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Emergence and maintenance of excitability: kinetics over structure ☆

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The capacity to generate action potentials in neurons and other excitable cells requires tuning of both ionic channel expression and kinetics in a large parameter space. Alongside studies that extend traditional focus on control-based regulation of structural parameters (channel densities), there is a budding interest in self-organization of kinetic parameters. In this picture, ionic channels are continually forced by activity in-and-out of a pool of states not available for the mechanism of excitability. The process, acting on expressed structure, provides a bed for generation of a spectrum of excitability modes. Driven by microscopic fluctuations over a broad range of temporal scales, self-organization of kinetic parameters enriches the concepts and tools used in the study of development of excitability.

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Over half a century of extensive scientific work teaches us that the phenomenon of excitability in biological membranes entails tuning of relations in a large parameter space. A balance of effective expression of ionic channel proteins having unique gating kinetics is required for the action potential phenomenon to emerge and be maintained. What is the nature of the processes that constrain the relations between parameters in the large combinatorial space of all possible configurations? While our understanding of the physics underlying membrane excitability is advanced compared to other physiological phenomena, we are in the dark when pushed to the corner with this question. Allegedly, even the basic Hodgkin-Huxley (HH) formal description of excitability

[1] — with only two types of voltage-gated ionic conducting proteins — is not easily tamed when the kinetic parameters of channel gating are modified (which occurs due to a rich protein state space and modulatory processes); or, when the ratio between the number of different channel proteins in the membrane is changed (due to differential protein turnover); or, when the membrane capacitance and current leak change (during massive cell growth, movement or contact of the cell with biological matrices that impact on membrane surface tension). The natural phenomenon of excitability is resilient to such changes, or (at least) apparently more robust than the formal, mathematical models used to describe it.

The problem, it is acknowledged, goes beyond the regulation of excitability; it belongs to a class of open questions that concern organization in biological systems in general, the emergence of macroscopic functional 'order' from a large space of potential microscopic 'disordered' configurations [2••]. Addressing this class of fundamental questions is challenging, at least in part, due to methodological limits in distinguishing relevant from irrelevant determinants distributed over broad spatial and temporal scales [3•,4•]. The presumed regulatory processes might operate at the levels of transcription, translation, protein folding and positioning, collective protein-protein interactions, protein degradation, protein kinetics and the biochemical modulations of these paths. What makes membrane excitability particularly attractive to study in this context is the relatively sound understanding of the functional end-product, the action potential, and its amenability to experimental manipulations at both microscopic (channel protein) and macroscopic (membrane potential) levels.

Emergence and maintenance of excitability is often considered in terms of arriving at and remaining about a manifold of 'solutions' embedded in a high dimensional space composed of two families of parameters, structural and kinetic. In the Hodgkin and Huxley original model, the main structural parameters are membrane capacitance (C_M), and maximal sodium ($\overline{g}_{Na}$), potassium ($\overline{g}_K$) and leak ($\overline{g}_\ell$) conductances, and the many kinetic parameters are expressed as six transition rate functions: $\alpha_n(v)$, $\beta_n(v)$, $\alpha_m(v)$, $\beta_m(v)$, $\alpha_h(v)$, $\beta_h(v)$. The tables and figures exposed by Hodgkin and Huxley in their report [1] suggest that kinetic parameters vary over a range of ca. ±20% and structural parameters over a factor of two or more.

A glimpse to the nature of the manifold that supports excitability in the Hodgkin–Huxley parameter space is

Figure 1
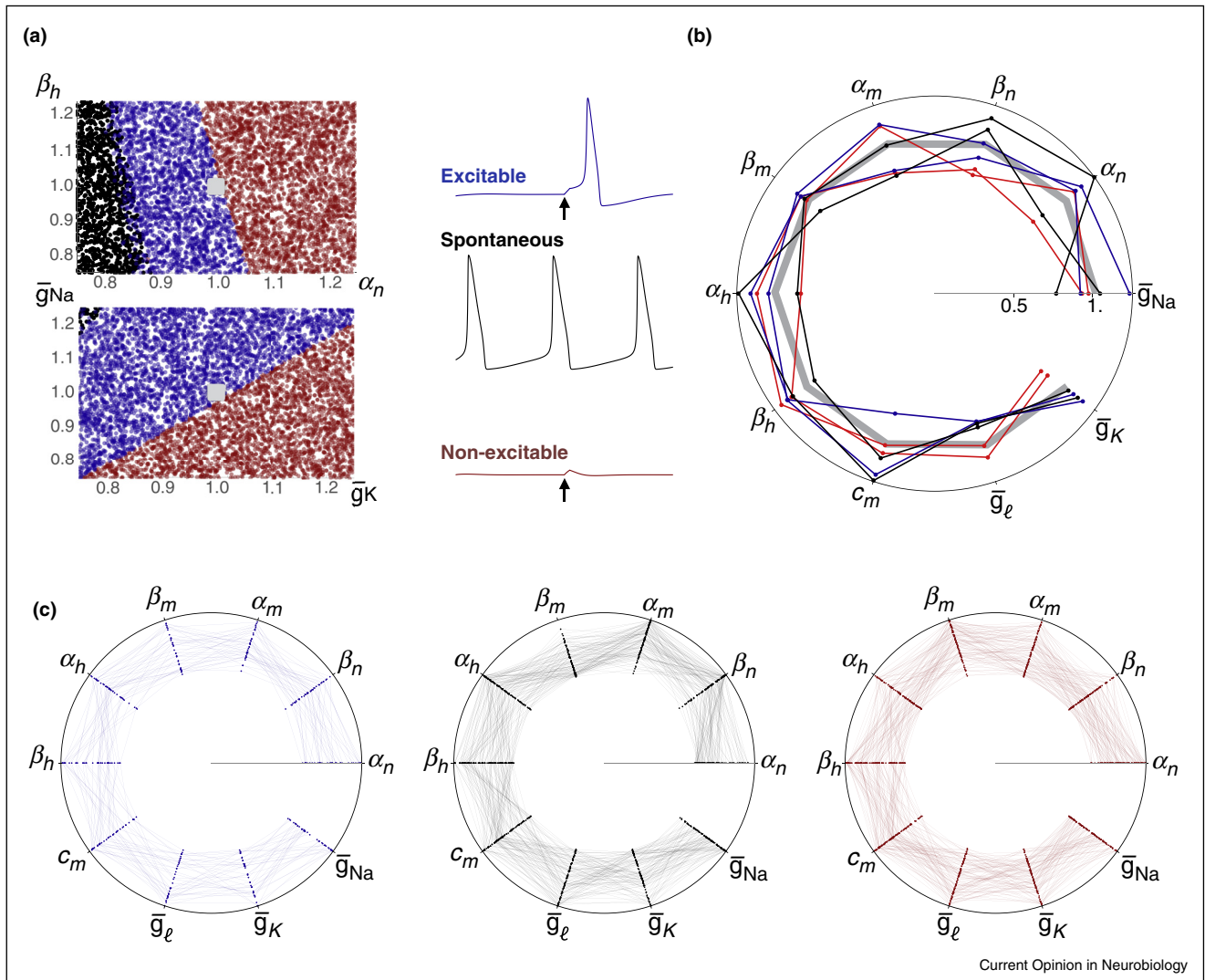
Manifold of excitability intuited. **(a)** Outcome of the original Hodgkin-Huxley model for membrane excitability with the values of the kinetic functions $\alpha_n(v)$ and $\beta_h(v)$ or structural parameters $\overline{g}_{Na}$ and $\overline{g}_K$ being scaled by randomly chosen factors over a fairly moderate range of 0.75–1.25 relative to their standard values (which are, interestingly, edgy; indicated by small gray squares in the middle of both examples). Classes of resulting excitability status were defined based on membrane response to a current stimulus (one millisecond long at x1.25 Hodgkin–Huxley original threshold stimulus) and depicted by color as indicated in the voltage traces to the right. In panel **(c)** the whole set of ten parameters was randomly perturbed 250 times over a range of 0.75–1.25 (that is, ±25%) relative to their standard values. Each set of parameters is presented as a line connecting the values in a polar plot; several examples shown in panel **(b)**, where the Hodgkin–Huxley original parameter set is depicted by a thick gray line. Each parameter set was classified as giving rise to an excitable solution [panel (c), left], spontaneously spiking [panel (c), middle] and non-excitable [panel (c), right]. Note that all three excitability modes distribute throughout the range tested.

provided in Figure 1, where either pairs of parameters (Figure 1a) or the entire set of ten parameters (Figure 1b,c) are randomly perturbed over a moderate range (±25% relative to the original HH values). Clearly, to maintain excitability a 'coordinated tuning' of physically independent entities (different protein populations and their kinetic parameters) is required. For each pair of parameters there exists an 'allowed' direction of change that is less prone to impact on excitability, and a 'not-allowed' direction that is more prone to cause a qualitative

modification of the macroscopic order. While imaginable in two-dimensional settings (Figure 1a), coordinated tuning becomes intricate when all parameters are considered simultaneously (Figure 1b,c).

The parameter range apparent in the Hodgkin and Huxley's 1952 *Journal of Physiology* paper is indicative to the fact that excitable cells actually utilize the space in maintaining functional order. But the most convincing evidence to that effect comes from a series of studies in