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ARTICLE

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On the Na^+,K^+ pump in fluctuating membrane potentials

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Abstract The present work investigates the usefulness of noise in the activity of the Na^+,K^+ pump. Random gating activity of the neighboring ion channels causes local fluctuations of the electric potential. They are modeled by a Markovian symmetric dichotomic noise, added to the membrane potential. The noise-averaged pump current is calculated for a general rectangular voltage signal and the model parameters of the effective two-state enzyme cycle are tuned to fit experimental results. Then, using these parameters, the amount of transported charge is calculated, and studied as a function of noise intensity. Signal and noise characteristics are identified at which fluctuations enhance pump activity. The biological impact of this phenomenon seems to be absent in physiological conditions for it occurs at noise amplitudes over 50 mV, which are unlikely to appear due to ion channels. However, under some conditions, externally applied dichotomic noise of intensity about 150 mV may sensibly increase the quantity of transported charge.

Keywords Stochastic fluctuations · Active transport · Voltage sensitivity

Introduction

One of the most investigated membrane enzymes is Na^+/K^+-ATPase, which also goes by the name of the Na^+,K^+ pump. For each molecule of adenosine triphosphate (ATP) hydrolyzed, the pump extrudes three Na^+ ions in exchange for two K^+ ions, giving rise to an electrical current and maintaining electrochemical gradients of these charged species. As a result of remarkable experimental efforts, an electrostatic access channel model of the enzyme has emerged (Gadsby et al. 1993; Hilgemann 1994; Nakao and Gadsby 1986; Sagar and Rakowski 1994), and the electrogenic steps of the enzyme cycle seem to be identified (Apell et al. 1987, 1998; Fendler et al. 1985, 1987, 1993; Friedrich and Nagel 1997; Friedrich et al. 1996; Gadsby and Nakao 1989; Nagel et al. 1987; Wuddel and Apell 1995). These steps are voltage sensitive.

The questions addressed in the present paper are the following. First, is the Na^+,K^+ pump sensitive to dichotomic voltage fluctuations of internal or external origin? Second, if so, can noise stimulate the activity of the enzyme? Third, do internal voltage fluctuations, stemming from the stochasticity of ion channel gating, have an influence on Na^+/K^+-ATPase in physiological conditions?

To this end, we have to look at the neighborhood of an individual pump. It contains ion channels that are protein structures, which enable specific ion species to diffuse in the direction dictated by their electrochemical potential gradients (Hille 1992). The most common types are the sodium and potassium channels. On each square micrometer of membrane area there are roughly 18 potassium channels and 60 sodium channels, while the number of Na^+/K^+ pumps is around 1000. These numbers are to be treated as average values; they depend on the cell type and may differ from one membrane region to another.

It is widely accepted that channel gating is a Markovian stochastic process (Hille 1992). Random channel activity generates local fluctuations of the membrane potential, with important consequences for membrane areas smaller than about 400 μm^2 (Chow and White 1996). We take account of these in the form of a symmetric Markovian dichotomic noise, while the voltage-sensitive steps of the Na^+/K^+-ATPase cycle will be described by the Astumian-Robertson (AR) model, with two conformational states of the enzyme (Astumian and Robertson 1989). An important feature of this effective

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enzyme cycle is the nonlinear (exponential) dependence of the rate constants on the membrane potential. It is known that experimental data on stationary currents, driven by the Na^+,K^+ pump, in human erythrocytes, are well fitted by this model at a specific background noise level (Fulinski 1994, 1997).

Methods

The AR model and voltage fluctuations

To calculate the current generated by the Na^+/K^+-ATPase we rely on the AR two-state model (Astumian and Robertson 1989). It was created to describe the effects of externally applied oscillating electric fields on the enzymatic activity of membrane proteins. Consider a class of identical enzymes, E, embedded in the phospholipid bilayer, each having two distinct conformational states, E and E*S, respectively. The enzyme cycle of the AR model is shown in Scheme 1, where α_{di} ($d=f$, r and $i=1$, 2) are the effective rate constants corresponding to the forward (f) and reverse (r) directions, while the index i labels the two pathways. Here S_1 and S_2 may represent two different chemical species (in the case of catalyzed production of S_2 from the substrate S_1) as well as one species (e.g. Na^+ in the case of Na,K pumps in the absence of extracellular potassium). The popularity of the model comes from its remarkable flexibility and simplicity. Its parameters are to be considered as effective quantities, i.e. they embody the effects of several elementary reaction steps. Also, E and E*S may represent several states of the enzyme in thermodynamic equilibrium.

The kinetic equation of the global process is given by:

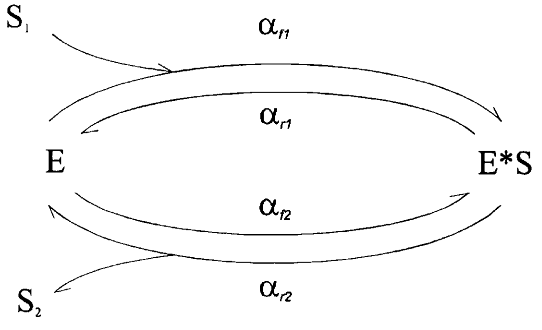
$$(\dot{E}) = -\sum_{i=1,2}\left\{\left[\alpha_{fi}[S_i] + \alpha_{ri}\right](E) - \alpha_{ri}\right\} \tag{1}$$

where $[S_i]$ are the concentrations of the transported substance, while (E) and (E^*S) are the probabilities to find the enzyme in the conformational states E and E*S, respectively. They are related by $(E)+(E^*S)=1$, used in the derivation of Eq. 1.

An essential feature of catalytic chemical reactions accompanied by electric charge dislocations (and, in particular, of ionic active transport) consists in the dependence of the effective rate constants on the membrane potential. The AR model considers an exponential dependence:

$$\alpha_{di} = \alpha^0_{di}\exp(-D_{di}\psi) \tag{2}$$

where $d=f$, r; $i=1$, 2; α^0_{di} are the rate constants for vanishing membrane potential; $D_{di}=\delta_i z_i$ if $d=f$ and $D_{di}=(\delta_i-1)z_i$ if $d=r$, where δ_i are symmetry factors which decompose the effects of electric work of charge transport in components corresponding to the forward and reverse reaction; z_i is the equivalent charge, also referred to as effective valence. It accounts for the fraction of the whole membrane potential sensed by the charge during translocation along the i-th pathway. The dimensionless voltage, ψ, is defined as $\psi=eV/(kT)$ and is a measure of the electric work compared to the energy of thermal fluctuations; here k is the Boltzmann constant, T is the absolute temperature, e is the elementary charge, and V is the transmembrane voltage.



Scheme 1

We work in stationary conditions (concentrations $[S_1]$ and $[S_2]$ are held constant), and the membrane potential is assumed to comprise two parts: an internal component and an external one. Thus, $\psi(t)=\psi_{int}(t)+\psi_{ext}(t)$, and we account for the stochastic fluctuations of the membrane potential by setting $\psi_{int}(t)=\psi_s+\gamma\cdot\xi(t)$, where ψ_s is the static membrane potential and the second term is the intrinsic noise. As argued by Fulinski (1994, 1998), the internal potential fluctuations are well described by a Markovian dichotomic noise. By definition, it has the properties: $<\xi(t)>=0$, $\xi(t)\subset\{-1, +1\}$, $\xi^2(t)=1$, and $<\xi(t)\xi(t')>=\exp(-\lambda|t-t'|)$, where $<\cdots>$ stands for the noise-averaged value. The inverse of the parameter λ represents the noise correlation time.

The kinetic equation of the transport process (Eq. 1) becomes:

$$(\dot{E}) = -[a_c - a_s\xi(t)](E) + [b_c - b_s\xi(t)] \tag{3}$$

where:

$$a_c = \sum_{i=1,2}\left\{\left[\alpha^0_{fi}\exp\left(-D_{fi}(\psi_s+\psi_{ext})\right)\cosh\left(D_{fi}\gamma\right)\right][S_i] + \left[\alpha^0_{ri}\exp(-D_{ri}(\psi_s+\psi_{ext}))\cosh(D_{ri}\gamma)\right]\right\} \tag{4}$$

$$a_s = \sum_{i=1,2}\left\{\left[\alpha^0_{fi}\exp\left(-D_{fi}(\psi_s+\psi_{ext})\right)\sinh\left(D_{fi}\gamma\right)\right][S_i] + \left[\alpha^0_{ri}\exp(-D_{ri}(\psi_s+\psi_{ext}))\sinh(D_{ri}\gamma)\right]\right\} \tag{5}$$

$$b_c = \sum_{i=1,2}\left[\alpha^0_{ri}\exp(-D_{ri}(\psi_s+\psi_{ext}))\cosh(D_{ri}\gamma)\right] \tag{6}$$

$$b_s = \sum_{i=1,2}\left[\alpha^0_{ri}\exp(-D_{ri}(\psi_s+\psi_{ext}))\sinh(D_{ri}\gamma)\right] \tag{7}$$

The cornerstone of the calculation of the noise-averaged current is the Shapiro-Loginov theorem (see Fulinski 1994, and references therein). It states that for any exponentially correlated noise $\xi(t)$ having zero mean value, and for any differentiable function $f(t)$:

$$\frac{d}{dt}\langle\xi(t)f(t)\rangle = -\lambda\langle\xi(t)f(t)\rangle + \left\langle\xi(t)\frac{d}{dt}f(t)\right\rangle \tag{8}$$

where λ is the noise correlation parameter. When applied for $f(t)=(E)(t)$ and combined with Eq. 3, averaged over noise it leads us to the system:

$$\begin{cases}\dot{x}(t) = -a_c x(t) + a_s y(t) + b_c\\ \dot{y}(t) = a_s x(t) - (\lambda + a_c)y(t) - b_s\end{cases} \tag{9}$$

where we denote: $x(t)\equiv\langle(E)(t)\rangle$ and $y(t)\equiv\langle\xi(t)(E)(t)\rangle$.

We limit our study to externally applied rectangular voltage signals. Voltage protocols of this kind constitute one of the most efficient methods in the investigation of the Na^+/K^+-ATPase enzyme cycle (Friedrich and Nagel 1997; Hilgemann 1994; Nakao and Gadsby 1986). On the other hand, the system of differential equations of the noise-averaged enzyme kinetics (Eq. 9) is exactly solvable, yielding:

$$\begin{cases}x^{(n)}(t) = C^{(n)}_1\exp\left(\Lambda^{(n)}_1 t\right) + C^{(n)}_2\exp\left(\Lambda^{(n)}_2 t\right) + A^{(n)}\\ y^{(n)}(t) = \dfrac{\Lambda^{(n)}_1 + a^{(n)}_c}{a^{(n)}_s}C^{(n)}_1\exp\left(\Lambda^{(n)}_1 t\right) + \dfrac{\Lambda^{(n)}_2 + a^{(n)}_c}{a^{(n)}_s}C^{(n)}_2\exp\left(\Lambda^{(n)}_2 t\right)\\ \qquad + B^{(n)}\end{cases} \tag{10}$$

where:

$$A^{(n)} = \frac{a_{\mathrm{s}}^{(n)} b_{\mathrm{s}}^{(n)} - \left(\lambda + a_{\mathrm{c}}^{(n)}\right) b_{\mathrm{c}}^{(n)}}{\left(a_{\mathrm{s}}^{(n)}\right)^2 - \left(\lambda + a_{\mathrm{c}}^{(n)}\right) a_{\mathrm{c}}^{(n)}} \tag{11a}$$

$$B^{(n)} = \frac{a_{\mathrm{c}}^{(n)} b_{\mathrm{s}}^{(n)} - a_{\mathrm{s}}^{(n)} b_{\mathrm{c}}^{(n)}}{\left(a_{\mathrm{s}}^{(n)}\right)^2 - \left(\lambda + a_{\mathrm{c}}^{(n)}\right) a_{\mathrm{c}}^{(n)}} \tag{11b}$$

are particular solutions of the inhomogeneous system and:

$$\Lambda_{1,2}^{(n)} = -\left(\frac{\lambda}{2} + a_{\mathrm{c}}^{(n)}\right) \pm \left[\left(\frac{\lambda}{2}\right)^2 + \left(a_{\mathrm{s}}^{(n)}\right)^2\right]^{1/2} \tag{12}$$

are the solutions of the characteristic equation corresponding to the homogenous system. The index n ($n \geq 2$) labels time intervals with constant values of the potential; for $t \in [(n-2)\tau, (n-1)\tau]$ the value of the externally applied potential is the constant $V(n)$ that corresponds to the dimensionless potential $\psi_{\mathrm{ext}}(n) = eV(n)/(kT)$. We have denoted by τ the duration of each interval of constant potential.

The noise-averaged probability current, defined by $\langle j(t) \rangle = \langle \dot{E}(t) \rangle$ is given in the interval n by:

$$\langle j(t) \rangle^{(n)} = \Lambda_1^{(n)} C_1^{(n)} \exp\left(\Lambda_1^{(n)} t\right) + \Lambda_2^{(n)} C_2^{(n)} \exp\left(\Lambda_2^{(n)} t\right) \tag{13}$$

The continuity constraint for the solutions and their first derivatives in the moments of potential jumps yields the following recurrence formulae for the constants:

$$\begin{aligned} C_1^{(n)} = {} & C_1^{(n-1)} \frac{\Lambda_1^{(n-1)} - \Lambda_2^{(n)}}{\Lambda_1^{(n)} - \Lambda_2^{(n)}} \exp\left[\left(\Lambda_1^{(n-1)} - \Lambda_1^{(n)}\right)(n-2)\tau\right] \\ & + C_2^{(n-1)} \frac{\Lambda_2^{(n-1)} - \Lambda_2^{(n)}}{\Lambda_1^{(n)} - \Lambda_2^{(n)}} \exp\left[\left(\Lambda_2^{(n-1)} - \Lambda_1^{(n)}\right)(n-2)\tau\right] \\ & + \Lambda_2^{(n)} \frac{A^{(n)} - A^{(n-1)}}{\Lambda_1^{(n)} - \Lambda_2^{(n)}} \exp\left[-\Lambda_1^{(n)}(n-2)\tau\right] \end{aligned} \tag{14}$$

$$\begin{aligned} C_2^{(n)} = {} & -C_1^{(n-1)} \frac{\Lambda_1^{(n-1)} - \Lambda_1^{(n)}}{\Lambda_1^{(n)} - \Lambda_2^{(n)}} \exp\left[\left(\Lambda_1^{(n-1)} - \Lambda_2^{(n)}\right)(n-2)\tau\right] \\ & - C_2^{(n-1)} \frac{\Lambda_2^{(n-1)} - \Lambda_1^{(n)}}{\Lambda_1^{(n)} - \Lambda_2^{(n)}} \exp\left[\left(\Lambda_2^{(n-1)} - \Lambda_2^{(n)}\right)(n-2)\tau\right] \\ & - \Lambda_1^{(n)} \frac{A^{(n)} - A^{(n-1)}}{\Lambda_1^{(n)} - \Lambda_2^{(n)}} \exp\left[-\Lambda_2^{(n)}(n-2)\tau\right] \end{aligned} \tag{15}$$

The value $n=1$ is reserved for $t<0$, corresponding to the equilibrium state (no current) in the absence of an externally applied potential, i.e. $V(1)=0$. Thus, $C_i^{(1)} = 0$ and the above relations yield the integration constants for subsequent time intervals ($n \geq 2$). Equations 10, 11, 12, 13, 14, 15 may be readily applied to any rectangular voltage protocol with successive stages of equal duration.

Results and discussion

The specific properties of Na$^+$/K$^+$-ATPase may be implemented in the above treatment by tuning the model parameters until the theoretical formula fits the experimental data on current (or charge) transported by this specific enzyme. The experiment we choose has been performed, using the giant patch technique, in the absence of K$^+$ ions (Friedrich and Nagel 1997). In this case, only three stages of the pump reaction cycle are available (see also Hilgemann 1994). In all of them the enzyme is phosphorylated. We associate the E*S state of the AR model with the enzyme with three Na$^+$ ions occluded, while the state E is assigned to the conformational state with ion binding sites open to the extracellular side of the membrane. Thus, both S_1 and S_2 represent extracellular sodium. This interpretation is at variance with earlier work based on the AR model (Fulinski 1994, 1997, 1998) and justifies the formula of the noise-averaged probability current $\langle j(t) \rangle = \langle \dot{E}(t) \rangle$ which yielded Eq. 13. The electric current generated by the pump is given by:

$$J(t) = Ne\rho\pi R^2 \langle j(t) \rangle \tag{16}$$

where $N=3$ is the number of ions transported by each active enzyme during one reaction step, e is the elementary charge, and ρ is the pump density of about 1000 μm^{-2} (Hilgemann 1994). The patch shape is approximated by a disc of radius $R = 12$ μm^2.

The recurrence relations, given in Eqs. 14 and 15, have been applied to obtain the time dependence of the current, represented in Fig. 1. It has been calculated using the parameters given in the figure legend, and shows a good fit to the experimental data of Friedrich and Nagel (1997).

The time integral of the current is the transported electric charge. Its maximal value during one rectangular voltage pulse, Q, is represented in the subsequent figures. They furnish information on pump efficiency as a function of signal and noise characteristics. The recur-

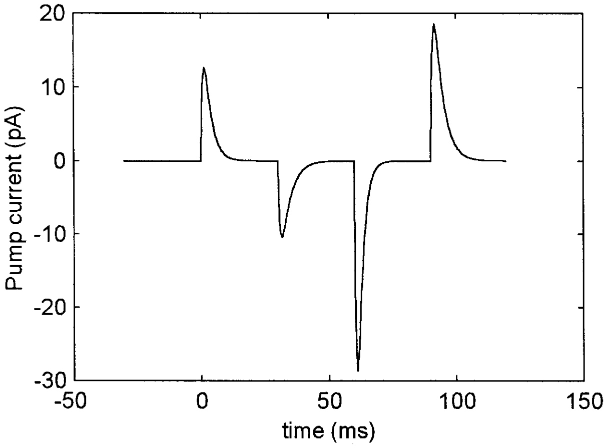
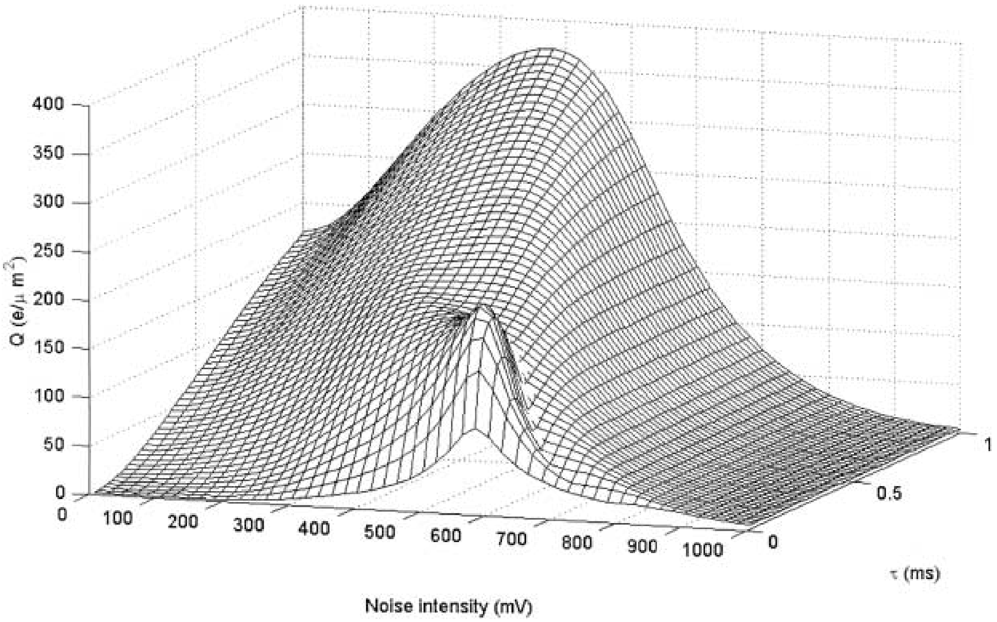


Fig. 1 Sodium currents obtained from the AR model, which fit the experimental data of Friedrich and Nagel (1997). The voltage protocol consists of rectangular pulses of 30 ms duration. The first transient current arises from the "on" phase, a voltage step from zero to 140 mV; the second corresponds to the "off" phase, from 140 mV to zero; the third is generated by the step from zero to –140 mV; and the last by the jump back to zero membrane potential. The noise level in these fitting procedures is set to the thermal noise limit ($\gamma = 1$). The values of model parameters are: $\alpha_{f1}^0[S_1] = 83$; $\alpha_{f2}^0[S_2] = 4.7$; $\alpha_{r1}^0 = 3$; $\alpha_{r2}^0 = 192$; $z_1 = 0.55$; $z_1 = 0.55$; $z_2 = 0.2$; $\delta_1 = 0.5$; $\delta_2 = 0.5$; $\lambda = 1000\, s^{-1}$; $\psi_{\mathrm{s}} = 0$

Fig. 2 The dependence of noise sensitivity on voltage-pulse duration. The notation Q stands for the maximal value of the translocated charge during one voltage pulse. The voltage protocol consists of successive values V_s, V_0+V_s, V_s, for each stage of duration τ. The holding potential is $V_s = 0$ mV, in accordance with the experimental conditions of Friedrich and Nagel (1997), while the amplitude of the depolarizing pulse is $V_0 = 135$ mV. Noise ranges from 1 to 1000 mV and τ is between 20 µs and 1 ms



rence computations, the numerical calculation of the peak value, Q, and the graphics were carried out using Matlab 5.2 (MathWorks, Natick, Mass., USA).

Figure 2 shows that noise can enhance the response of Na^+/K^+-ATPase to an externally applied voltage pulse. Starting from a holding potential $V_s = 0$ mV, as in the experiment just mentioned, a depolarizing voltage jump of $V_0 = 135$ mV is considered and, after the time τ, the membrane potential is set back to the holding value. We remark that the larger the pulse duration, the smaller the noise amplitude able to stimulate the pump. However, a considerable increase of the amount of translocated charge is determined by dichotomic fluctuations of amplitudes over 100 mV. A pronounced peak of Q versus noise intensity appears for τ between 10 and 200 µs, but the increase of Q by more than one order of magnitude would happen only at unreasonably high noise amplitudes. In our opinion, this peak is irrelevant from the biophysical point of view, since at such voltages electroporation of the membrane (Winterhalter and Helfrich 1987) and functional changes of the enzyme are expected. The very assumption, that the AR model with fitted parameters is a valid approximation of the pump activity, is not expected to be true in this regime. The range of noise intensities has been chosen so large in order to capture the shape of the plot, but we have to keep in mind that amplitudes above 200–300 mV are unreasonable.

The holding potential also affects the noise sensitivity of the pump. As shown in Fig. 3a, the more negative the holding potential, the more pronounced the influence of low-amplitude dichotomic fluctuations. A more detailed picture of the interesting part of the same graph is given in Fig. 3b. For example, at a holding potential of –70 mV, addition of noise with 150 mV amplitude doubles the maximum of translocated charge.

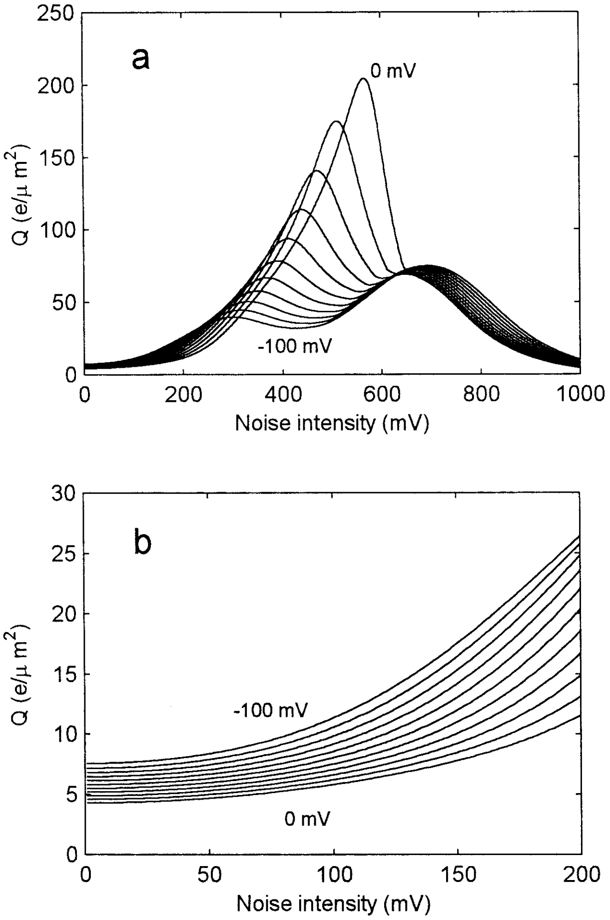


Fig. 3 The effect of noise on Q at different holding potentials, V_s, ranging from –100 to 0 mV, in 10 mV increments: **a** for noise intensities up to 1 V; **b** shows details in the biophysically interesting domain of noise intensities under 200 mV. In each case the signal amplitude is $V_0 = 135$ mV and $\tau = 100$ µs is the duration of the pulse

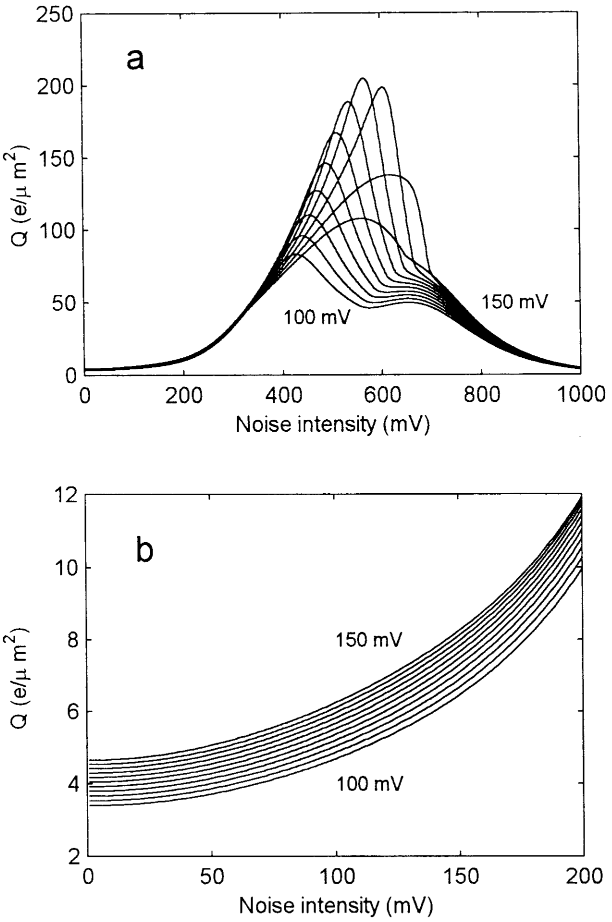


Fig. 4 The dependence of Q on noise for various amplitudes of the depolarizing voltage pulse: **a** overview; **b** shows details at low noise intensities. The signal amplitude, V_0, takes values from 100 to 150 mV in 5 mV increments. The holding potential is $V_s = 0$ mV and pulse duration is $\tau = 100$ μs

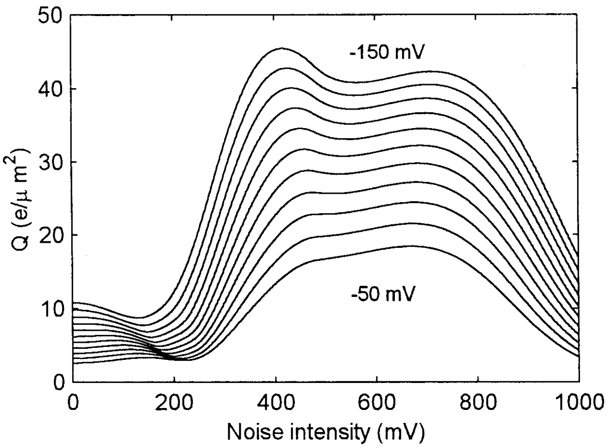
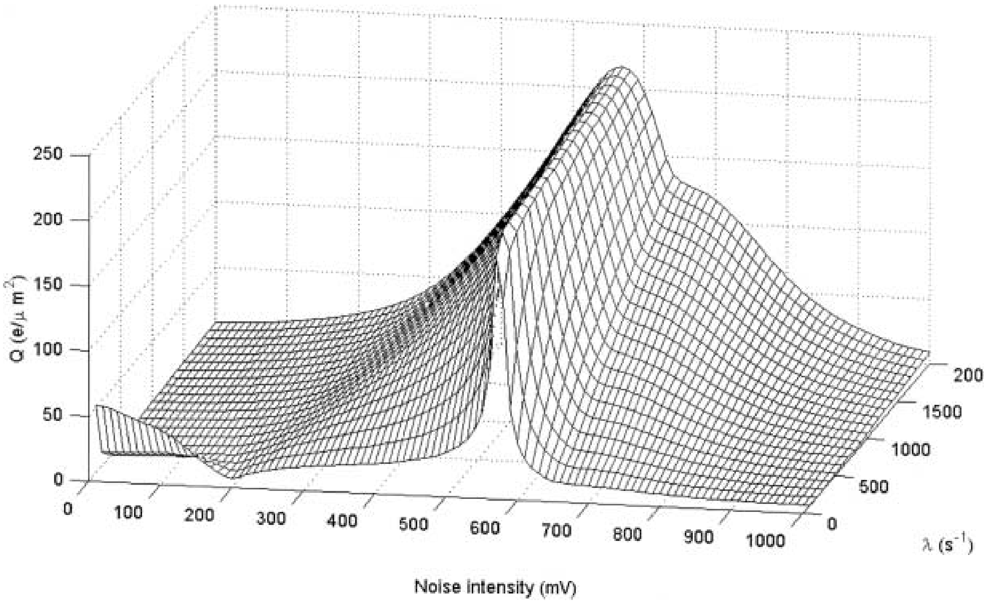


Fig. 5 The maximum of transported charge versus noise intensity in the context of hyperpolarizing signals of amplitudes between –50 and –150 mV in 10 mV steps. The pulse starts at $V_s = 0$ mV and lasts $\tau = 100$ μs

The modifications of Q with signal amplitude are presented in the next two figures. Figure 4a tracks the results of incrementing the signal amplitude in 5 mV steps. Below 100 mV the peak height is increasing monotonously, just like in the interval from 100 to 135 mV. In the interesting domain, of noise levels below 200 mV (Fig. 4b), we note that the signal amplitude has little effect on noise sensitivity: the response to depolarizing voltage jumps is stimulated by noise irrespective of the size of the jumps.

Figure 5 illustrates the same analysis for hyperpolarizing signals of amplitudes between –150 mV and –50 mV in steps of 10 mV. At variance with the context of depolarizing signals, in this case the peaks increase with signal amplitude for all the values of V_0, while in the low-noise regime the response of the pump to noise depends on the amplitude of the voltage pulses. In some

Fig. 6 Pump response versus noise intensity for different values of the correlation parameter, λ. The holding potential is taken to be $V_s = 0$ mV, the signal amplitude is $V_0 = 135$ mV, and the pulse duration is $\tau = 100$ μs



cases the noise enhances, but in others diminishes, the charge transfer.

Finally, we turn to the dependence of Q on the correlation parameter, λ, of the dichotomic fluctuations of membrane potential. Inspecting Fig. 6, we remark that, near the fitted value $\lambda = 1000\ \mathrm{s}^{-1}$, modifications of this parameter cause only slight changes of the shape of the graph representing Q versus noise intensity. The high values near the origin arise from the fact that the theory is singular in the limit $\lambda \rightarrow 0$.

We end this section with some concluding remarks. The present study shows that the AR model offers a fair description of the reaction steps of $\mathrm{Na}^+/\mathrm{K}^+$-ATPase in the absence of extracellular K^+ ions. The electrogenic steps the phosphorylated pump undergoes can be driven back and forth by externally applied electric fields. The exact solution, given above for any rectangular voltage protocol, can be tuned (via model parameters) in order to fit the experimental findings.

The Shapiro-Loginov theorem is helpful in investigating the effect of exponentially correlated stochastic fluctuations on enzyme kinetics. Under suitable conditions, the maximal translocated charge increases as noise is intensified, indicating that the pump works as an energy converter, partially transforming the energy of the stochastic signal (fluctuations of the membrane potential) into regular response energy: mechanical work needed for charge translocation. This conclusion, however, is based on the effective enzyme cycle of the AR model, which, even if it reproduces experimental results, does not give any information concerning ion movements. An exciting topic for further investigations could be the analysis of noise-induced effects in a model which is more closely related to the pump structure and function. By overcoming the technical difficulties, one could be able to explain also the mechanism of energy conversion.

In the framework of the AR model we note that the $\mathrm{Na}^+/\mathrm{K}^+$-ATPase is practically unaffected by a dichotomic voltage noise of amplitudes under 50 mV. This indicates that, in physiological conditions, the pump is not influenced by the stochastic nature of channel gating. Sensible gain from noise appears at typical noise amplitudes above 100 mV, unlikely to appear from internal sources, but possible to be obtained from external ones.

Direct verification of the theoretical results presented here may be imagined, by using a generator of exponentially correlated noise to externally apply the voltage fluctuations, in an experimental setup similar to that of Gadsby et al. (1993) or Hilgemann (1994). Employing specific blockers to rule out the contributions of ion channels, one is left, apart from thermal noise, with the stochastic fluctuations of external origin with adjustable properties. Since thermal noise is in the intensity range that leaves the pump unaffected, only fluctuations caused by the generator may be responsible for eventual noise-induced effects.

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