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Optimal sizes of ion channel clusters

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Abstract. – Voltage-dependent conductance of ion channels is key for the generation of action potentials. Ion channels are opening and closing stochastically due to thermal noise and introduce *internal noise* into the membrane potential of the cell. The noise power depends on the size of the ion channel cluster that generates the action potential (the hillock). We show that the encoding of small sinusoidal signals in terms of spikes can be enhanced by channel noise if the cluster size is in a certain range.

Stochastic resonance describes the amplification of weak signals in bistable or excitable systems in the presence a proper amount of noise (for a review, see [1]). This effect has been observed in sensory neurons [2–4] and has been described theoretically in a number of studies (see, *e.g.*, [5, 6]). Common to most of these studies is that noise has been added externally to a sub-threshold signal. As the external noise level is increased, optimal encoding of the sub-threshold signal in the spike train (quantified by spectral measures [1] or information theoretical measures [7, 8]) is achieved at a certain finite noise level. Further increase of the noise is detrimental for the signal encoding.

In a simple threshold-fire model for neurons [9] it has been shown that the maximum SNR found by varying the excitability at a given noise level decreases monotonously with increasing noise. Thus, adding noise externally is not the best strategy to optimize signal encoding if other parameters such as the excitability can be adjusted.

At a given temperature, a certain level of *internal* noise is present. Ion channel proteins, *e.g.*, change their conformation thermally and visit their "open"-state on occasion. When the channel is open, ions can move across the cell membrane, leading to internal thermal conductance fluctuations. Intrinsic fluctuations of the membrane potential induced by channel fluctuations have been modeled by using a kinetic scheme [10–13] that explicitly mimics the opening and closing of ion channels and their effect on the macroscopic conductance of the membrane. The replacement of these kinetic schemes by less time-consuming stochastic differential equations is subject of current research [11, 14]. It is clear, however, that simply adding noise to the injected current is not a physiologically meaningful way of modeling channel noise [14].

In this paper we use such a kinetic Hodgkin-Huxley model for patches of excitable membranes [10–13] ranging from 0.1 μm^2 to 500 μm^2 in conjunction with a sub-threshold sinusoidal signal (injected current). The main question we are studying is whether and under what circumstances intrinsic channel fluctuations can be exploited to enhance the encoding of

a sub-threshold signal. Petracci *et al.* [15] have studied this question with *a single ion channel* by varying the temperature. Although there was clear evidence for a timing of the opening and closing of the channel with the phase of the sinusoid, no optimal temperature (consistent with optimal encoding) was found. Since intrinsic noise levels are determined by the size of the ion channel clusters, our hypothesis amounts to a *cluster-size resonance* with respect to the encoding of a sub-threshold signal.

After a brief description of the model, we discuss spiking rates and regularity as the cluster size is changed. The mean interspike interval and the variance of the interspike intervals both exhibit a minimum as a function of the size of membrane patch. For the parameter values documented for the giant squid axon [16] this minimum is at a membrane size of about 50 μm^2–100μm^2. Similarly, in the oscillatory regime, where the macroscopic membrane (large membrane size) beats periodically, the spontaneous spike rate first increases for increasing cluster sizes but then decreases while the interspike interval becomes more and more uniform [17]. We then inject a periodic, sub-threshold current. In the macroscopic limit (limit of large membrane area) such a stimulus does not trigger action potentials and thus the signal is not encoded in a spike train. For decreasing cluster sizes, however, channel noise aids the subthreshold signal in generating action potentials and thus, encoding becomes possible. Whether the encoding is optimal depends on the intensity of channel noise which in turn is determined by the size of the cluster. We find that for a given signal frequency there is an optimal size of the ion channel cluster at which the spike trains optimally encode the sub-threshold signal.

Channel fluctuations are caused by the random opening and closing of channels which is thought to be caused by thermal hopping of the channel protein between different conformational states. We adopt the classic model for the ion channels introduced by Hodgkin and Huxley that models the potassium channel by four identical gates that stochastically switch between an open state and a closed state. The open probabilities $p_n, n = 1, 2, 3, 4$ for the four gates n are described by the rate equation

$$\dot{p}_n(t) = -\left(\alpha_{\rm K}(v) + \beta_{\rm K}(v)\right) p_n(t) + \alpha_{\rm K}(v)\,, \tag{1}$$

where $\alpha_{\rm K}(v)$ and $\beta_{\rm K}(v)$ are the voltage-v–dependent opening and closing rates of a potassium channel gate

$$\alpha_{\rm K}(v) = \frac{0.01(10-v)}{\exp\left[(10-v)/10\right]-1}\,, \qquad \beta_{\rm K}(v) = 0.125\exp\left[-\frac{v}{80}\right]\,. \tag{2}$$

The trans-membrane voltage v is measured here and in all equations below in mV. The physiologic cellular resting potential of -65 mV has been subtracted from all voltages in order to shift the resting potential to $v = 0$ mV. The potassium channel is open only when all four gates are open, *i.e.* with probability $p_1p_2p_3p_4$.

The sodium channel consists of four gates. Three identical fast gates increase their opening probability q_1, q_2, q_3 when the voltage v becomes larger than the resting potential. The slower fourth deactivation gate decreases its open probability q_4 when the membrane potential increases. The gate variables obey the following rate equations:

$$\begin{aligned} \dot{q}_n(t) &= -\left(\alpha^f_{\rm Na}(v) + \beta^f_{\rm Na}(v)\right) q_n(t) + \alpha^f_{\rm Na}(v)\,, \\ \dot{q}_4(t) &= -\left(\alpha^s_{\rm Na}(v) + \beta^s_{\rm Na}(v)\right) q_4(t) + \alpha^s_{\rm Na}(v)\,, \end{aligned} \tag{3}$$

with the opening and closing rates

$$\alpha^f_{\rm Na}(v) = \frac{0.1(25-v)}{\exp\left[(25-v)/10\right]-1}\,, \qquad \beta^f_{\rm Na}(v) = 4.0\exp\left[-\frac{v}{18}\right]\,,$$

$$\alpha^s_{\rm Na}(v) \;=\; 0.07\exp\left[-\frac{v}{20}\right], \qquad \beta^s_{\rm Na}(v) = \frac{1}{\exp\left[(30-v)/10\right]+1}. \tag{4}$$

For the simulation of the gates and channels we assume that all the gates open and close according to a two-state Markov process with voltage-dependent opening and closing rates. We update the open-probabilities of all gates every 10 μs and select the new state by drawing a random number. This method is clearly more inefficient than the schemes used, *e.g.*, in [11,12], where populations of channels that share their numbers of open gates are updated by drawing the numbers of switching channels from a binomial distribution. We use our scheme also for heterogeneous channel distributions where the other schemes cannot be applied.

For the density of the sodium and potassium channels (number of channels per area) we use $\rho_{\rm Na} = 60/\mu{\rm m}^2$ and $\rho_{\rm K} = 20/\mu{\rm m}^2$, respectively. The single-channel conductances of the sodium and potassium channels are given by $\gamma_{\rm Na} = \gamma_{\rm K} = 20$ pS. Except for $\rho_{\rm K} = 20/\mu{\rm m}^2$ these values have been reported for the giant squid axon [16]. Using a membrane capacitance of 1 $\mu{\rm F/cm}^2$ we end up with the following kinetic Hodgkin-Huxley equations:

$$\dot v = -\left(\frac{N^{\rm open}_{\rm K}}{\tau_{\rm K}N_{\rm K}}\,(v-v^{\rm rev}_{\rm K}) + \frac{N^{\rm open}_{\rm Na}}{\tau_{\rm Na}N_{\rm Na}}\,(v-v^{\rm rev}_{\rm Na}) + \frac{1}{\tau_{\rm L}}\,(v-v_{\rm l})\right) + I_{\rm in}(t)\,, \tag{5}$$

where $v^{\rm rev}_{\rm K} = -12$ mV, $v^{\rm rev}_{\rm Na} = 115$ mV and $v_{\rm l} = 10.6$ mv denote reversal potentials of the potassium systems, sodium system and leakage system, respectively. The time constants are given by

$$\begin{aligned} \tau_{\rm K} &= \frac{1}{36}\ {\rm ms}\,,\\ \tau_{\rm Na} &= \frac{1}{120}\ {\rm ms}\,,\\ \tau_{\rm L} &= 3.3\ {\rm ms}\,. \end{aligned} \tag{6}$$

We have subtracted the resting potential from the transmembrane voltage and the reversal potentials so that $v = 0$ denotes the resting potential.

To verify the accuracy of our kinetic simulation we have 1) verified that the deterministic dynamics of the Hodgkin-Huxley equations is approached for large channel numbers, 2) verified that the results are independent of the particular random number generator used in the simulations, and 3) found agreement with the previous results in [12] for action potential rates at large dc currents.

The mean interspike interval $\langle T\rangle$ of the ion channel cluster is shown as a function of its size in fig. 1a. For large cluster sizes, $\langle T\rangle$ is increasing exponentially as expected (see also previous investigations in [11] and the results of Langevin approximations in [14]). For small and increasing cluster sizes, however, $\langle T\rangle$ first decreases, reaches a minimum and increases (see also [18]). Our results for the rate $1/\langle T\rangle$ differ quantitatively from the results in [18] by factors 2-3 but agree qualitatively. It is interesting to note that the results obtained in [11] by using Gilespie's method seem to not reproduce our results (and that in [18]) for small cluster sizes, while the agreement for large cluster sizes is very good.

For small numbers of channels, stochastic opening of almost *any* sodium channel results in an action potential and thus the rate of spontaneous action potentials increases with size. For larger number of channels, however, the common membrane voltage couples the random opening and closing events more tightly, resulting in collective events of a large portion of available channels at the same time. The relative fluctuations of the interspike intervals (see fig. 1b) exhibit a relative minimum approximately where the spike rate displays a relative

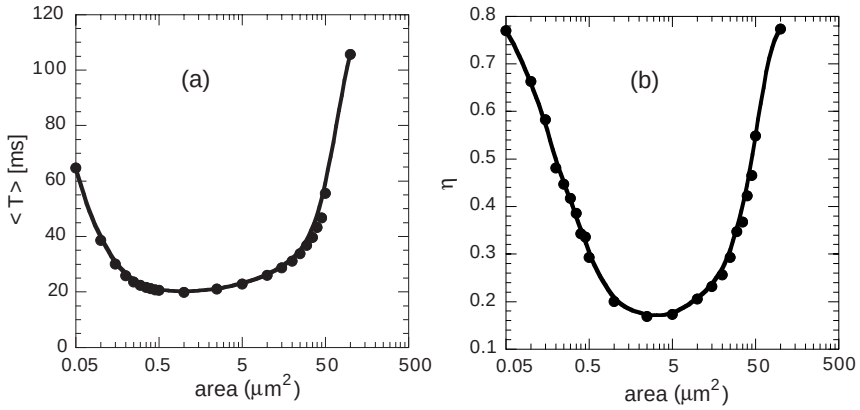

Fig. 1 – The average interspike interval $\langle T \rangle$ (a) and the relative fluctuations $\eta = \sqrt{\langle (T - \langle T \rangle)^2 \rangle} / \langle T \rangle$ (b) are shown as a function of the cluster size at zero external stimulus.

maximum. Thus, as the spontaneous spike rate increases with increasing cluster size, the cluster beats more regular. The power spectrum of the spike train exhibits a broad peak where the relative fluctuations are minimal [17].

We now study the kinetic Hodgkin-Huxley model in the presence of a sub-threshold sinusoidal stimulus (injected current). In case of dc stimulus one finds excitable dynamics (*i.e.* a stable fixed point) for a dc current less than about $A_c = 7$ μA/cm^2. For a current interval of 2 μA/cm^2 to A_c a stable limit cycle coexists with the stable fixed point giving rise to periodic bursts and skipping [12]. For ac stimulus, the excitation threshold depends strongly on the frequency of the stimulus and can be substantially smaller than for a dc stimulus [19]. In the deterministic limit (*i.e.* for large channel numbers) an injected current with amplitude 1 μA/cm^2 and frequency 16 Hz (corresponding to a period of 63 ms) is a sub-threshold stimulus and does not trigger action potentials. In fig. 2, we show a number of interspike interval histograms (ISIH) for increasing membrane sizes. Encoding of the periodic signal is represented by interspike intervals in the vicinity of the period of the stimulus $T = 63$ ms.

In the deterministic limit the Hodgin-Huxley equations describe refractoriness, an important property that keeps the membrane from reverberating. The ISIHs for large membrane areas clearly reflect this refractoriness, *i.e.* the ISIHs are zero for times less than about 15 ms. Refractoriness is, however, not a property of small membranes. Substantial numbers of intervals shorter than the deterministic refractory period and even an additional peak can be observed in, *e.g.*, the ISIH for a membrane size of 0.5 μm^2.

For larger membrane sizes the ISIH develops a peak in the vicinity of the period of the stimulus which becomes most pronounced at membrane sizes in the range of 50–100 μm^2. The peak decays for larger membrane sizes. This result indicates that there is an optimal cluster size for the encoding of subthreshold signals. A similar result has been obtained independently by Schmid, Goychuk and Hänggi [20] by using an approximative set of stochastic differential equations [14]. Note that the physiologic resting potential of -65 mV has not been subtracted from the voltages in this accompanying paper [20], leading to different expressions for the opening and closing rates. The ISIHs for small cluster sizes (0.05 μm^2–1 μm^2) also show peaks in the vicinity of the period of the signal that undergo another maximum at a membrane size of about 0.25 μm^2 (not shown here).

A spectral analysis of the neuronal spike train also supports the hypothesis of optimal

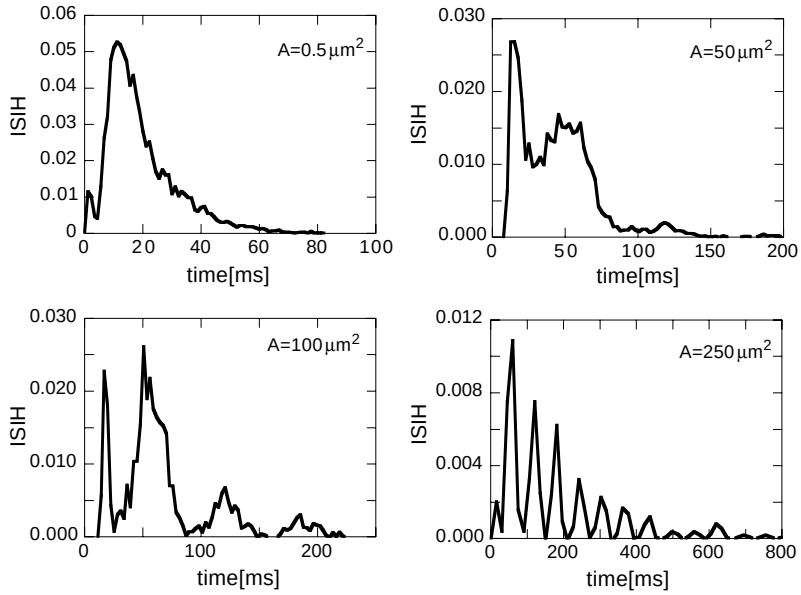

Fig. 2 – Normalized interspike interval histograms of the action potentials generated by ion channel clusters with indicated areas A are shown.

cluster sizes. We approximate the neuronal spike train by a train of δ-spikes at the central positions t_n of the action potentials, *i.e.*

$$v(t) = \sum_n \delta(t - t_n)\,. \tag{7}$$

The power spectrum, defined by the Fourier transform of the correlation function (averaged over the observation interval T_o)

$$k_\mathrm{av}(\tau) = \frac{1}{T_\mathrm{o}} \int_0^{T_\mathrm{o}} v(t)v(t+\tau)\mathrm{d}t = \frac{1}{T_\mathrm{o}} \sum_{nm} \delta(t_n - t_m - \tau)\,, \tag{8}$$

is obtained as

$$S(\omega) = \int_{-\infty}^{\infty} \exp[-i\omega\tau] k_\mathrm{av}(\tau)\mathrm{d}\tau = \frac{1}{T_\mathrm{o}} \left| \sum_n \exp[-i\omega t_n] \right|^2 . \tag{9}$$

We have used time intervals long enough to produce 5000 action potentials at each size of the membrane. Most notably, we found a narrow peak at the frequency of the periodic stimulus. From general considerations one expects that the spectral line at the frequency of the stimulus should be δ-shaped in Fokker-Planck equations and master equations with periodic coefficients [21].

The finite length of the spike trains, however, widens these peaks. The weight of the peak, indicating the periodicity of the spike train, is obtained by integrating the power spectrum over the frequency (see also [22]). The integral exhibits a step at the frequency of the stimulus. Its height represents the weight of the peak and its width the width of the peak. The step height, therefore, is a measure of the signal encoding in the spike train. In figs. 3(a) and (b)

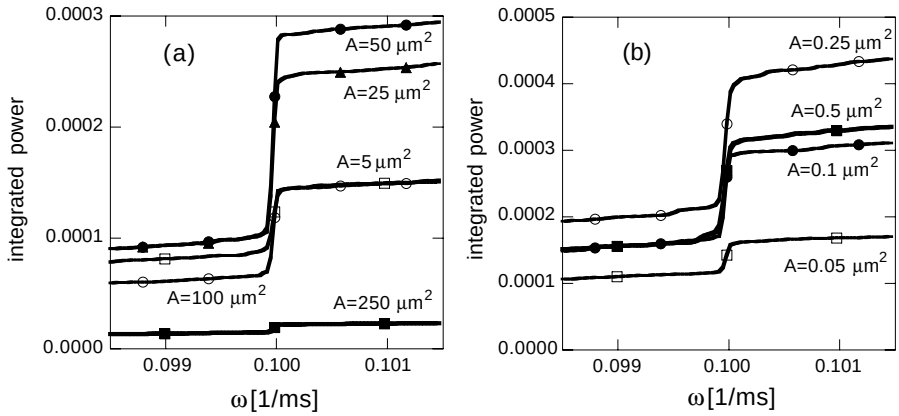

Fig. 3 – The integrated power spectrum is shown for various larger (a) and smaller (b) cluster sizes. The step height at the stimulus frequency $\Omega = 0.1$ is a measure for the signal encoding.

the integrated power spectra are shown for various membrane sizes. There are two relative maxima of the step sizes at different membrane sizes. A maximum at a relatively small cluster size of the membrane (see fig. 3b) at about 0.25 μm^2) and another one at a large membrane size (see fig. 3a). We interpret this double resonance as a consequence of the non-monotonous dependence of the spontaneous spike rate on the cluster size reported above (see fig. 1(a)). The same amount of noise (number of spontaneous spikes per second) is produced by two different cluster sizes. Thus, assuming that optimal encoding is controlled by noise, one expects two optimal cluster sizes at least for a certain range of frequencies.

Discussion. – We have shown that internal channel noise in ion channel clusters can enhance a sub-threshold stimulus at certain sizes. It is important to note that no external noise is necessary for this effect to occur. It is only *internal* channel noise regulated by the size of the cluster that enhances the sub-threshold signal. While the concrete optimal cluster size depends on the signal frequency, typically we find a small optimal cluster, where only a few channels are present and a large optimal cluster size with several hundred or thousand channels. The double maximum is due to a non-monotonous dependence of the spontaneous spiking rate on the size of the membrane. Finite sizes of ion channel clusters occur in various places in neurons. Action potential generation, *e.g.*, is believed to happen in the hillock of the neuron that comprises an area of only a few μm^2. The nodes of Ranvier play the role of boosters along the axon to reshape the action potential between the passive myelinated regions of the axon. The numbers of channels are finite and are subject to modulation by, *e.g.*, changes of channel expression in glia. Regulation of the density of ion channels in order to optimize encoding performance seems feasible.

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