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Multiple thresholds in a model system of noisy ion channels

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Voltage-activated ion channels vary randomly between open and closed states, influenced by the membrane potential and other factors. Signal transduction is enhanced by noise in a simple ion channel model. The enhancement occurs in a finite range of signals; the range can be extended using populations of channels. The range increases more rapidly in multiple-threshold channel populations than in single-threshold populations. The diversity of ion channels may thus be present as a strategy to reduce the metabolic costs of handling a broad class of electrochemical signals.

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Voltage-activated ion channels are essential elements in biological signal transduction, playing important roles in synaptic transmission, generation of neural action potentials, regulation of membrane potentials and intracellular Ca^{2+} concentrations, and other cellular functions [1–4]. The gating dynamics of the channels allow the nonconductive cell membrane to take part in electrical conduction and signaling. Channels vary between a conducting or open state and a nonconducting or closed state, with intermediary states in the transition being unstable and short-lived. The transition between open and closed states is influenced by a broad assortment of factors, principally the membrane potential, but also including hormones, toxins, protein kinases and phosphatases, and thermal fluctuations. Voltage-activated channels are functionally diverse in their sensitivity to depolarization; indeed, Lee *et al.* [5] identify no fewer than five distinct activation thresholds for Ca^{2+} channels.

Channel gating dynamics are intrinsic stochastic transitions that depend strongly on external factors, so that the channel constitutes a single-molecule sensor or communication channel, transforming membrane potentials into noisy ionic currents. Noise can have surprising effects in many nonlinear systems. Perhaps the best known of these is stochastic resonance (SR), wherein the presence of noise enhances the response of a thresholding system to a weak periodic signal (for a review, see Ref. [6]). SR has been experimentally demonstrated in a system of parallel ion channels [7], and studied theoretically in numerous systems (see, e.g., Refs. [8–14]). In this work, we use a simple ion channel model to further investigate the stochastic nature of voltage-activated ion channels, characterizing the limits that noise imposes on information transduction in individual channels and systems of channels.

We make use of a discrete model in which the channel switches between distinct open and closed states, omitting the dynamics of the transition process. Such a discrete model captures the bistable nature of the channel dynamics. By omitting the transition dynamics, we assume that any stimulus to the channel varies slowly compared to the time scale of channel opening and closing. We can extend this assumption to a quasistatic approximation, where the channel is always in equilibrium, and describe the channel opening probability by using the steady state (time $t \to \infty$) probability for the permissive state [15], also called the activation function of the channel. This probability is given by

$$P_\infty = \frac{1}{1 + e^{-zF(V-V_0)/RT}}, \tag{1}$$

where z is the (dimensionless) valence of the "gating particles," F is Faraday's constant, V is the transmembrane potential, R is the ideal gas constant, and T is the temperature. The parameter V_0 is a bias (or noisy threshold) in the potential to which the channel tends to open. Gailey *et al.* [10] have investigated noise in model ion channels essentially identical to the ones defined by Eq. (1), demonstrating that stochastic resonance occurs.

For notational clarity, we lump several of the parameters into a thermal noise parameter α, such that

$$\alpha = \frac{RT}{zF}. \tag{2}$$

The definition in Eq. (2) amounts to changing the units of measure for the temperature to volts. At room temperature and with $z=1$, α is approximately 25 mV.

Using Eq. (2), the channel opening probability becomes

$$p(V;\alpha) = \frac{1}{1 + e^{-(V-V_0)/\alpha}}, \tag{3}$$

with a corresponding probability of remaining closed of $q(V;\alpha)=1-p(V;\alpha)$. For single channels, or populations of channels with homogeneous behavior, we can take $V_0=0$ without loss of generality; the behavior for other values of V_0 can be recovered by translating the potential in Eq. (3) by the desired value for the threshold potential. In heterogeneous populations of channels, the differing values of the threshold potentials can have a profound effect on the behavior of the system of channels, as we will demonstrate below.

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For a system of N channels, each of which are exposed to the same transmembrane potential V but with different realizations of the noise (i.e., we have independent, identically distributed noise), we let Z_N be the number of channels that open during the time interval. The expected state of the membrane, i.e., Z_N, can be calculated in a straightforward fashion. The expectation value $\langle Z_N\rangle(V;\alpha)$ and variance $\sigma^2_{Z_N}(V;\alpha)$ can be expressed using $p(V;\alpha)$, $q(V;\alpha)$, and N, giving

$$\langle Z_N\rangle(V;\alpha) = Np(V;\alpha), \tag{4}$$

$$\sigma^2_{Z_N}(V;\alpha) = Np(V;\alpha)q(V;\alpha). \tag{5}$$

In calculating Eqs. (4) and (5), we have made use of the independence of the noise for the channels.

We will focus on the behavior of ion channels near the threshold value. To explore the ability of the ion channels to serve as a transducer of electrical signals, we reproduce the input potential by decoding the state of the membrane (i.e., the numbers of open and closed channels). Near the threshold, this gives rise to linear decoding rules. The basic approach is similar to the "reverse reconstruction" using linear filtering that has been applied with great effect to the analysis of a number of biological systems (see, e.g., Refs. [16–20]). Despite the quite different nature of the signals we consider, our static population analysis (below) shares the key features of the temporal analyses in the cited works. Specifically, by comparing the actual input to an estimate derived from the systemic response, we can work at greater remove from the details of the systems. We thus bypass the need for complete descriptions of the transmission process and of the manner in which the system response is used. This permits general limits to be established on the signal-transducing ability of a population of channels, regardless of what the actual mechanisms may be.

We expand the expected number of open channels $\langle Z_N\rangle(V;\alpha)$ to first order near the threshold (i.e., $V\to 0$), giving

$$\langle Z_N\rangle(V;\alpha) = \frac{N}{2} + \frac{N}{4\alpha}V + O(V^2). \tag{6}$$

An example of the linear approximation is shown in Fig. 1.

Dropping the higher order terms and inverting Eq. (6) suggests a linear decoding rule of the form

$$\hat{V}_N = 4\alpha\left(\frac{Z_N}{N} - \frac{1}{2}\right), \tag{7}$$

where $\hat{V}_N$ is the estimate of the input potential. Combining Eqs. (4) and (7), we can show that

$$\langle \hat{V}_N\rangle(V;\alpha) = 4\alpha\left(p(V;\alpha) - \frac{1}{2}\right). \tag{8}$$

The expected value of $\hat{V}_N$ is thus seen to be independent of N; for notational simplicity, we drop the subscript and write $\langle \hat{V}\rangle$. Note that, as the thermal noise increases, the expected value of the decoded potential closely matches the input potential over a broader range.

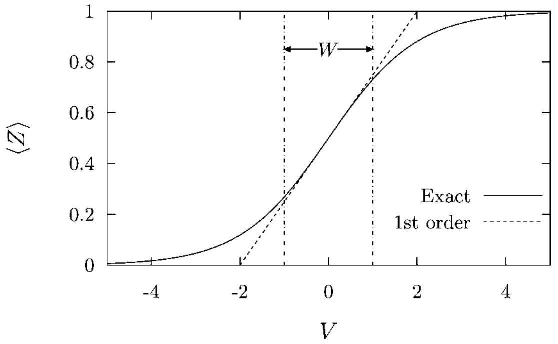

FIG. 1. First order approximation of the expectation value for the channel opening. Near the threshold potential ($V_0=0$) of the channel, the expectation is nearly linear. Further from the threshold, the expectation value saturates at either 0 or 1, where the linear approximation diverges from the true value. The values shown here are based on thermal noise $\alpha=1$, giving a response width $W=2$.

We must also consider the uncertainty of the potential value decoded from the state of the membrane. This leads to a total decoding error $\Delta\hat{V}_N$ with the form

$$\Delta\hat{V}^2_N(V;\alpha) = \langle(\hat{V}_N - V)^2\rangle = \varepsilon^2(V;\alpha) + \sigma^2_{\hat{V}_N}(V;\alpha), \tag{9}$$

where

$$\varepsilon(V;\alpha) = \langle\hat{V}\rangle(V;\alpha) - V, \tag{10}$$

$$\sigma^2_{\hat{V}_N}(V;\alpha) = \langle(\hat{V}_N - \langle\hat{V}\rangle(V;\alpha))^2\rangle = \frac{16\alpha^2}{N}p(V;\alpha)q(V;\alpha). \tag{11}$$

Using Eq. (3), we can derive several properties that are useful for understanding the role of noise in the channel behavior. In particular, it is straightforward to show that $\langle\hat{V}\rangle(V;\alpha)=V\langle\hat{V}\rangle(1;(\alpha/V))$, $\varepsilon(V;\alpha)=V\varepsilon(1;(\alpha/V))$, and $\sigma^2_{\hat{V}_N}(V;\alpha)=V^2\sigma^2_{\hat{V}_N}(1;\alpha/V)$, for all $V\neq 0$. Thus the noise dependence for both the reconstructed stimulus and its uncertainty can be understood with a single stimulus. The total error $\Delta\hat{V}^2_N(1;(\alpha/V))$ is minimized for a nonzero value of the noise parameter α, analogous to the stochastic resonance effect; see Fig. 2.

In Fig. 3, we show how $\Delta\hat{V}^2_N$ varies with the number of channels N. As N increases, the error curve flattens out into a broad range of similar values. Thus the presence of noise enhances signal transduction without requiring a precise relation between V and α. This effect is analogous to the "stochastic resonance without tuning" first reported by Collins *et al.* [21] and previously explored in two-state systems not dissimilar to the one investigated here (see, e.g., Ref. [22]).

Informally stated, SR without tuning allows for a wider range of potentials to be accurately decoded from the channel states for any particular value of α. To make this notion of "wider range" precise, we again focus our attention on the expected behavior of the channels (see Fig. 1). The expected

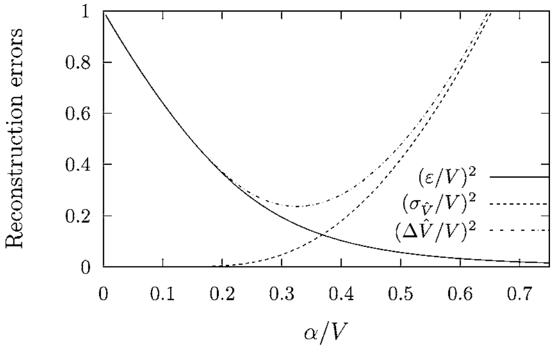

FIG. 2. Comparison of decoding error sources. The values shown here are calculated for a single channel. The minimum in $\Delta\hat{V}^2$ occurs for nonzero thermal noise, analogous to stochastic resonance.

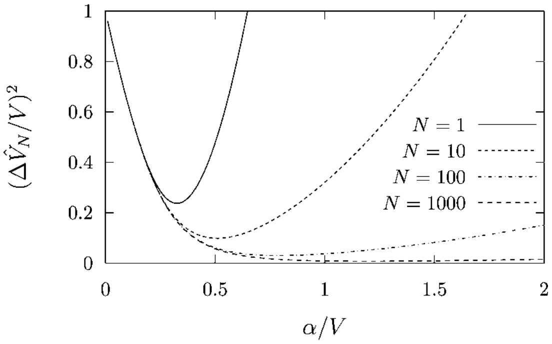

FIG. 3. Effect of the number of channels on the decoding error. As N becomes large, the error curve flattens out, indicating a broad range of noise values that all give similar accuracy in the decoding process.

channel response $\langle Z\rangle$ matches well with the linear approximation when $|V|<\alpha$. From this, the width W can be defined to be 2α. Other definitions for the response width are, of course, possible, but we still should observe that the width is proportional to α, since the probability for channel opening depends only on the ratio of V and α [Eq. (3)]. The same width is found for multiple identical channels, because the total expected current is proportional to the single channel behavior, without broadening the curve in Fig. 1.

The response width can thus be increased by increasing the thermal noise parameter α. As seen in Figs. 2 and 3, such an increase ultimately leads to a growth in the decoding error $\Delta\hat{V}_N^2$. As α becomes large, $\Delta\hat{V}_N^2$ is dominated by $\sigma_{\hat{V}_N}^2$ and we have the asymptotic behavior

$$\Delta\hat{V}_N^2(V;\alpha) = O\left(\frac{\alpha^2}{N}\right), \tag{12}$$

based on Eq. (11). The growth in $\Delta\hat{V}_N^2$ with increasing α thus can be overcome by further increasing the number of channels in the population. Therefore the response width W is effectively constrained by the number of channels N, with $W=O(\sqrt{N})$ for large N.

An arbitrary response width can be produced by assembling enough channels. However, this approach is inefficient, and greater width increases can be achieved with the same number of channels. Consider instead dividing up the total width into M subranges. These subranges can each be covered by a subpopulation of N channels, with the subpopulations having different thresholds from one another. The width of each subrange is $O(\sqrt{N})$, but the total width is $O(M\sqrt{N})$. Thus the total response width can increase more rapidly as additional types of channels are added. Conceptually, multiple types of channels arise naturally as a way to provide a wide range of accurate responses, with multiple channels in each type providing independence from any need to "tune" the thermal noise to a particular level.

To describe the behavior of channels with different thresholds, much of the preceding analysis can be directly applied by translating the functions along the potential axis to obtain the desired threshold. However, system behavior was previously explored near the threshold value, but heterogeneous populations of channels have multiple thresholds. Nonetheless, we can produce a comparable system by simply assessing system behavior near the center of the total response width.

To enable a clean comparison, we set the thresholds in the heterogeneous populations so that a linear decoding rule can be produced. A simple approach that achieves this is to space the thresholds of the subpopulations by $2W=4\alpha$, with all channels being otherwise equal. The subpopulations with lower thresholds provide an upward shift in the expected number of open channels for higher threshold subpopulations, such that the different subpopulations are all approximated to first order by the same line. Thus the expected total number of open channels leads to a linear decoding rule by expanding to first order and inverting, as was done earlier for homogeneous populations. Note that this construction requires no additional assumptions about how the channel states are to be interpreted.

To illustrate the effect of multiple types of channels, we begin with a homogeneous baseline population $M=1$ of $N=1000$ channels with $V_0=0$ and apply a potential V with thermal noise $\alpha=1$. Using the definition above, the response width is $W=4$. We then consider two cases, homogeneous and heterogeneous, in each of which we increase the response width by doubling the number of channels while maintaining similar error expectations for the decoded currents.

In the homogeneous case, we have a single population ($M=1$) with $N=2000$ channels. Doubling the number of channels allows us to increase the temperature parameter α by a factor of $\sqrt{2}$ with similar expected errors outside the response width. Thus we observe an extended range, relative to the baseline case, in which we can reconstruct the stimulus potential from the state of the channels (Fig. 4).

In the heterogeneous case, we instead construct two subpopulations ($M=2$) with $N=1000$ channels. We leave the thermal noise parameter unchanged at $\alpha=1$. One of the subpopulations is modified so that the channel thresholds lie at $+W=2$, while the other is modified so that the channel thresholds lie at $-W=-2$. The resulting system of channels has a broad range in which we can reconstruct the stimulus potential with low error, markedly superior to the baseline

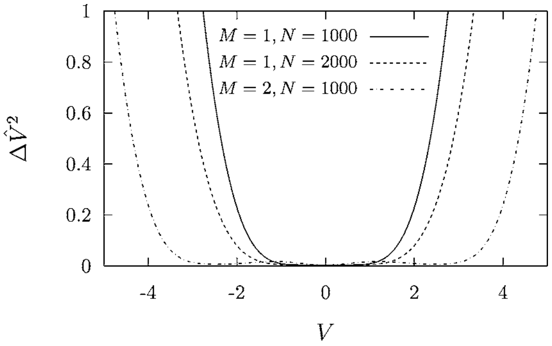

FIG. 4. Total decoding error in homogeneous and heterogeneous populations of channels. The heterogeneous channel population ($M=2$, $N=1000$) has a broader "basin" of low error values than the baseline ($M=1$, $N=1000$) and homogeneous ($M=1$, $N=1000$) populations.

and homogeneous cases (Fig. 4). The approach used in this example can be directly extended to three or more subpopulations.

The foregoing analysis and example suggest that the diversity of channel types found in a living cell are present as an information processing strategy, providing a means to efficiently handle a broad class of electrochemical signals. The superior scaling properties of heterogeneous populations of channels can have a profound impact on the cellular metabolism; large numbers of channels imply a large energetic investment, both in terms of the proteins needed to construct the channels and of the increased demand on ion pumps that accompanies the greater ionic currents [3]. The action potentials generated in neurons can require a significant energetic cost [23], making the tradeoff between reliably coding information and the metabolic costs potentially quite important.

In this picture, we expect that different types of cells will require different numbers of functionally different ion channels. Cells that perform sophisticated signaling and respond to a broad variety of signals will need a large number of functionally different ion channels, while cells that are more specialized to a narrower class of signals are likely to have a smaller number of functional types. This appears to be generally consistent with the comparatively large variety of ion channels found in excitable cells such as neurons [4].

It is interesting to reconsider the work of Lee *et al.* [5] in light of the analysis presented here. In their work, five Ca^{2+} channels with distinct thresholds are tabulated, including three *T*-type channels interpreted as being important for the electrical responsiveness of neurons. However, a full understanding of the physiological roles of the channels remains to be found. The present analysis indicates that signal transduction by any given type of channel is intrinsically limited, regardless of the details of how the state of the channels is used. The multiple types of channels with their various thresholds provide a metabolically and evolutionarily favorable means to overcome those limits.

Although we have used a specific model consisting of channels with thermal fluctuations modulating an input potential, we expect that the key result is more widely applicable. The demonstration of the advantage of multiple channel types largely follows from two factors that are not specific to the model channels. First, the distance of the input potential from the threshold is proportional to the level of the thermal noise, and, second, the total variance of the inputs to the channels is proportional to the number of channels. Ultimately, a multiplicity of functional types of channels with varying thresholds arises because the independently distributed noise provides a natural scale for the system.

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