A response to Professor Noble's paper: Ordered disorder to drive physiology

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Abstract

In this paper, Anant Parekh and his colleagues discuss the precise ways in which stochasticity is harnessed in biology. In particular, they discuss voltage-gated Ca2+ channels that allow ions to move across cell surfaces, and how they open and close in a probabilistic fashion. They then explain in detail how evolution has harnessed this level of disorder through mechanisms such as channel clustering.

Ion channels occupy a central and indispensable role in the physiology of animal cells. These remarkable miniscule machines move ions rapidly in and out of cells, changing the electric potential cross the cell surface. Ion channels might be considered the quarks or building blocks of the nervous system; their activity forms the core of our ability to detect and respond to our environment, form thoughts and translate them into actions. Ion channels are found in all cells, across all species where they are essential for the ability of the immune system to combat infection and for the heart to beat.

Ion channels are unique amongst molecules that populate the physical and life sciences because the proteins can be studied at an individual level using a form of electrophysiology called patch clamp recording. Physicists and chemists cannot tell us how one molecule will behave; they can only predict behaviour for the population as a whole. Studies on single ion channels have revealed channels often exist in two main states: open and closed (Figure 1). Open channels are the functional form, permitting ions to move rapidly across the cell surface. Surprisingly, detailed single molecule studies have shown that many voltage-gated Ca2+ channels, which drive neurotransmitter release or the ability of the heart to pump blood, have a low likelihood of opening (or open probability) upon stimulation. The open probability is typically <0.1. This means that, if stimulated 10 times, the Ca2+ channel will

open, on average, just once. This is hardly an effective way to rapidly propagate electrical signals across a nerve cell, where speed and timing are critical. How has biology managed to extract order from a stochastic system? Perhaps the first solution came by ensuring a favourable statistical outcome by increasing numbers. Cells often express hundreds or thousands of the same type of Ca2+ channel at the same time. Consider a cell with 1000 channels, not an unrealistic number in heart muscle for example. Each individual channel has an open probability of say 0.01. But, with 1000 channels, 10 channels on average would open with each stimulus. We do not know which 10 channels will open but 10 will open. Since each channel can conduct many Ca2+ ions, ~10 open channels at the same time will lead to a significant change in electric potential across the cell, ensuring propagation of electrical activity. In this regard, for an electrical signalling mechanism, it matters not which ion channels open as long as a few do to change the potential across the cell surface.

Electric signalling is harnessed in relative simple metazoans and multi-cellular organisms ostensibly to allow the animal to move rapidly towards a food source or away from a predator. As biological complexity increases, more nuanced responses are required as well as stimulus-induced long-lasting changes in the complement of genes expressed. Most of these responses are driven by Ca2+ channels, which double up as signal transducers providing trigger Ca2+ to activate downstream pathways independent of electrical activity. How does the Ca2+ channel turn on the relevant pathway, such as a protein (called a transcription factor) that moves to the nucleus to control expression of a particular set of genes? If the transcription factor is located away from the channel, it would not know precisely when the channel opened and this would induce a further level of unpredictability in addition to the uncertainty in knowing when a channel will open.

It turns out that Ca2+ channels have private conversations with the transduction pathway, accomplished through a physical interaction between the channel and the transcription factor that relays information from the channel to the cell nucleus, where most of the genetic material is housed. Typically, a triumvirate of additional proteins is required to ensure these restricted communications take place with functional impact on the cell: a scaffolding protein that binds to the channel, the transcription factor itself and a protein that ensures the factor is activated only when the appropriate stimulus is received.

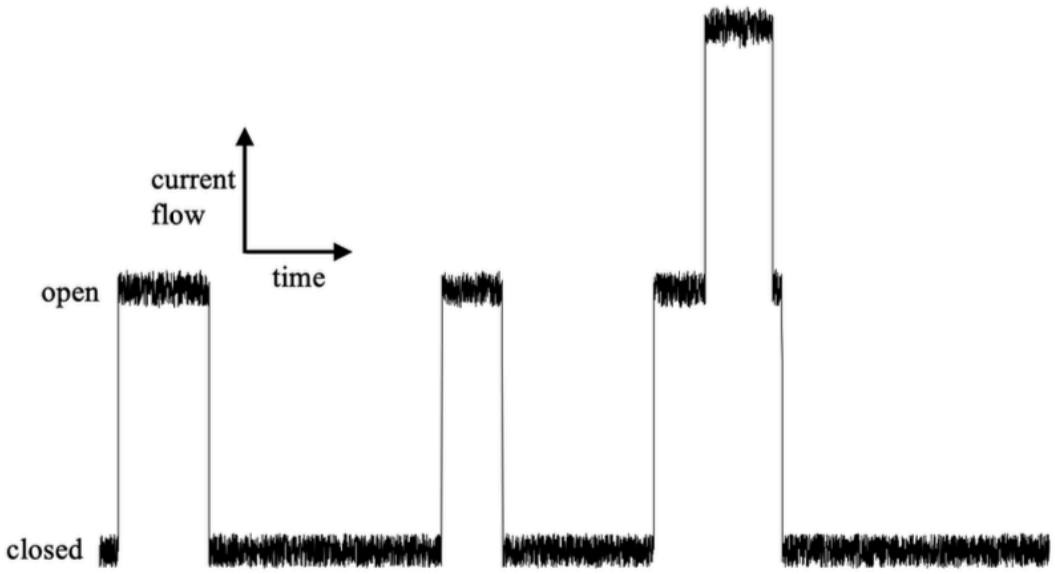

Figure 1. Single channel properties of a K+ channel. Closed denotes the channel in the closed (non-conducting) state and open represents the functional, conducting conformation. The channel is in the closed state for ~70% of the time shown. Note the two open events that superimpose towards the end of the trace, indicating the presence of two independent channels. Openings typically last 1 millisecond.

Producing three proteins for every Ca2+ channel is energetically costly for a cell and imposes physical constraints on the cell surface. Moreover, Ca2+ channels can signal to different transcription factors and so different sets of triumvirates are required and all cannot be juxtaposed against each Ca2+ channel. How does the cell ensure signal transduction through different pathways is faithfully recruited by Ca2+ channels that behave stochastically? Evolution has employed the process of channel clustering to solve this problem. In many cell types, Ca2+ channels are concentrated into small regions, often accommodating tens of channels closely spaced together. Each channel can bind a different triumvirate but, because the channels are so packed, the opening of any one channel will generate a local Ca2+ signal that is detected by all the triumvirates. Which channel in a cluster opens is therefore not important; it is sufficient for any one channel to activate. In this way, biology has harnessed the principles of carefully selecting neighbours and habiting in a dense local population to convert the inherent disorder at the level of a single molecule into a high fidelity and predictable outcome. At a microscopic scale, this is an example of how collectivism triumphs over individualism.

Perhaps biology has managed to reconcile a form of quantum mechanics with Newtonian pre-determinism; figuring out a way to convert the stochastic and unpredictable behaviour at a single molecule level into a smooth, reliable and predictable macroscopic response.[1]

[1] This essay is reproduced from *The Language of Symmetry* (Eds. Rattigan, Noble & Hatta), 2023