to the change in transmembrane voltage and its sharper peak. Also note how 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.



Conclusions

These tools are a potentially useful proxy for assessing a system’s heat responses, which are difficult to measure in-lab. The calculated current provides a reference for model calibration between these stochastic computations and experimental measurements. This nonequilibrium thermodynamical approach to ion channel model analysis can provide a detailed window into the energetic responses of each system, allowing further comparison between the realistic thermodynamic functionality of different channel types and an additional criterion for model construction.

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[3] P. M. Riechers and J. P. Crutchfield, Fluctuations when driving between nonequilibrium steady states, J. Stat. Phys. **168**, 873 (2017).
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