Journal club

Federico Minutoli - UniGe

Computational Neuroengineering

Cellular Function Given Parametric Variation in the Hodgkin and Huxley Model of Excitability

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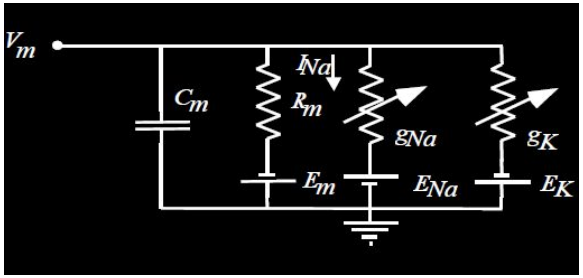
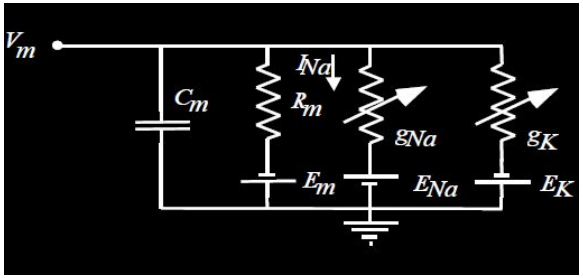
Background

Hodgkin and Huxley model

- The HH model represents the cornerstone of quantitative models of neuronal excitability
- The heart of HH is a description of time- and voltage-dependent conductances of Na+ and K+ channels in terms of their gating particles (m, h, and n, respectively)



Hodgkin and Huxley model



- The HH model represents the cornerstone of quantitative models of neuronal excitability
- The heart of HH is a description of time- and voltage-dependent conductances of Na+ and K+ channels in terms of their gating particles (m, h, and n, respectively)
- Gating particles are rates (between 0 and 1), that were introduced to describe the dynamics of the conductances scaled from a maximal conductance. They can be either *activating* or *inactivating* and obey to first-order kinetics.

$$g_{Na} = \bar{g}_{Na} \cdot m^3 h \qquad g_K = \bar{g}_K \cdot n^4$$

$$(1 - p_i) \xleftrightarrow{\alpha_i(V), \beta_i(V)} = p_i$$

$$\frac{dp_i}{dt} = \alpha_i(V)(1 - p_i) - \beta_i(V) p_i$$

$$p_{i,t\to\infty}(V) = \frac{\alpha_i(V)}{\alpha_i(V) + \beta_i(V)}$$

Steady-state solution

$$\tau_i(V) = \frac{1}{\alpha_i(V) + \beta_i(V)}$$

Time constant

Previous research

Cell types, Network homeostasis and compensation from a biologically plausible Ion channel expression model

Timothy O'Leary et al, 2014

Simple model that encodes an *activity set point* in single neurons, from the autonomous regulation of which homeostasis can emerge.

Homeostasis, Failure of homeostasis and degenerate Ion channel regulation

Timothy O'Leary, 2018

Cellular's robustness to perturbation derives from degenerate co-expressed channel types that compensate the role of others, as they share overlapping roles in shaping electrophysiological properties.

Both approaches kept kinetics (***K***) constant and only looked at channel densities (***S***), as almost all of the homeostatic-based models of excitability regulation used to do.

Aim of the paper

Dimensionality reduction

- Macroscopic cellular function is maintained despite extensive intrinsic variations (both inter- and intra-cellular) in underlying elementary constituents, including the size of the cell, the ratio between different channels and the number, distribution, and kinetics of their proteins.
- Macroscopic invariance to microscopic variations points to a significant gap between the high-dimensional level of description captured by biophysical measurements and the lower, physiological dimensionality, to which cellular function is actually sensitive.

How is reliable physiological function maintained in the cells despite considerable variability in the value of key parameters of multiple interacting processes that govern that function?

Excitability regulation

- Show that **slow inactivation**, a ubiquitous activity-dependent feature of Na and K channels, is a powerful *local homeostatic control mechanism* that stabilizes excitability amid changes in parameters across a wide range of different time scales, sub-second to many minutes/hours, when changes of excitability state are considered as dynamics within the (soonly defined) ***S-K*** plane.

Methodology

Parameters space

- Even the simplest Hodgkin–Huxley formulation (a single compartment with two voltage-dependent conductances in Na and K) is very sensitive to fluctuations that occur amidst more than 10 parameters.

- Despite that, HH's excitability outcome can be shown to depend solely on two physiological dimensions - cellular-level structural (***S***) and protein-intrinsic kinetics (***K***) - expressed as simple combinations of actual HH parameters that can be extracted from voltage-clamp data.

- Structural parameters describe the properties of the cell, and refer to membrane surface area, its capacitance and the densities of its ion channels. Kinetic parameters are those that describe the opening and closing rates of the conductances.

Experiment

A collage of slightly modified images extracted from the 1952 ***original*** report of Hodgkin and Huxley. (**A**) The table indicates ranges of cellular-level structural parameters. (**B**) The graphs depict protein-level kinetic parameters, expressed as six transition rate functions superposed with data points.

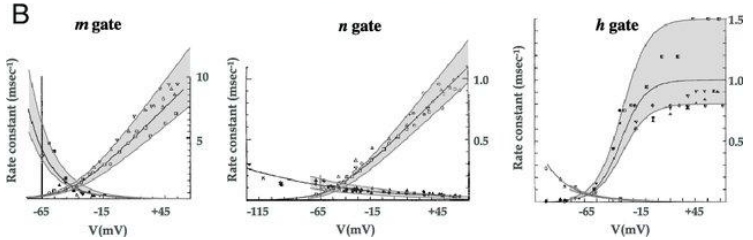
Structural parameters

A

Parameter	Values chosen for mathematical model		Experimental values	
			Mean	Range
Membrane Capacitance	1.0	C_M (μF/cm^2)	0.91	0.8 to 1.5
Sodium Nernst Potential	+50	V_{Na} (mV)	+44	+30 to +54
Potassium Nernst Potential	-77	V_K (mV)	-76	-74 to -79
Leak Nernst Potential	-54	V_l (mV)	-54	-61 to -43
Maximal Sodium Conductance	120	g_{Na} (mS/cm^2)	120	65 to 260
Maximal Potassium Conductance	36	g_K (mS/cm^2)	34	26 to 49
Maximal Leak Conductance	0.3	g_{leak} (mS/cm^2)	0.26	0.13 to 0.50

Kinetic parameters

B

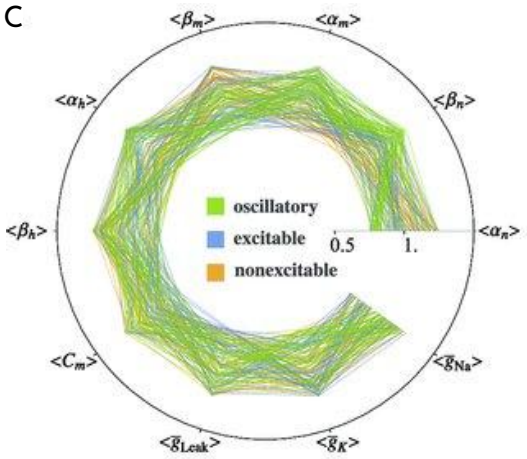


Assumptions:

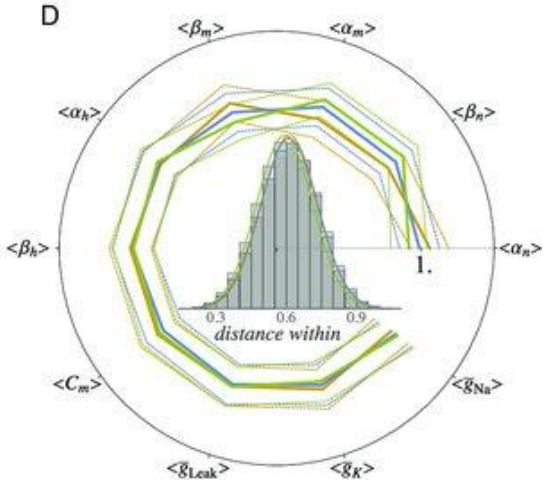
- Uniformity in the +-25% range from HH original values and marginal independency.
- Linear scaling of transition rate functions.

Experiment

10k realizations of a full Hodgkin-Huxley model, each uniquely defined by a vector of 10 scaling parameters. Responses are classified to three excitability statuses: excitable, non-excitable and oscillatory (pacemaker).



Polar plots of 100 results for each excitability status.

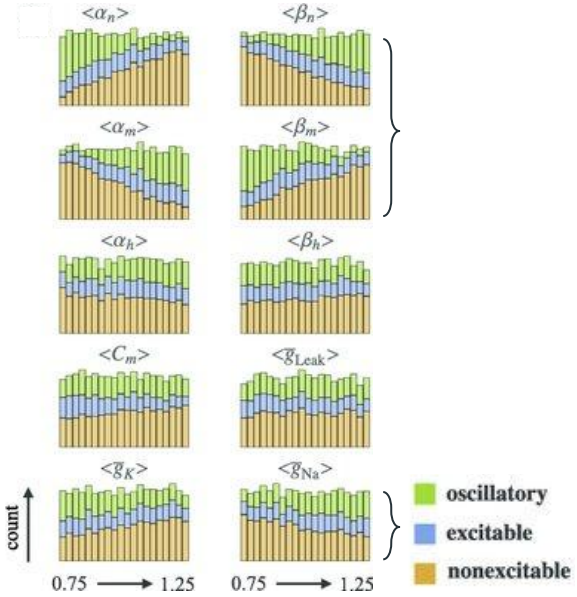


Mean vectors, standard deviations and histograms of Euclidean distance between vectors of different classes.

Results

Parameters analysis

Histograms of the three excitability statuses, constructed from the data (10k Hodgkin-Huxley realizations), for each of the freely fluctuating scaling parameters.



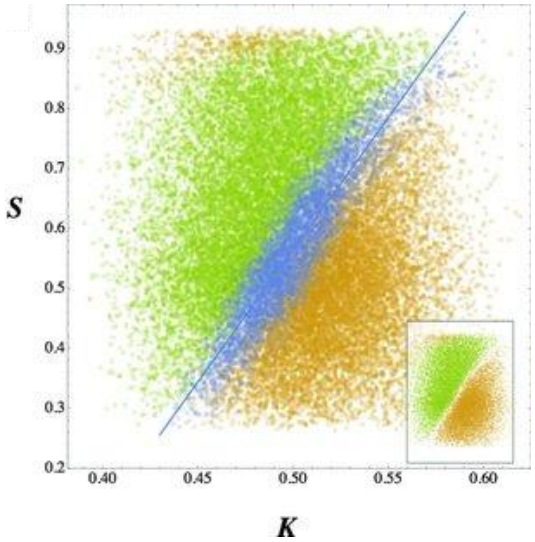
Condition for instability near threshold

$$-g_{fast} > \frac{C_m}{\tau_{slow}}$$

Structural parameters (g_{fast}, C_m) ←
→ *Fast positive feedback*

Kinetic parameters (tau_{slow}) ←
→ *Slow negative feedback*

S–K plane: Definition



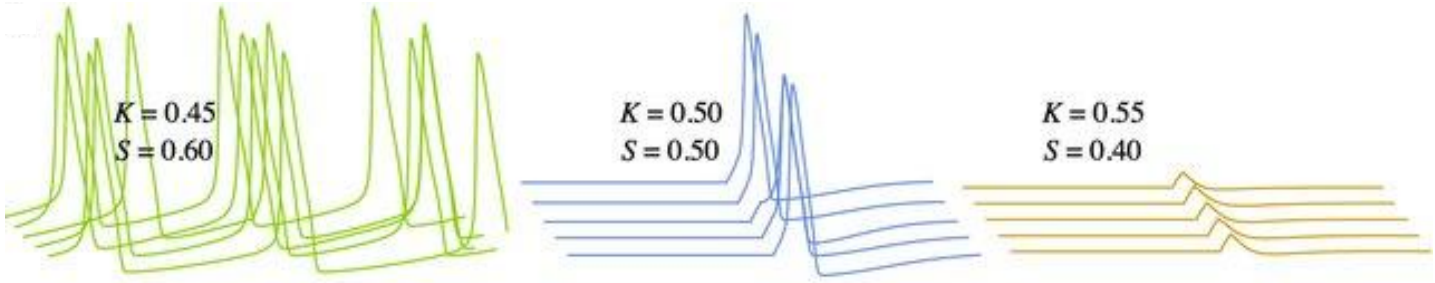
$$\begin{cases} \tau_{slow} \propto \mathcal{K} = \dfrac{\alpha_n + \beta_m}{\alpha_n + \beta_m + \alpha_m + \beta_n} \\ -g_{fast} \propto \mathcal{S} = \dfrac{\bar{g}_{Na}}{\bar{g}_{Na} + \bar{g}_K} \end{cases}$$

When examined in the 2D ***S–K*** space, the HH model reveals order that is impossible to detect in the more explicit higher dimensional representation.

S–K plane: Properties

Some points deserve attention in relation to the numerically calculated ***S-K*** plane:

- Improved inter-class separation in the 2D plane that shows a steep separation of extreme states which leads to an apparent invariance of the system to variations in maximal conductances (fixed **K**).
- Several experiments with different S;K pairs (0.60;0.45, 0.50;0.50, and 0.40;0.55) showed a more robust outcome since the **S** and **K** dimensions (simple rational functions of 1st degree) attenuate the effect of individual HH parameters and, in turn, seem better predictors.
- Response shape (integral) inference through navigation within the ***S-K*** plane



Proposed solution

Towards

- The tractability of the system in the **S-K** plane enables regulation by an activity-dependent rule acting as one physiological entity. A possible regulation rule would involve inverse relations between electrical activity and the actual value of the structural dimension (**S**).

- Many physiological processes that modulate membrane ion channels may realize such adaptation, covering a wide range of spatial and temporal scales, by naturally constraining S to hover around the diagonal of excitability phase - i.e., Slow inactivation of Na conductance, Ca-dependent activation of K conductance (fast time scale) or regulation of Na/K protein expression (slow time scale).

- Why *slow inactivation* (of Na channels) is interesting?
  - Historically neglected as a regulator to maintain excitability status.
  - Impacts the **value of** $\bar{g}_{\mathrm{Na}}$ on a wide range of time scales (sub-second to many minutes).
  - Inactivation is *local* as it doesn't require central control from CNS; it happens automatically as a consequence of activity, like a normalizing force in extended excitable tissues.

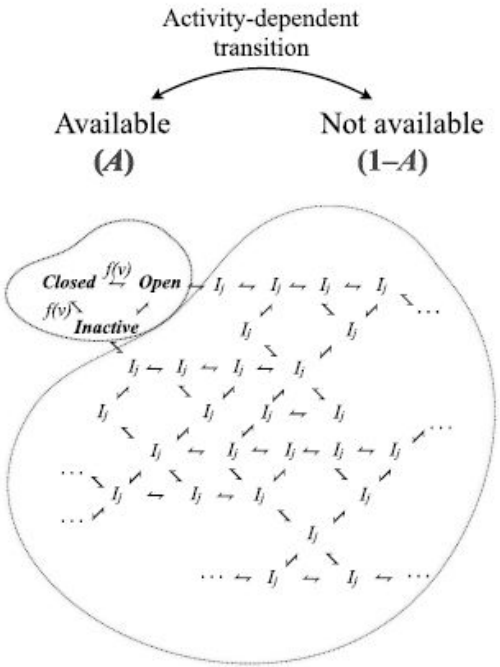
Dynamics in the S–K plane

To understand the potential impacts of Na slow inactivation on dynamics within the **S–K** plane, channel gating beyond the time scale of a single action potential is considered. Slow inactivation is represented as a macroscopic dynamic system, where channels move between two states, driven by activity:

- Available, **A**, that comprises the states, besides the open state itself, from which the channel may arrive to the open state within the time scale of a single action potential - i.e., closed states or very first inactive states treated in the standard HH model

- Not available, **1 - A**, a large interconnected pool of slow inactive states from which transition to the open state within the time scale of an action potential is impossible. Theory and experiments show that, in such a scheme, the multiplicity of slow inactive states entails a power law scaling of recovery from (**1 - A**) to **A** as a function of time spent in (**1 - A**). Thus, unlike standard Hodgkin–Huxley gates, the rate of recovery from slow inactivation does not have a uniquely defined characteristic time scale, but, rather, the time scale is determined by the distribution of channels in the space of inactive states during activity.

Visual demonstration

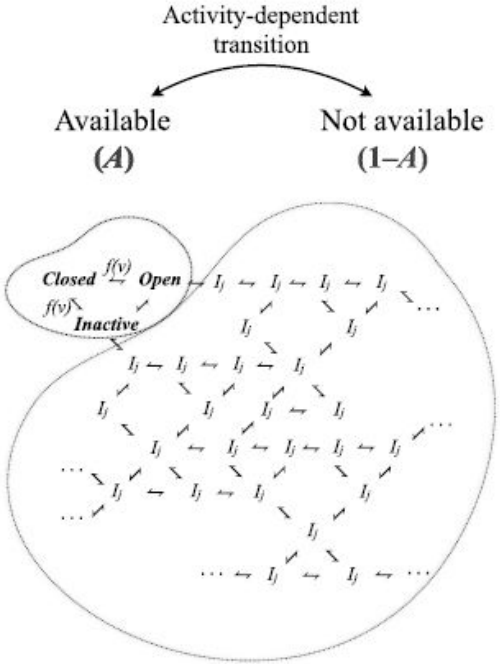


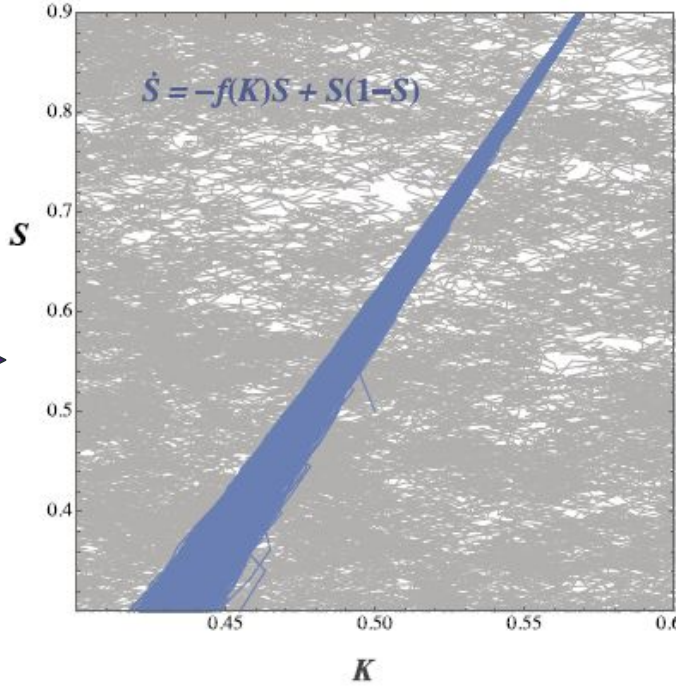
The kinetics of A ⟷ (1 - A) may be qualitatively described by an adaptive rate model:

$$\dot{A} = -f(\gamma)A + g(A)(1 - A)$$

- As A strongly impacts the value of $g_{Na'}$ it is instructive to fix A = $g_{Na'}$ where the Na conductance, unlike in HH original formalism, is not a constant as, when long-term effects are sought, it might be treated as a dynamic variable that modulates the reservoir of slow-inactivation.
- By fixing g_K to a constant, the adaptive rate model qualitatively captures the dynamics of $g_{Na}/(g_{Na} + g_K)$, that is, exactly the definition of **S**...

Visual demonstration





Critical analysis

Strengths

- The study was able to incorporate kinetics parameters within homeostatic regulation of neuronal excitability function, which opens up to possibly more complex dynamics of the regulator.

- The proposed **S-K** framework greatly enhances the interpretability of the problem, leaving room to many future experiments, while still capturing non-linearities of the high-dimensional HH model, as it identifies proper scales in analyses of cellular phenomena, where the phenomenon of interest is low-dimensional and explainable in simple physiological terms.

- Slow inactivation is an appropriate candidate, as it plays an important role in controlling membrane excitability by governing the availability of Na channels, and its defection is already often associated with common diseases of cell excitability.

Limitations

- Oversimplifying assumptions in the experiment may be questioned (linear scaling, Nernst potentials cut off and uniformity of the distributions), which is confirmed by the authors (*"We created a straw man"*)

- Shortcomings of the Hodgkin-Huxley model, like not being able to capture bursting, adaptation and post-inhibitory rebound; also, since the authors focus on the classic formulation it doesn't cover other types of ionic channels, like Ca2+, or persistent channels of Na and K, which may show different behaviours from what has been observed here.

- As the authors state, many more possible formulations of **S** and **K** could have been chosen, even with more complex dynamics, outside of the rational functions domain Q.

- *Correlation does not imply causation*

Thank you!