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Thermal fluctuations and the minimum electrical field that can be detected by a biological membrane

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ABSTRACT

Thermal electrical noise in living cells is considered to be the minimum threshold for several biological response mechanisms that pertain to electric fields. Existing models that purport to explain and interpret this phenomena yield perplexing results. The simplest model, in which the biomembrane is considered to be a linear dielectric, yields an equilibrium noise level that is several orders of magnitude larger than what is observed experimentally. An alternative approach of estimating the thermal noise as the Nyquist noise of a resistor within a finite frequency bandwidth, yields little physical insight. In this work, we argue that the nonlinear dielectric behavior must be accounted for. Using a statistical mechanics approach, we analyze the thermal fluctuations of a fully coupled electromechanical biomembrane. We develop a variational approximation to analytically obtain the benchmark results for model fluid membranes as well as physically reasonable estimates of the minimum electrical field threshold that can be detected by cells. Qualitatively, at least, our model is capable of predicting all known experimental results. The predictions of our model also suggest that further experimental work is warranted to clarify the inconsistencies in the literature.

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1. Introduction

Over the last several decades, the response of biological systems to external electro-magnetic fields has attracted much attention and controversy. Several important biological processes in cell, such as electroporation (Joshi et al., 2001, 2002; Weaver, 2000), activation of ion gated channels (Jones, 1998; Brownell et al., 2010) among many others, are directly related to the interaction of cells with an imposed electric field. The source of the electric field could be ionic concentration gradients in the local environment of the cell or simply an external stimuli. While the former is of interest due to the fundamental quest to understand transduction mechanisms and signaling in cells, the latter—disruption of biological processes by very weak extremely low frequency fields (ELF) from external sources of electricity—has also been an active topic of discussion (Astumian et al., 1997; Bezrukov and Vodyanoy, 1997; Repacholi and Greenebaum, 1999; Valberg et al., 1997; Simko and Mattsson, 2004; Litvak et al., 2002). It is generally supposed that below a certain threshold–i.e. the thermal–electrical noise, the cell cannot detect an electrical field. As it is schematically shown in Fig. 1, most (typical) external ELF

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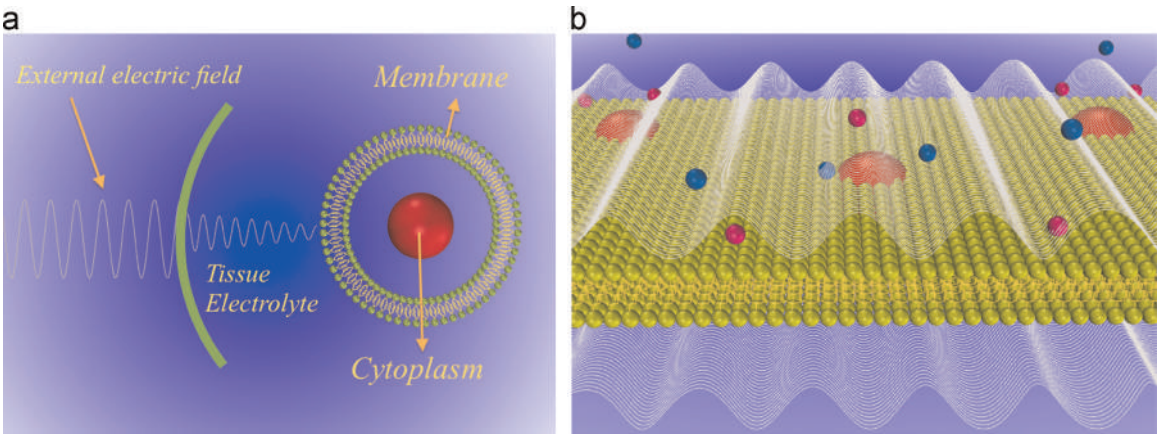

Fig. 1. (a) An external electrical field is weakened by the tissue, reducing to about 10^{-6} times the original value by the time it impinges on the cell membranes. (b) Thermally fluctuating electric field on the surface of the membrane, in equilibrium. Only electrical fields larger than the thermal noise threshold of the membrane are expected to be detected and therefore induce electromechanical conformational changes.

field levels, are severely diminished at the cell level. Whether the electrical field sources are external or internal, the question of the limit of electrical field detection by cells is of fundamental interest.

The limit for electrical field detection is that the field should exceed, *at least*, the noise generated by thermal fluctuations in the cells. Although widely studied theoretically, e.g. Oosawa (1973), Fay (1997), Weaver et al. (1998) and Vaughan and Weaver (2005), experimental results have been somewhat scarce (McLeod et al., 1987; Cleary et al., 1988; Goodman et al., 1983).

In a frequently quoted, and relatively simple, model to estimate the noise threshold (Adair, 2000; Adair et al., 1998; Weaver and Astumian, 1990), the cell-membrane is considered to be a resistor–capacitor system with corresponding values of membrane resistivity and dielectric permittivity respectively. In the so-called Johnson–Nyquist noise of a RC circuit, the time averaged noise voltage at low frequencies can be obtained as

$$\overline{V}_{k_BT} = \sqrt{4Rk_BT\,\Delta\nu} \tag{1}$$

where k_B is the Boltzmann constant (Joule/Kelvin), T is the temperature (Kelvin) and $\Delta\nu$ accounts for the frequency bandwidth (Hz). Using this model, Adair (1991) estimated the thermal noise of a spherical cell with radius $r \approx 10^{-5}$ m and $R \approx 4 \times 10^6 \Omega$, to be $\overline{V}_{k_BT} \approx 2.6 \times 10^{-6}$ V for a frequency bandwidth of about 100 Hz. Adair (1991) recognized that the wisdom of considering the entire cell with its attendant complexities is dubious. A meaningful and more relevant estimate of the noise threshold is likely if the membrane noise limit is examined rather than that of the entire cell. From this point of view, he estimated the noise for a small piece of membrane with area $d^2 \approx 2.5 \times 10^{-17}\mathrm{m}^2$, within a frequency band of 100 Hz, to be $\overline{V}_{k_BT} \approx 0.02$ V. Here d is the typical thickness of the membrane (~5 nm).

We may also consider a (yet another) alternative approach. Consider the membrane of size $\mathbb{S} = (0, L)^2$ as a linear dielectric surface in equilibrium with a thermal bath. Thermal fluctuations will lead to a spatially fluctuating and non-uniform polarization field: we identify $P(\mathbf{x})$ as the out-of-plane dipole areal density at point $\mathbf{x}$. Then, for a membrane with permittivity ϵ, the electrostatic contribution to the total Hamiltonian can be written as

$$H = \int_{\mathbb{S}} \frac{1}{2} aP(\mathbf{x})^2 d\mathbf{x} \tag{2}$$

where $a = 1/(\epsilon - \epsilon_0)d$. Discretizing the above Hamiltonian in the real space, in which each degree of freedom ($\mathbf{x}_i$) has an area of A_0–that fluctuates independently; we obtain

$$H = \sum_{\mathbf{x}_i} \frac{1}{2} aP(\mathbf{x}_i)^2 A_0, \tag{3}$$

The equipartition theorem immediately yields an estimate of the polarization fluctuation: $\langle P^2 \rangle = k_BT/aA_0$. Assuming that A_0 has the same order of magnitude as d^2, the thermal noise of the voltage across the membrane is $\overline{V}_{k_BT} = \sqrt{k_BT/\epsilon_0 d}$. This gives us a value as large as 0.3 V at room temperature. Although this approach is based on fundamental statistical mechanics, the result is physically unreasonable and the ambiguity in deciding the patch of membrane that fluctuates independently (i.e. A_0) offers little insight.

Most other models also predict noise thresholds that are similar in magnitude to the ones described in the preceding paragraphs. In sharp contrast, for some large mammalian cells, experiments (McLeod et al., 1987; Cleary et al., 1988; Goodman et al., 1983) suggest values that are almost 1000 times smaller than all the theoretical models!

Elucidation of the puzzling discrepancies as outlined in the preceding paragraphs is the key objective of this work. In Section 2, we present our central physical ideas and formulate the corresponding Hamiltonian that accounts for nonlinear dielectric behavior and coupled electromechanical behavior of fluid membranes. The statistical mechanics of the nonlinear estimation of the noise threshold in model fluid membranes is outlined in Sections 3 and 4. Experiments indicate that the limit of noise-detection is frequency dependent. We discuss the modification of our results, that account for finite frequency bandwidth, in Section 5. In Section 6, we speculate on the relevance of the model fluid membrane results for real biological membranes, and finally discuss and compare our results with experiments in Section 7.

2. Central ideas and formulation

The dielectric behavior of biological membranes (whether model or real) is nonlinear. The assumption of linearity i.e., the notion that the polarization is linearly proportional to the electric field $\mathbf{P} \propto \mathbf{E}$ implies that a membrane is capable of being polarized to unrealistically high values at high fields. This is of course physically incorrect. Aside from the obvious fact pertaining to the limits imposed by dielectric breakdown, it is expected that beyond a certain field, a limit will be reached where all the relevant microscopic dipoles in the membrane have been aligned. Corresponding to this, the polarization will saturate—in other words, there is an upper limit to which the membranes are capable of being polarized (hence forth referred to as the saturation polarization). The most compelling evidence of this, at least among recent works, is provided by the experiments and modeling of Raphael et al. (2000) — and indeed, their estimate of the saturation polarization (on the specific membrane that they studied) is not only far below the dielectric breakdown limit but also below that of the polarization corresponding to the resting voltage.

This concept is schematically illustrated in Fig. 2(a) where we compare the linear dielectric behavior to the dipole saturating trend in which the change in the polarization field becomes negligible once it approaches P_S. In other words, the membrane cannot be polarized to arbitrarily large values by an imposed electrical field and is restricted to a finite range. There is close analogy of this problem to the confinement of *mechanical* fluctuations between confined hard walls—-here the amplitude of the thermal–mechanical fluctuations is restricted by the hard walls. This analogy is depicted in Fig. 2(b) in which the membrane's polarization cannot exceed the yellow bounds. The problem of thermal–mechanical fluctuations of a confined membrane has been discussed by a number of works (Kleinert, 1999; Bachmann et al., 2001) including a few recent ones: Freund (2013) and Hanlumyuang et al. (2014). Since the strict finite range is difficult to treat analytically (and may not be physical anyway) we mimic the saturation phenomena with a smooth nonlinear function shown in blue in Fig. 2(a).

Now consider a membrane of $\mathbb{S} = (0, L)^2$ and thickness $d \ll L$. The membrane is described by the state variables (P, h): $\mathbb{S} \to IR$, where P is the out-of-plane polarization area density and h is the out-of-plane displacement of the mid-plane of the membrane. For simplicity (and almost completely justifiable in most situations), we have neglected the in-plane components of the polarization. Let $\frac{1}{2}K_h$ be the mean curvature of mid-plane and within a linearized elastic approximation:

$$K_h(\mathbf{x}) = \nabla^2 h(\mathbf{x}). \tag{4}$$

Although the effect of electromechanical coupling will later be found to be negligible, for the sake of completeness, here we take it into account and postulate that the total Hamiltonian of the membrane can be written as

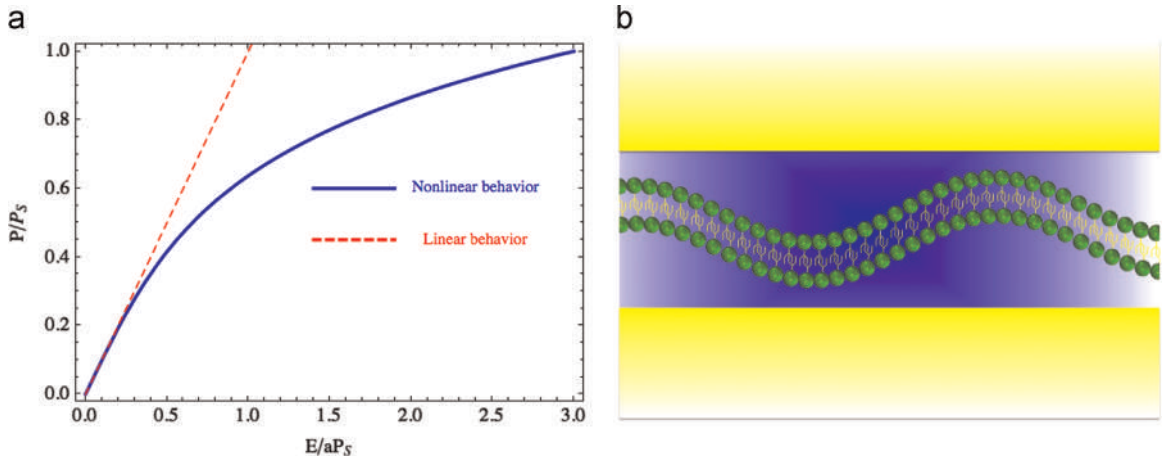

Fig. 2. (a) Comparison of linear and nonlinear dielectric behavior of biomembranes. (b) Much like the classical problem of steric interaction of a fluctuating membrane or how thermal fluctuations of membranes are restricted by hard walls, in the present case, the polarization fluctuations are considered to be restricted by limits on maximum polarization that can be achieved by the membrane. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

$$H[P,h]=\int_{\mathbb{S}}\frac{1}{2}\kappa_b K_h^2+\frac{1}{2}a|P|^2+fPK_h+g(P)\,ds, \tag{5}$$

where κ_b and f are the bending modulus and the flexoelectric coefficient of the membrane respectively, and the non-quadratic function $g(P)$ is designed to increasingly penalize the fluctuations of the polarization field as it gets close to a saturation value. The simplest form of $g(P)$ is a higher order polynomial of polarization—such that its contribution to the electrostatic energy is negligible at fields that correspond to well below the saturation point, P_s. We remark that the analogy to non-linear elastic–plastic behavior is evident. From this point of view, we propose $g(P)$ as below:

$$g(P)=aP^2\left(\varepsilon_4\frac{P^2}{P_s^2}+\varepsilon_6\frac{P^4}{P_s^4}+\varepsilon_8\frac{P^6}{P_s^6}+\cdots\right), \tag{6}$$

were ε_i are phenomenological scalar constants that represent the nonlinear behavior. In the absence of flexoelectric coupling (i.e., $f=0$), the out-of-plane electric field is given by

$$E=\frac{\partial}{\partial P}\left(\frac{1}{2}aP^2+g(P)\right)=aP\left(1+4\varepsilon_4\frac{P^2}{P_s^2}+6\varepsilon_6\frac{P^4}{P_s^4}+8\varepsilon_8\frac{P^6}{P_s^6}+\cdots\right). \tag{7}$$

The function in Eq. (7) can mathematically represent the nonlinear behavior, shown in Fig. 2(a). Furthermore, the energy cost for the change in polarization field is compared for the cases of linear and non-linear behavior in Fig. 3(a). Specifically, by taking into account the higher order terms of the polynomial function $g(P)$, the energy cost increases rapidly for the change in polarization field approaching P_S.

As a result of using the new energy function (5), the distribution of the fluctuating polarization field is no longer Gaussian. Basic statistical mechanics tells us that the probability of occurrence of a certain change of polarization can be expressed as an exponential function:

$$p(P)\propto\exp(-H(P)/k_BT), \tag{8}$$

indicating that, the higher polarization values (with the attendant larger energy cost) are less probable. Accordingly, the nonlinear function $g(P)$ ensures lower probability for largers value of the polarization. We have shown this qualitatively in Fig. 3(b). Our modified Hamiltonian, which accounts for the nonlinear dielectric behavior, essentially *confines* the thermal fluctuations of the polarization field in a finite range of $|P/P_S|\le 1$. For such a non-Gaussian distribution of the fluctuating field, the equipartition theorem is inapplicable, and analytical solutions are hard to come by. However, we develop here a variational approximation to obtain an estimation of the fluctuations—that yields analytical expressions. It is worthwhile to remark that the subject of thermal-mechanical fluctuations of the membranes has been extensively investigated. For example, in a pioneering work, Helfrich (1973, 1978) proposed that the thermal fluctuations of a membrane soften the renormalized bending modulus. Also, in the context of dealing with non-quadratic Hamiltonians, Kantor and Nelson (1987) have discussed the crumpling transition in polymerized membranes, Kardar and Nelson (1988) studied the fluctuations of self avoiding tethered membranes and Bowick and Guitter (1997) investigated the tubular transition of self avoiding

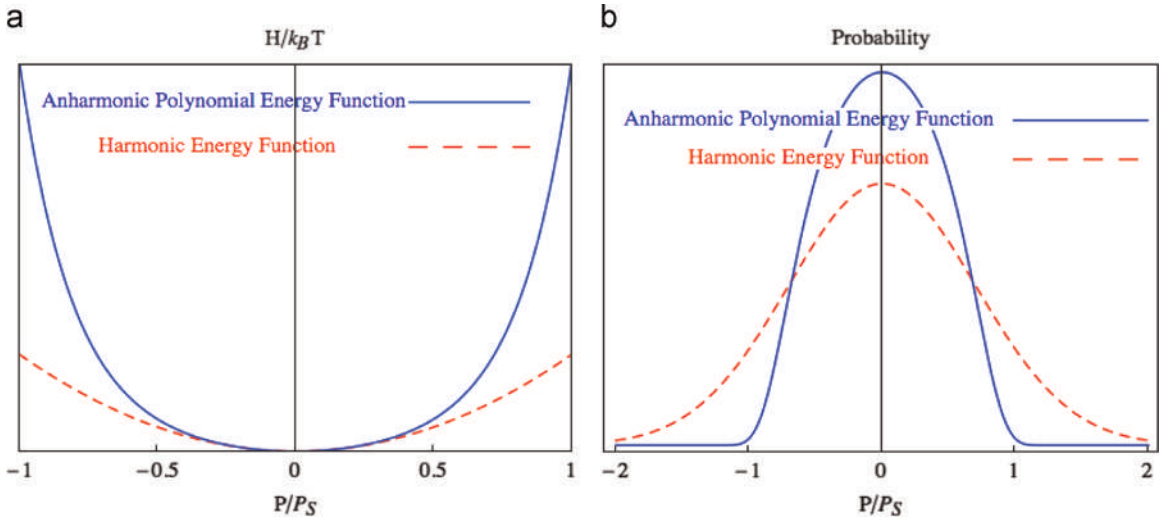

Fig. 3. (a) Comparison of linear and nonlinear energy costs for change in polarization field. The blue curve is representing the nonlinear behavior, and mimics the hard (walls) restrictions on the fluctuations. (b) Comparison of probability distributions for the linear and nonlinear dielectrics. The higher order terms in the energy formulation make the smaller values of the polarization more probable and consequently decreases the fluctuations. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this article.)

anisotropic membranes. Several other examples abound which we avoid citing for the sake of brevity. Furthermore, in the context of the somewhat more complicated and *hard* membrane materials, the reader is referred to the following sample of works: investigation of graphene fluctuations by Gao and Huang (2014) and co-workers, DNA, by Argudo and Purohit (2014), and twin-boundaries in crystalline metals by Chen and Kulkarni (2013).

3. Thermal fluctuations

The Hamiltonian of the system (5) can be rewritten as

$$H = H^q + H^{nq}, \tag{9}$$

where H^q is the quadratic part of the Hamiltonian that includes the first three terms of (5), and H^{nq} is the last term of (5) "Non-quadratic". Due to the presence of the non-quadratic terms, the equipartition theorem is not applicable; it is hopeless to compute the exact free energy and thermal fluctuations in closed-form. Nevertheless, we can employ a variational approximation based on the Bogoliubov inequality (Safran and Samuel, 1994) that asserts the following:

$$F \le F_{\text{var}} := F_0 + \langle H - H_0 \rangle_{H_0}, \tag{10}$$

where F is the actual free energy of the system, $H_0[P, h]$ is any Hamiltonian, F_0 is the free energy associated with the Hamiltonian H_0:

$$F_0 = -k_B T \log Z_0, \quad Z_0 = \int e^{-H_0[P,h]/k_B T} D[P, h], \tag{11}$$

and $\langle \ \rangle_{H_0}$ denotes the expectation value with respect to the Hamiltonian H_0.

To make analytical progress, we select a quadratic Hamiltonian H_0 that in Fourier $\mathbf{q}$-space is given by

$$H_0[P, h] = \frac{L^2}{2} \sum_{\mathbf{q} \in \mathcal{K}} \left\{ G_h(\mathbf{q}) |h_{\mathbf{q}}|^2 + G_P(\mathbf{q}) |P_{\mathbf{q}}|^2 + G_f(\mathbf{q}) h_{\mathbf{q}} P_{-\mathbf{q}} \right\} \tag{12}$$

where $\mathcal{K} := \{\mathbf{q} = 2\pi/L(\nu_x, \nu_y) : \nu_x, \nu_y \in \mathbb{Z},\ 2\pi/L \le |\mathbf{q}| \le 2\pi/d\}$, $G_h(\mathbf{q})$, $G_P(\mathbf{q})$ and $G_f(\mathbf{q})$ are set of propagators that will be determined later, and $h_{\mathbf{q}}$ ($P_{\mathbf{q}}$) is the Fourier transformation of $h(\mathbf{x})$ ($P(\mathbf{x})$):

$$\begin{aligned} h_{\mathbf{q}} &= \frac{1}{L^2} \int_{\mathbb{S}} h(\mathbf{x}) \exp(-\imath \mathbf{q}.\, \mathbf{x})\, d\mathbf{x}, \\ P_{\mathbf{q}} &= \frac{1}{L^2} \int_{\mathbb{S}} P(\mathbf{x}) \exp(-\imath \mathbf{q}.\, \mathbf{x})\, d\mathbf{x}. \end{aligned} \tag{13}$$

For the Hamiltonian (12), by the equipartition theorem we find the free energy F_0 to be

$$F_0 = \alpha_F + \sum_{\mathbf{q}} \frac{k_B T}{2} \log(4 G_h(\mathbf{q}) G_P(\mathbf{q}) - G_f(\mathbf{q})^2), \tag{14}$$

where α_F is a constant of no consequence. Also, for simplicity we consider only the first two terms in (6). Then, to within a constant,

$$\langle H - H_0 \rangle_{H_0} = \frac{L^2}{2} \sum_{\mathbf{q} \in \mathcal{K}} \left\{ \kappa_b |\mathbf{q}|^4 \langle |h_{\mathbf{q}}|^2 \rangle_{H_0} + a \langle |P_{\mathbf{q}}|^2 \rangle_{H_0} + 2f |\mathbf{q}|^2 \langle |h_{\mathbf{q}} P_{-\mathbf{q}}| \rangle_{H_0} - \frac{k_B T}{L^2} \right\} + a \int_{\mathbb{S}} \left\langle \varepsilon_4 \frac{P^4}{P_s^2} + \varepsilon_6 \frac{P^6}{P_s^4} \right\rangle_{H_0} d\mathbf{x}. \tag{15}$$

All the quadratic correlations can be calculated using the equipartition theorem:

$$\begin{aligned} \langle |h_{\mathbf{q}}|^2 \rangle_{H_0} &= \frac{4 k_B T G_P(\mathbf{q})}{L^2 (4 G_h(\mathbf{q}) G_P(\mathbf{q}) - G_f(\mathbf{q})^2)}, \\ \langle |P_{\mathbf{q}}|^2 \rangle_{H_0} &= \frac{4 k_B T G_h(\mathbf{q})}{L^2 (4 G_h(\mathbf{q}) G_P(\mathbf{q}) - G_f(\mathbf{q})^2)}, \\ \langle h_{\mathbf{q}} P_{-\mathbf{q}} \rangle_{H_0} &= \frac{-2 k_B T G_f(\mathbf{q})}{L^2 (4 G_h(\mathbf{q}) G_P(\mathbf{q}) - G_f(\mathbf{q})^2)}. \end{aligned} \tag{16}$$

The last two terms of (15), which are higher order correlations, can be estimated by invoking Wick's theorem (Kleinert, 1989) as below:

$$\langle P^4 \rangle_{H_0} = 3 \langle P^2 \rangle_{H_0}^2, \quad \langle P^6 \rangle_{H_0} = 15 \langle P^2 \rangle_{H_0}^3. \tag{17}$$

in which $\langle P^2 \rangle_{H_0} = \sum_{\mathbf{q} \in \mathcal{K}} \langle P_{\mathbf{q}}^2 \rangle_{H_0}$. Minimization of the variational free energy F_{var} with respect to the unknown propagators

furnishes an upper bound of the exact free energy. Now let $\eta = \sum_{\mathbf{q}\in\mathcal{K}} \langle P_{\mathbf{q}}^2\rangle_{H_0}$ and $\chi(\mathbf{q}) = 4G_h(\mathbf{q})G_P(\mathbf{q}) - G_f(\mathbf{q})^2$. Then substituting (16) and (17) into F_{var} (10), results in the following simplified form:

$$F_{\text{var}} = \sum \mathbf{q}\in\mathcal{K}\frac{k_BT}{2}\log(\chi(\mathbf{q})) + \frac{2k_BT}{\chi(\mathbf{q})}\left(\mathbf{q}^4\kappa_bG_P(\mathbf{q}) + aG_h(\mathbf{q}) + f\mathbf{q}^2G_f(\mathbf{q})\right) + \frac{3a\eta^2L^2\epsilon_4}{P_s^2} + \frac{15a\eta^3L^2\epsilon_6}{P_s^4} \tag{18}$$

We minimize the free-energy with respect to $G_h(\mathbf{q})$, $G_P(\mathbf{q})$ and $G_f(\mathbf{q})$ and obtain

$$\begin{aligned}
0 = \frac{\partial F_{\text{var}}}{\partial G_h(\mathbf{q})} &= -2k_BT\left\{a\frac{12G_f(\mathbf{q})^2\epsilon_4P_s^2\eta + 90a\eta^2G_f(\mathbf{q})^2\epsilon_6}{P_s^4\chi(\mathbf{q})^2} + \frac{aG_f(\mathbf{q})^2 + 4G_P(\mathbf{q})^2|\mathbf{q}|^4\kappa_b}{\chi(\mathbf{q})^2} + \frac{G_P(\mathbf{q})(4fG_f(\mathbf{q})|\mathbf{q}|^2 + G_f(\mathbf{q})^2)}{\chi(\mathbf{q})^2}\right.\\
&\qquad\left. -\frac{4G_h(\mathbf{q})G_P(\mathbf{q})^2}{\chi(\mathbf{q})^2}\right\}\\
0 = \frac{\partial F_{\text{var}}}{\partial G_P(\mathbf{q})} &= -2k_BT\left\{a\frac{48\eta\epsilon_4P_s^2G_h(\mathbf{q})^2 + 360\eta^2\epsilon_6G_h(\mathbf{q})^2}{P_s^4\chi(\mathbf{q})^2} + G_h(\mathbf{q})\frac{4G_h(\mathbf{q})(a - G_P(\mathbf{q})) + 4f|\mathbf{q}|^2G_f(\mathbf{q})}{\chi(\mathbf{q})^2}\right.\\
&\qquad\left. +\frac{(G_h(\mathbf{q}) + |\mathbf{q}|^4\kappa_b)G_f(\mathbf{q})^2}{\chi(\mathbf{q})^2}\right\}\\
0 = \frac{\partial F_{\text{var}}}{\partial G_f(\mathbf{q})} &= k_BT\left\{\frac{24a\eta G_f(\mathbf{q})G_h(\mathbf{q})(2\epsilon_4P_s^2 + 15\eta\epsilon_6)}{P_s^4\chi(\mathbf{q})^2}, + \frac{4G_f(\mathbf{q})}{\chi(\mathbf{q})^2}\left(G_h(\mathbf{q})(a - G_P(\mathbf{q})) + |\mathbf{q}|^4\kappa_bG_P(\mathbf{q})\right),\right.\\
&\qquad\left. +\frac{8f|\mathbf{q}|^2G_h(\mathbf{q})G_P(\mathbf{q}) + 2f|\mathbf{q}|^2G_f(\mathbf{q})^2 + G_f(\mathbf{q})^3}{\chi(\mathbf{q})^2}\right\},
\end{aligned} \tag{19}$$

wherein for differentiating the higher order correlations $\langle P^4\rangle_{H_0} = 3\eta^2$ and $\langle P^6\rangle_{H_0} = 15\eta^3$ we used the chain rule to write:

$$\frac{\partial\eta^n}{\partial G} = n\eta^{n-1}\sum_{\mathbf{q}\in\mathcal{K}}\frac{\partial\eta}{\partial G(\mathbf{q})} = n\eta^{n-1}\sum_{\mathbf{q}\in\mathcal{K}}\frac{\partial}{\partial G(\mathbf{q})}\langle P^2(\mathbf{q})\rangle_{H_0} \tag{20}$$

Solving the equations in (19) for the unknown propagators yields

$$\begin{aligned}
G_h(\mathbf{q}) &= |\mathbf{q}|^4\kappa_b\\
G_P(\mathbf{q}) &= a\left(1 + \frac{12\eta\epsilon_4}{P_s^2} + \frac{90\eta^2\epsilon_6}{P_s^4}\right)\\
G_f(\mathbf{q}) &= -2f|\mathbf{q}|^2.
\end{aligned} \tag{21}$$

Subsequent substitution in the expression for η, gives us

$$\begin{aligned}
\eta &= \langle P^2\rangle_{H_0}\\
&= \frac{1}{L^2}\int\langle P^2(\mathbf{x})\rangle_{H_0}\\
d\mathbf{x} &= \frac{1}{L^2}\int\sum_{\mathbf{q},\mathbf{q}'\in\mathcal{K}}\langle P_{\mathbf{q}}P_{\mathbf{q}}e^{\imath(\mathbf{q}+\mathbf{q}')\cdot\mathbf{x}}\rangle_{H_0}\\
d\mathbf{x} &= \frac{1}{L^2}\sum_{\mathbf{q},\mathbf{q}'\in\mathcal{K}}\delta(\mathbf{q}+\mathbf{q}')\langle P_{\mathbf{q}}P_{\mathbf{q}}\rangle_{H_0}\int d\mathbf{x} = \sum_{\mathbf{q}\in\mathcal{K}}\langle P_{\mathbf{q}}^2\rangle_{H_0}\\
&= \sum_{\mathbf{q}\in\mathcal{K}}\frac{4k_BTG_h(\mathbf{q})}{L^2(4G_h(\mathbf{q})G_P(\mathbf{q}) - G_f(\mathbf{q})^2)}\\
&= \sum_{\mathbf{q}\in\mathcal{K}}\frac{k_BT\kappa_b}{L^2(\kappa_b\xi - f^2)}
\end{aligned} \tag{22}$$

where $\xi = a(1 + 90\eta^2\epsilon_6/P_s^4 + 12\eta\epsilon_4/P_s^2)$ and η can be solved for to estimate the polarization fluctuation. Further details on the variational approach and its accuracy in the context of the current problem are provided in the Appendix.

4. Thermal fluctuations of the electric field

The computation of polarization correlation in Section 3 allows the estimation of the root mean square electric field. The

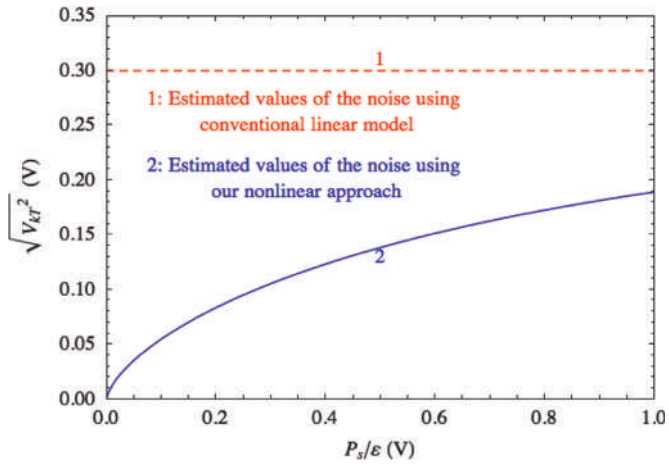

Fig. 4. Calculated values of noise with different P_s.

polarized membrane induces an electric field that can be calculated using Maxwell's equations. Here we may consider two ideal boundary conditions: (1) non-conducting boundary conditions, in which the membrane exterior has the permittivity of vacuum and (2) conducting boundary condition, in which the surrounding electrolyte is perfectly conductive. The real boundary conditions are somewhere between these two extremes—we will find that our final results (at the level of approximation we are interested in) are insensitive to these two bounding boundary conditions. Accordingly, we feel justified in avoiding the more complex nonlinear Poisson–Boltzmann framework. In the first case, we write the Maxwell equation as below:

$$\mathrm{div}\left(-\epsilon_0 \nabla \phi + \frac{P}{d}\chi(z)\mathbf{e}_z \right) = 0, \tag{23}$$

where

$$\chi(z) = 1 \quad \text{if} \quad z \in \left[-\frac{d}{2}, \frac{d}{2}\right] \quad \text{otherwise} = 0.$$

The solution can be conveniently found in Fourier space:

$$\phi(\mathbf{x}, z) = \sum_{\mathbf{q}\in\mathcal{K}} \hat{\phi}(\mathbf{q}, z)\mathbf{e}^{\mathrm{i}\mathbf{q}.\mathbf{x}},$$
$$\hat{\phi}(\mathbf{q}, z) = \frac{\hat{P}_{\mathbf{q}}}{2d\epsilon_0|\mathbf{q}|}(e^{|\mathbf{q}|z} - e^{-|\mathbf{q}|z})e^{-|\mathbf{q}|d/2}. \tag{24}$$

The ensuing voltage difference across the thickness of the membrane is

$$\Delta\hat{\phi}(\mathbf{q}) = \hat{\phi}(\mathbf{q}, d/2) - \hat{\phi}(\mathbf{q}, -d/2) = \frac{P_{\mathbf{q}}(1 - e^{-d|\mathbf{q}|})}{d\epsilon_0|\mathbf{q}|}. \tag{25}$$

The autocorrelation of the potential can be obtained by summing over all possible modes:

$$\langle V^2\rangle = \sum_{\mathbf{q}\in\mathcal{K}} \langle \Delta\hat{\phi}(\mathbf{q})^2\rangle = \sum_{\mathbf{q}\in\mathcal{K}} \frac{\langle P_{\mathbf{q}}^2\rangle(1 - e^{-d|\mathbf{q}|})^2}{d^2\epsilon_0^2|\mathbf{q}|^2}. \tag{26}$$

The above sum can be approximately calculated by replacing it with an integration. For conducting boundary conditions, Eq. (26) simply reduces to

$$\langle V^2\rangle = \frac{1}{\epsilon_0^2}\sum_{\mathbf{q}\in\mathcal{K}} \langle P_{\mathbf{q}}^2\rangle. \tag{27}$$

5. Power spectrum of the fluctuating electric field

The power spectrum of the electric field is the ensemble average of the time average of the power dissipation per unit frequency bandwidth and may be used to estimate the frequency dependence of our results (Kittel, 2004). This is necessary

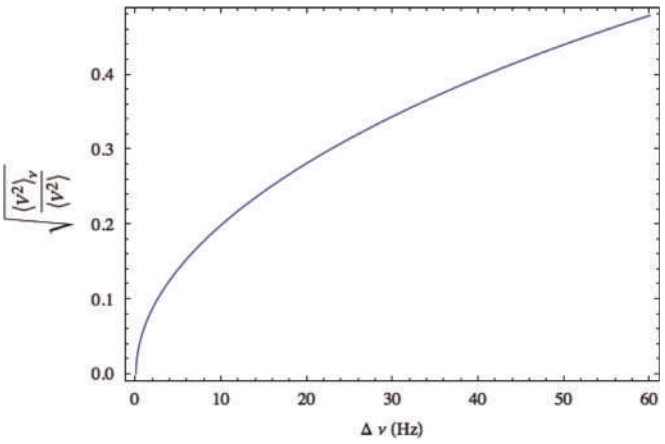

Fig. 5. Calculated thermal noise in the presence of time-dependent fields. The relaxation time is considered to be 1 ms. Typically the frequencies of imposed electric fields do not exceed 60 Hz, and most are, usually, lower. For frequencies less than 10 Hz, the effect of frequency is quite significant.

since experimental results indicate the noise threshold to be sensitive to the frequency of the applied field. This can be explained physically by considering the fact that the membrane is heavily occupied by fluctuating charges and dipoles, that can dissipate energy and generate noise during conformational transitions. Since the external fields are mostly time dependent – usually sinusoidal – it is best to compare the frequency spectrum of the thermal noise with that of the external field. In this section we calculate the power spectrum of the fluctuating voltage, from which we can estimate the Nyquist noise of the membrane. To this end, we assume a relaxation time, τ, during which the state of the system does not change. The relaxation time in biological membranes, depends on the diffusion constants of the membrane, dipoles and charges, and is roughly of the order of a millisecond (Phillips et al., 2009). This level of approximation, as will be seen in Section 6 where we present our results, suffices to draw experimentally relevant conclusions.

The relaxation process is well-known to be an exponential decay in the effect of random fields:

$$C(\tau) \propto e^{-t/\tau} \tag{28}$$

Then the power spectrum of the fluctuating electric field is obtained as

$$G(\nu) = 4\int_0^\infty \langle V^2\rangle e^{-t/\tau}\cos(2\pi\nu t)\,dt = \frac{4\langle V^2\rangle\tau}{1+(2\pi\nu\tau)^2} \tag{29}$$

This value is equivalent to the Nyquist noise power in a resistor — $4Rk_BT$. For low frequency ranges in which $\nu\tau \ll 1$, the power is almost constant — frequency-independent— and the fluctuating voltage is considered to be white noise. In this case the Nyquist noise for different frequency bandwidth can be calculated by simply multiplying the power by the frequency bandwidth: $\langle V^2\rangle_\nu = 4Rk_BT\Delta\nu$. However, at high frequencies, since the power spectrum is no longer a constant, the Nyquist noise should be calculated by integrating Eq. (29) over all possible values of the frequency. Assuming that the frequencies from external electrical fields do not exceed 60 Hz, to draw a comparison with the thermal noise, we have calculated the noise, $\langle V^2\rangle_\nu$ for different frequency bandwidth, up to 60 Hz—the results are shown in Fig. 5. As evident, at very low frequencies (0–10 Hz), the noise threshold can be as much an order of magnitude smaller than the associated high-frequency value, $\langle V^2\rangle$.

6. Relevance to real biological membranes

So far, we have considered model fluid membranes. Real biological membranes are highly heterogeneous and are covered with a large fraction of proteins. In such a crowded environment, polarization is spatially correlated within its plane. This non-locality of the polarization may play a significant role. One simple (and completely *phenomenological*) way to take this into account is to add a term proportional to the spatial gradient of the polarization. This notion is inspired from similar considerations in crystalline ferroelectrics and approximations made in the quantum mechanical density functional theory. Let δ be the smallest correlation length. Then we can modify the quadratic part of the original Hamiltonian (5) as follows:

$$H^q = \int_{\mathbb{S}} \frac{1}{2}\kappa_b(\nabla^2 h(\mathbf{x}))^2 + \frac{1}{2}aP(\mathbf{x})^2 + \frac{1}{2}a\delta^2|\nabla P(\mathbf{x})|^2 + fP(\mathbf{x})\nabla^2 h(\mathbf{x})d\mathbf{x}. \tag{30}$$

To estimate the strength of the polarization gradient term or alternatively, the order of magnitude of δ, we make two distinct arguments—both lead to similar results and are likely to bound the actual value: (1) We may consider the polarization correlation to be linked with the tension correlation. The rationale is that the electromechanical conformation of the

Table 1
Estimated values of thermal noise limit in cell membranes.

Frequency (H)	Experimental values (V/cm)	Linear dielectric model (V/cm)	Nyquist noise in the equivalent RC circuit (V/cm)	Present model for a pure lipid bilayer (V/cm)	Predicted values for a real bio-membrane (V/cm)
	Chicken fibroblasts[a] Cleary et al. (1988)				
1	0.6	6.1×10^5	3.6×10^3	1×10^3	100
	Bovine fibroblasts[a] McLeod et al. (1987)				
10^{-1}	300	6.1×10^5	1.1×10^3	320	30
1	2.1	6.1×10^5	3.6×10^3	1×10^3	100
10^1	1.5	6.1×10^5	1.1×10^4	3.2×10^3	300
10^2	30	6.1×10^5	3.6×10^4	9.5×10^3	900
10^3	600	6.1×10^5	1.1×10^5	1.5×10^4	1400

[a] The noise was calculated for a cell of size $L \approx 150\ \mu m$. Considering the thickness of the membrane to be $d \approx 5$ nm, we have converted the reported cell-level value to the membrane noise value.

mechanosensitive channels are coupled to the tension of the membrane (Paul and Phillips, 2005). (2) A geometrical argument may be made that δ ought to scale with the average inter-protein distance. Based on the first argument, using a result given by Liu and Sharma. (2013), we consider the ratio of the two-point tension–correlation with respect to self-correlation:

$$\eta = \frac{\langle |\nabla h(0) \nabla h(\boldsymbol{\delta})| \rangle}{\langle |\nabla h(0)|^2 \rangle} = \frac{\sum_{\mathbf{q}} \langle q^2 h_{\mathbf{q}}^2 \rangle \mathbf{e}^{\mathbf{i}\mathbf{q}\cdot\boldsymbol{\delta}}}{\sum_{\mathbf{q}} \langle q^2 h_{\mathbf{q}}^2 \rangle} \tag{31}$$

where $\boldsymbol{\delta}$ is the relative position vector between two points. By integrating over all modes, for different values of $\boldsymbol{\delta}$, we find that for $\boldsymbol{\delta} \geq 5d$ the ratio is less than 0.1, which is essentially negligible. Therefore, we conclude that for biological membranes, the minimum correlation length is at least $5d$.

According to Linden et al. (2012), biological membranes are extremely crowded. They estimate that 30–55% of the area of the lipid membrane is occupied by various types of protein channels. The radius of the channels in their open state is roughly about 2–3 nm. Using these values, the average distance between the centers of the proteins can be estimated to be about 6–12 nm. This argument provides an alternative way to estimating δ.

Recalculating the fluctuations of polarization, using Eq. (30) for the quadratic part of the total Hamiltonian (9), gives the estimated noise for different values of δ. For $\delta \approx 10$ nm, we obtain values of noise voltage which is almost one order of magnitude smaller than what we obtained earlier in Section 4.

7. Results and discussion

For quantitative results, we must estimate P_s. The breakdown voltage of the membrane is around 1 V—-and the polarization corresponding to this represents a strict upper bound. As it can be appreciated from Fig. 2(a), significantly higher electric fields are required to polarize a membrane close to P_s. Evidently $P_s \to \infty$, represents the linear case which corresponds to the quadratic Hamiltonian. Indeed, our nonlinear numerical results coincide with the linear estimates discussed in the introduction of the paper if P_s is taken to be very large. The variation of the noise threshold with respect to choice of P_s is shown in Fig. 4 where the abscissa corresponds to the voltage corresponding to P_s. To solve the Maxwell equation in Section 4, we used the conducting boundary condition, since it gives us the upper bound of the voltage noise. In our calculations, we have assumed that $\kappa_b = 25 k_B T$, $\epsilon = 2\epsilon_0 =$, $f^2/\kappa_b \approx a/2$. For the higher order terms, since the dominant parameter is P_s we have set ε_i equal to 1. We have verified that this does not significantly alter our results. The linear framework yields noise threshold around 0.3 V. Even if we adopt the excessively simple model that the dielectric response is almost linear up until the strict upper limit of the breakdown voltage, our models predict a noise threshold that is still much lower than 0.3 V. To further refine our estimate of P_s, we take recourse in recent experimental work (Raphael et al., 2000) that has documented nonlinear dielectric properties for a specific biomembrane (of outer hair cells in the ear). There is significant diversity among biological membranes, however, their linear dielectric behavior is markedly similar *and* since our primary interest is in order of magnitude estimates, we have used the experimental estimate of P_s by Raphael et al. (2000) as a representative value.

According to their model, the length change of the outer hair cell with voltage, can be explained by a nonlinear relationship between the flexoelectric coefficient and the applied electric field. To explain the nonlinear dependence of flexoelectric coefficient on the membrane voltage, they proposed a nonlinear relationship between the polarization density and the electric field. Their work suggest that for dipole moments less than 10D, the dielectric behavior of the membrane is linear. Considering the dipole density of such membranes to be about $6000/\mu m^2$, we estimate P_s/ϵ to be less than 10 mV.

Using these estimates, our calculations of the noise threshold appear in Table 1 where a comparison is also made with known experimental results and other models. We have converted the estimated voltage noise to the electric field noise, by using the thickness of the membrane: $\overline{E}_{k_BT} = \overline{V}_{k_BT}/d$. Some comments related to the frequency effect and the consideration of gradient of polarization (relevant for real biological membranes) are warranted. Consideration of both effectively reduce the noise threshold estimates by an order of magnitude. For example, consideration of the gradient of polarization term along with the estimate of $\delta = 10$ nm (see Section 6) leads to the noise threshold estimate that is almost 10 times smaller that for a model fluid membrane. The experimental values in the second column evidently have significant scatter. The notable aspect however, as already emphasized briefly in the Introduction, is how low these are compared to the estimates from conventional models (column 3). We note that in the cited experimental references and prior works, the noise estimates were made for the entire cell. In Table 1, we have converted the noise values from the cell level to the membrane level through the following relations: $E_{mem} \approx E_{cell} \times L/d$, in which L is the size (radius) of the cell. Here, we have assumed that the electric field is uniform across the thickness of the membrane and cell, and used the equation: $\overline{V}_{k_BT} = \overline{E}_{mem} \times d = \overline{E}_{cell} \times L$. The fourth column is the Nyquist noise at different frequencies. The results of our model for pure lipid bilayers are shown in column 5. In the last column, we have provided the estimated values of noise in real biological membranes, where we have (phenomenologically) considered the interactions between the channels and other physical inhomogeneities, using $\delta \approx 10$ nm.

8. Concluding remarks

In summary, we have pointed out the rather large discrepancy that exists between the (experimentally estimated) minimum electric field that an ideal fluid membrane can detect and what the existing theoretical models predict. A consistent accounting for the influence of the nonlinear dielectric behavior of membranes on the thermal fluctuations of the membrane electric field appears, in large part, to address this issue. The dielectric nonlinearity can be explained physically by the dipole saturation phenomena, and the consequent fact that there is an upper limit, P_S to which a membrane is capable of being polarized. Our mathematical framework yields analytical solution for the thermal electrical noise of membranes. In real biological membranes (as opposed to fluid membranes), we must contend with more complex situations. Proteins, salts, charged objects, ionic flux and the polarized double layers are some of the items that may contribute to the fluctuations of electric field in real biological membranes. To some extent, phenomenologically, we consider the effect of inhomogeneities through an added energetic term that sets the scale for the membrane in-plane correlations of polarization. The predictions of our theoretical framework provide noise estimates that are of the same order of magnitude as experiments. In particular, our work provides both a benchmark estimate for model fluid membranes (which should be experimentally testable) and reasonable predictions for biological membranes (where significantly more complexity may be expected). Further experimental studies are required to understand and clarify the quantitative aspects of dielectric nonlinearity in biological membranes and settle the rather large scatter in the existing experimental data.

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Appendix A. Details on the variational approximation

Kleinert and co-workers introduced the so-called variational perturbation method (VPT) to handle the statistical mechanics of anharmonic Hamiltonians (Kleinert, 1989, 2009). A straightforward perturbation approach (expanded around, say, a quadratic Hamiltonian) results in a divergent series. On the other hand, variational approximation using trial function, while effective, works best if the trial function is an "inspired" guess. The VPT combines both approaches and it has been shown that the resulting series converges exponentially. In the present work, we have used the VPT while retaining only the first term. This approach is extensively used to deal with thermal fluctuations of fluid membranes in different contexts (Palmieri and Safran, 2013; Brewster et al., 2009; Pieruschka et al., 1994; Podgornik and Parsegian, 1992; Weikl and Lipowsky, 2001).

In this appendix we present some calculations that provide some assurance to the quality of our approximation. Consider the following Hamiltonian which, while anharmonic in the polarization field, ignore the mechanical displacement fields:

$$H = \int \frac{1}{2} a P^2 + \frac{a\varepsilon_4}{P_S^2} P^4 \tag{32}$$

The advantage of the Hamiltonian in (32) that includes a fourth order polarization term (but no field derivatives) is that the partition function and the free energy can be obtained in closed-form and therefore provides a simple (but related) test case to assess the approximation we have used in this work. To deal with the path integral in the partition function, we first discretize the Hamiltonian (32). To this end we assume that the membrane consists of 2N molecules located at

$\mathbf{x} \in \mathcal{L} = \Lambda(n_1, n_2)$: $n_1, n_2 = 1, \ldots, m$, where $\Lambda = L/m$. The total number of degrees of freedom are $N = m^2$ and each has an area of $A_0 = \Lambda^2$. Given that the area density of the dipole moment at point $\mathbf{x}$ is $P(\mathbf{x})$, the dipole moment $\tilde{P}(\mathbf{x})$ at this point can be calculated by: $\tilde{P}(\mathbf{x}) = P(\mathbf{x})A_0$. Substituting this into Eq. (32) and summing over all degrees of freedom, we obtain

$$H = \sum_{\mathbf{x}\in\mathcal{L}} \frac{1}{2} a \frac{\tilde{P}^2(\mathbf{x})}{A_0} + a\epsilon_4 \frac{\tilde{P}^4(\mathbf{x})}{A_0^3 P_S^2} \tag{33}$$

The partition function is

$$Z = \int \exp(-\beta H) = \int \exp\left(-\beta\left(\sum_{\mathbf{x}\in\mathcal{L}} \frac{1}{2} a \frac{\tilde{P}^2(\mathbf{x})}{A_0} + a\epsilon_4 \frac{\tilde{P}^4(\mathbf{x})}{A_0^3 P_S^2}\right)\right) \prod_{\mathbf{x}\in\mathcal{L}} d\tilde{P}(\mathbf{x}) = \prod_{\mathbf{x}\in\mathcal{L}} \frac{e^{aA_0\beta P_S^2/32\epsilon_4} A_0 P_S K_{\frac{1}{4}}\left(\frac{a\beta A_0 P_S^2}{32\epsilon_4}\right)}{2\sqrt{2\epsilon_4}} \tag{34}$$

where $K_{1/4}$ is the modified Bessel function of the second kind. The free energy per unit area is: where $K_{1/4}$ is the modified Bessel function of the second kind. The free energy per unit area is

$$f = \frac{F}{NA_0} = -\frac{k_B T}{NA_0} \log Z = -\frac{aP_S^2}{32\epsilon_4} - \frac{k_B T}{A_0} \log \frac{A_0 P_S K_{\frac{1}{4}}\left(\frac{aA_0 P_S^2}{32k_B T\epsilon_4}\right)}{2\sqrt{2\epsilon_4}} \tag{35}$$

In the limits of $P_S \to \infty$ or $\epsilon_4 \to 0$, which corresponds to the quadratic Hamiltonian, we obtain

$$f_L = -\frac{k_B T}{2A_0} \log \frac{2\pi k_B T A_0}{a} \tag{36}$$

Also the fluctuations of the dipole moment at each point $\mathbf{x}' \in \mathcal{L}$ can be obtained using the partition function (34):

$$\langle \tilde{P}^2(\mathbf{x}')\rangle = \frac{1}{Z} \int \tilde{P}^2(\mathbf{x}') \exp\left(-\beta\left(\sum_{\mathbf{x}\in\mathcal{L}} \frac{1}{2} a \frac{\tilde{P}^2(\mathbf{x})}{A_0} + a\epsilon_4 \frac{\tilde{P}^4(\mathbf{x})}{A_0^3 P_S^2}\right)\right) \prod_{\mathbf{x}\in\mathcal{L}} d\tilde{P}(\mathbf{x}) = \frac{A_0^2 P_S^2}{8\epsilon_4}\left(\frac{K_{\frac{3}{4}}\left(\frac{aA_0 P_S^2}{32k_B T\epsilon_4}\right)}{K_{\frac{1}{4}}\left(\frac{aA_0 P_S^2}{32k_B T\epsilon_4}\right)} - 1\right) \tag{37}$$

The root mean square of the voltage across the membrane is given by

$$V_{\text{exact}} = \sqrt{\langle V^2\rangle} = \frac{\sqrt{\langle \tilde{P}^2(\mathbf{x}')\rangle}}{A_0\epsilon_0} \tag{38}$$

To compare the exact results with that of the variational approximation, we calculate the free energy per unit area and the root mean square of the voltage across the membrane, by minimizing the right hand side of the inequality (10) with respect to the trial parameter. To start, consider the trial Hamiltonian as below:

$$H_0 = \sum_{\mathbf{x}\in\mathcal{L}} \frac{1}{2} \bar{a} \tilde{P}^2(\mathbf{x}) \tag{39}$$

where $\bar{a}$ is the trial dielectric parameter. Using the above Hamiltonian, we calculate the right hand side of the inequality (10) as below:

$$\begin{aligned} F_{\text{var}} &= \alpha_F + \frac{k_B T}{2} \sum_{\mathbf{x}\in\mathcal{L}} \log \bar{a} + \sum_{\mathbf{x}\in\mathcal{L}} \frac{a}{2A_0} \langle \tilde{P}^2(\mathbf{x})\rangle_{H_0} + \sum_{\mathbf{x}\in\mathcal{L}} \frac{a\epsilon_4}{A_0^3 P_S^2} \langle \tilde{P}^4(\mathbf{x})\rangle_{H_0} \\ &= \alpha_F + \frac{k_B T}{2} \sum_{\mathbf{x}\in\mathcal{L}} \log \bar{a} + \sum_{\mathbf{x}\in\mathcal{L}} \frac{a}{2A_0} \frac{k_B T}{\bar{a}} + \sum_{\mathbf{x}\in\mathcal{L}} \frac{3a\epsilon_4}{A_0^3 P_S^2} \left(\frac{k_B T}{\bar{a}}\right)^2 \end{aligned} \tag{40}$$

where we have used Wick's theorem to obtain the higher order correlation function $\langle \tilde{P}^4(\mathbf{x})\rangle_{H_0} = 3\langle \tilde{P}^2(\mathbf{x})\rangle_{H_0}^2$. Also, we have directly used the equipartition theorem to calculate the correlation function: $\langle \tilde{P}^2(\mathbf{x})\rangle_{H_0} = k_B T/\bar{a}$. Minimization of the variational free energy with respect to the trial dielectric parameter, provides us with an upper bound of the exact free energy:

$$\frac{\partial F}{\partial \bar{a}} = \sum_{\mathbf{x}\in\mathcal{L}} \left(\frac{k_B T}{2\bar{a}} - \frac{k_B T a}{2A_0 \bar{a}^2} - \frac{6a\epsilon_4}{A_0^3 P_S^2 \bar{a}^3} (k_B T)^2\right) := 0 \tag{41}$$

The solution of Eq. (41) will give us the renormalized dielectric parameter as below:

$$\bar{a} = \frac{a}{2A_0}\left(1 + \sqrt{1 + \frac{48 k_B T \epsilon_4}{aA_0 P_S^2}}\right) \tag{42}$$

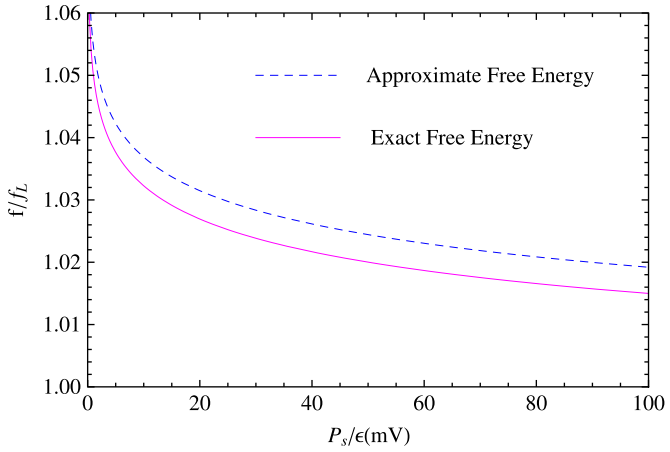

Fig. 6. Comparison of the exact free energy and the corresponding approximate one.

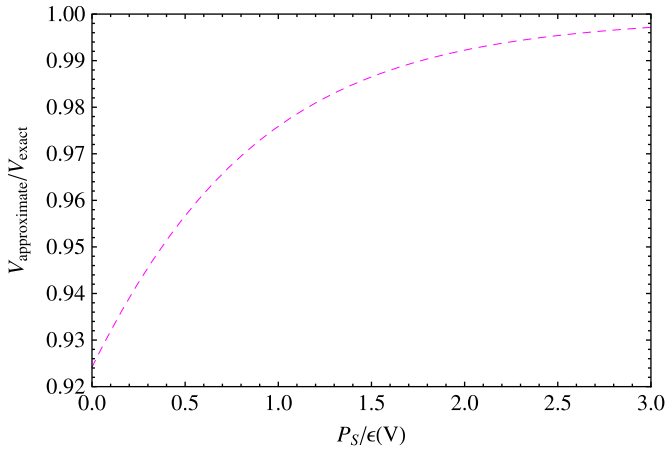

Fig. 7. Comparison of exact root mean square of the voltage and the corresponding approximate one.

The renormalized dielectric parameter may be substituted in (39) and by recourse to the equipartition theorem, we may calculate the free energy per unit area, fluctuations of the dipole moment, and eventually the root mean square of the voltage across the membrane. A comparison between the variational approximation obtained using (42), and the exact values of the free energy per unit area and the root mean square of the voltage, from Eqs. (35) and (38), respectively, is depicted in Figs. 6 and 7. In Fig. 6, the free-energies are normalized with respect to the one obtained from the quadratic Hamiltonian (the linear dielectric case, (36). The variational free energy which is shown is dashed blue is always above the exact free energy (magenta). On the other hand, since the variational free energy is always greater than the exact free energy, the estimated fluctuations (obtained from variational method) will be always smaller than the exact fluctuations. We have also compared the estimated and the exact root mean square of the voltage in Fig. 7. The vertical axis in this plot is the ratio of the variational estimate with respect to the exact value. For any values of P_S, the error is less than 10%. In case more accurate results are of interest, progressing to the second order of the variational perturbation method (Kleinert, 1989, 2009) is required.

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