Thermal fluctuations of electric field and solute density in biological cells

J. A. Fay
Department of Mechanical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts 02193
(Received 23 May 1996; revised manuscript received 2 June 1997)

Thermal fluctuations of ionic densities in a biological cell's electrolyte creates random electric fields and solute density fluctuations. Using two common models of cellular components, the capacitor-resistor membrane model and the uniform electrolyte cytoplasm model, we determine the RMS values of these random variables and their frequency and wave number spectra by including independent variations of both anion and cation densities. In the membrane, the inequality of ionic mobilities skews the frequency spectra to much lower frequencies characteristic of solute transport, rather than current transport, through the membrane. In the cytoplasm electrolyte, the electric field wave number spectrum declines approximately exponentially with increasing wave number, leading to an algebraically declining spatial correlation function; the time correlation function also declines algebraically. The cytoplasm solute density fluctuations behave normally, with exponential spatial and algebraic temporal correlation functions. The RMS electric field of the cytoplasm is estimated at $\sim 2\times 10^7$ V/m, about a factor of 10^3 higher than that of the membrane. [S1063-651X(97)13109-9]

PACS number(s): 87.22.Fy, 05.40.+j, 41.20.Cv, 82.60.Lf

I. INTRODUCTION

The thermally induced fluctuations of electric potential and field in cells and cell membranes have been considered a significant factor in understanding the electrical environment of cellular processes. Two methods have been employed to define the statistical properties of electric variables. Estimates of the electric field by Barnes [1] and Adair [2], and the derivation of the membrane potential power spectrum by Procopio and Fornes [3], rely on a model based upon a capacitor-resistor element of an electric circuit. In this model, the root-mean-square (RMS) amplitudes of the electrical variables are expressed in terms of the electrical properties of the cell components and their macroscopic dimensions. A complementary view, developed by Oosawa [4], considers the cell interior as a uniform electrolyte for which the RMS values are found to be independent of the cell dimensions. These seemingly incompatible results deserve some reconciliation.

The electrical circuit model, based upon classical fluctuation theory, equates the RMS electrical energy stored in a capacitor of volume V to the thermal mean value of $k_BT/2$, from which it follows that the mean square electric field of the capacitor, $\langle E^2\rangle$, is equal to $k_BT/\epsilon V$, where ϵ is the electric permittivity of the cell component. Thus the cell volume is a determining factor of $\langle E^2\rangle$. The power spectrum of $\langle E^2\rangle$ may then be derived by applying the fluctuation-dissipation theorem [3].

Oosawa derives the fluctuations of electrical variables of an electrolyte considered as a continuous medium, determining the free energy density of the electrolyte after expanding the electric field as a Fourier series in wave number space. The spatial correlation function of the electric field has a magnitude of $\sim k_bT\kappa^3/\epsilon$ at a distance κ^{-1}, the inverse of the Debye-Huckel wave number κ of the electrolyte. Thus the effective capacitor volume of the electrolyte is κ^{-3}, which is much smaller than the cell volume by about five to ten orders of magnitude, depending upon whether one is considering the membrane or the cytoplasm.

In both approaches the fluctuation of an electric variable is related to the fluctuation of the net electric charge, which is taken to be the single independent thermodynamic variable. But the cell and its environment are electrolytes, composed of several chemically distinct anions and cations, each of which should be considered a separate independent thermodynamic variable. The electric charge fluctuations are then coupled to those of all the electrolyte ions through the contributory effects of all these variables to the free energy of the cell system.

In this paper we reconsider the two models of cell fluctuations, the capacitor-resistor and the continuum electrolyte, but explicitly include both anion and cation variability, for a completely dissociated equal valency solute. We choose as independent variables the net charge and the solute density. We then determine the RMS value and frequency spectrum of the electric field and solute density in the case of the capacitor-resistor model, and in addition the spatial spectra for the continuum electrolyte model. From these spectra we then derive the time correlation functions, and in the electrolyte case, the spatial correlation functions.

In Sec. II below we consider the capacitor-resistor model of the cell membrane, showing that the coupling of the anion and cation flows is reflected in a more complex frequency spectrum than previous treatments. This spectrum is dominated by a slow mode arising from solute fluctuations in the cytoplasm. The electrolyte analysis of Sec. III borrows from Chandler and Anderson [7] the wave number decomposition of the electric component of the free energy density of an electrolyte, leading to the wave number and frequency spectra of the electric field. For the solute density fluctuations, a cutoff of the wave number spectrum is devised to satisfy the statistical requirements of the configuration integral of the solute considered as a perfect solution. In Sec. IV the various parameters of these relations are estimated for a typical cell cytoplasm and membrane. Section V discusses the implications of this analysis and its findings.

II. THE CELL AS A CAPACITOR-RESISTOR

A biological cell may be modeled as a thermodynamic system consisting of a cytoplasm enclosed by the cell outer

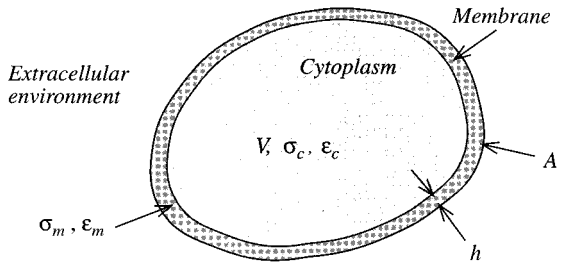

FIG. 1. A diagram of the biological cell model. Symbols denote the physical properties of the cytoplasm and membrane used in this analysis.

membrane, as in Fig. 1. Ignoring the various structures within the cytoplasm, such as the nucleus, mitochondria, etc., we can consider the cytoplasm to be an electrolyte of uniform solute concentration $\overline{n_s}$, having an electrical conductivity σ_c and permittivity ϵ_c. The membrane surrounding the cytoplasm has a thickness h that is very small compared to the cell dimension V_c/A, where V_c is the cell cytoplasm volume and A its membrane area. Furthermore, the membrane electrical conductivity σ_m is small enough compared to σ_c that the potential difference within the cytoplasm $\delta\phi_c$ is much smaller than that across the membrane, $\delta\phi_m$:

$$\frac{\delta\phi_c}{\delta\phi_m}\sim\frac{\sigma_m(V/A)}{\sigma_c h}\ll 1. \tag{2.1}$$

Thus we may regard the cytoplasm as one plate of a capacitor, having a uniform potential, and its extracellular fluid as the other, the membrane providing the dielectric medium between the two (relatively) conducting plates. The cell capacitance C is thus

$$C=\epsilon_m\frac{A}{h}=\frac{\epsilon_m V_m}{h^2}, \tag{2.2}$$

where ϵ_m is the permittivity and V_m the volume of the cell membrane.

The cell membrane permits the movement of ions and molecules between the cytoplasm and the extracellular fluid. It may be considered to be a semipermeable membrane with different permeabilities to different ions and molecules. More important, it is an active membrane that maintains a difference in the concentrations of Na^+ and K^+ between the cytoplasm and the extracellular fluid, the former being relatively rich in K^+ and the latter rich in Na^+. This so-called ion pumping mechanism is maintained by chemical reactions within the membrane [5], so that the cell may be regarded as a thermodynamic system in a dynamic steady state equilibrium. The ion pumping is accompanied by a potential difference, called the resting potential, between the cytoplasm and the extracellular fluid, of about -100 mV. In what follows, the equilibrium values of the thermodynamic variables, denoted by an overline, are those of this resting state. The change in value of these variables from the equilibrium (resting) state is denoted by the prefix Δ.

For simplicity, consider the cytoplasm electrolyte at equilibrium to consist of a single completely dissociated salt of equal number of anions and cations ($\overline{N_+}=\overline{N_-}$) each having equal magnitude of electric charge Ze. With respect to fluctuations of these variables, there are two degrees of freedom, one for each ion type. We select as independent variables the net electrical charge Q and the average ion number N_s:

$$Q=Ze(N_+-N_-),\quad \overline{Q}=0,$$

$$N_s=\frac{1}{2}(N_++N_-),\quad \overline{N_s}=\overline{N_+}=\overline{N_-}, \tag{2.3}$$

where $\overline{N_s}$ is the equilibrium number of solute molecules. With this choice, Q is entirely an electrical variable while $2N_s$ is the number of ions in the cytoplasm.

We turn next to the determination of the mean square values of the fluctuations ΔQ and ΔN_s of these extensive variables. In the vicinity of thermodynamic equilibrium, the cell free energy change ΔA is second order in the increments of the independent variables:

$$\Delta A=\frac{1}{2}\left(\frac{\partial^2 A}{\partial Q^2}\right)(\Delta Q)^2+\frac{1}{2}\left(\frac{\partial^2 A}{\partial N_s^2}\right)(\Delta N_s)^2$$

and their ensemble or time averaged mean square values are

$$\langle(\Delta Q)^2\rangle=k_BT\left(\frac{\partial^2 A}{\partial Q^2}\right)^{-1},$$

$$\langle(\Delta N_s)^2\rangle=k_BT\left(\frac{\partial^2 A}{\partial N_s^2}\right)^{-1}, \tag{2.4}$$

where k_B is Boltzmann's constant. The contribution of the charge Q of the membrane capacitor to the free energy of the cell is $(Q)^2/2C$ and that of $2N_s$ ions in the cytoplasm (for fixed $Q=0$) is $N_skT\ln(N_s/V_c)$, so that

$$\langle(\Delta Q)^2\rangle=k_BTC, \tag{2.5}$$

$$\langle(\Delta N_s)^2\rangle=\overline{N_s}. \tag{2.6}$$

Alternatively, these fluctuations may be expressed in terms of the intensive variables, the membrane electric field $E_m\equiv Q/hC$, and the cytoplasm solute number density $n_s\equiv N_s/V_c$:

$$\langle(\Delta E_m)^2\rangle=\frac{k_BT}{h^2C}=\frac{k_BT}{\epsilon_m V_m}, \tag{2.7}$$

$$\langle(\Delta n_s)^2\rangle=\frac{\overline{n_s}}{V_c}. \tag{2.8}$$

A. Transport of charge and solute

Despite the inhomogeneity of both membrane and cytoplasm, we assume that the transport of charge and solute within them may be regarded as that of a uniform electrolyte. For either anions or cations, the volume flux may be given as

$$n_\pm\mathbf{v}_\pm=\mu_\pm(n_\pm Z_\pm e\mathbf{E}-k_BT\nabla n_\pm), \tag{2.9}$$

where μ is the ion mobility, n the ion number density, and $\mathbf{v}$ the ion drift velocity. Because we use charge and solute number as independent variables, we define an electric current density $\mathbf{j}$ and, for symmetry, a solute ''electric current'' density $\mathbf{j}_s$ as

$$\mathbf{j} \equiv e(n_+ Z_+ \mathbf{v}_+ + n_- Z_- \mathbf{v}_-),$$

$$\mathbf{j}_s \equiv Ze(n_+ \mathbf{v}_+ + n_- \mathbf{v}_-). \tag{2.10}$$

By combining Eqs. (2.9) and (2.10) and using the following parameters:

$$\alpha \equiv \frac{\mu_+ - \mu_-}{\mu_+ + \mu_-}, \tag{2.11}$$

$$\kappa^2 \equiv \frac{2n_s Z^2 e^2}{\epsilon k_B T}, \tag{2.12}$$

where κ is the familiar Debye-Huckel wave number, Eqs. (2.10) assume the form

$$\mathbf{j} = \sigma \mathbf{E} - \frac{\alpha\sigma}{\epsilon\kappa^2} \nabla(2Zen_s), \tag{2.13}$$

$$\mathbf{j}_s = \alpha\sigma \mathbf{E} - \frac{\sigma}{\epsilon\kappa^2} \nabla(2Zen_s). \tag{2.14}$$

Note that, for equal anion and cation mobilities, $\alpha = 0$ and the charge and solute currents $\mathbf{j}$ and $\mathbf{j}_s$ are uncoupled.

B. Frequency spectrum and time correlation function

The time or frequency spectrum of a fluctuating random variable $\Delta\psi\{t\}$ may be found by forming the Langevin equation describing the time decay of the variable. For a single degree of freedom, the Langevin equation for $\Delta\psi\{t\}$ has the form

$$\frac{d}{dt}(\Delta\psi) + \lambda \Delta\psi = \Delta\Psi\{t\}, \tag{2.15}$$

where λ^{-1} is the macroscopic decay time of fluctuations and $\Delta\Psi\{t\}$ is the excitation function of the fluctuations, a random function of time whose correlation function is a δ function. To determine the spectrum of $\Delta\psi$, we square the time transform of Eq. (2.15) to find

$$(\omega^2 + \lambda^2)(\Delta\tilde{\psi})^2 = (\Delta\tilde{\Psi})^2,$$

$$\langle (\Delta\psi)^2 \rangle = \int_0^\infty (\Delta\tilde{\psi})^2 \, d\omega$$

$$= (\Delta\tilde{\Psi})^2 \int_0^\infty (\omega^2 + \lambda^2)^{-1} \, d\omega, \tag{2.16}$$

where the tilde identifies the time transform and where $(\Delta\tilde{\Psi})^2$ is a function of λ but not of ω. We prefer to express the right-hand side of the equations of the form of Eq. (2.16) in terms of a normalized spectral density $\mathcal{T}\{\omega\}$ whose integral is unity:

$$\langle (\Delta\psi)^2 \rangle \equiv k_B T \left(\frac{\partial^2 A}{\partial \psi^2} \right)^{-1} \int_0^\infty \mathcal{T}\{\omega\} \, d\omega. \tag{2.17}$$

The time correlation function $C_{\Delta\psi}\{t'\}$ of the random variable $\Delta\psi$ is related to the spectral density by [6]

$$C_{\Delta\psi}\{t'\} \equiv \langle (\Delta\psi\{t\})(\Delta\psi\{t+t'\}) \rangle \tag{2.18}$$

$$= \langle (\Delta\psi)^2 \rangle \mathcal{C}\{t'\}, \tag{2.19}$$

where

$$\mathcal{C}\{t'\} \equiv \int_0^\infty \mathcal{T}\{\omega\} \cos \omega t' \, d\omega \tag{2.20}$$

is the normalized time correlation function.

For the special case of Eq. (2.15) having a single degree of freedom, we find

$$\mathcal{T}\{\omega\} = \frac{2\lambda/\pi}{\lambda^2 + \omega^2}, \tag{2.21}$$

$$\mathcal{C}\{t'\} = \exp(-\lambda t'). \tag{2.22}$$

We now proceed to derive the Langevin equation for the biological cell, which has two degrees of freedom, for the extensive variables ΔQ and ΔN_s. The conservation of charge and ionic molecules requires that

$$\frac{d(\Delta Q)}{dt} + jA = 0,$$

$$\frac{d(2Ze\Delta N_s)}{dt} + j_s A = 0. \tag{2.23}$$

By use of Eqs. (2.13) and (2.14), these macroscopic conservation equations may be transformed into the form

$$\frac{d(\Delta Q)}{dt} + \Omega \Delta Q + \alpha\eta\Omega(2Ze\Delta N_s) = 0,$$

$$\frac{d(2Ze\Delta N_s)}{dt} + \alpha\Omega\Delta Q + \eta\Omega(2Ze\Delta N_s) = 0, \tag{2.24}$$

where

$$\Omega \equiv (\sigma/\epsilon)_m, \tag{2.25}$$

$$\eta \equiv A/h\kappa^2 V_c. \tag{2.26}$$

The dimensionless parameter η is the ratio of the capacitance of the membrane to that of the cytoplasm, and is much smaller than unity for a typical cell, having a value of $\sim 10^{-3}$ (see Table I).

For the special case of equal ionic mobilities ($\alpha = 0$), the Langevin equations for ΔQ and ΔN_s (and thus E and n_s) are not coupled and each has the form of Eq. (2.15). The corresponding normalized frequency spectra and correlation functions are

TABLE I. Typical properties of a biological cell.

	d (m)	h (m)	A (m^2)	V (m^3)	ϵ (F/m)	σ (S/m)	n_s (mol/m^3)	κ (m^{-1})	Ω (s^{-1})	η
Cytoplasm	10^{-5}			5.2×10^{-16}	6.9×10^{-10}	1.1	10^2	10^9	1.6×10^9	
Membrane		2.4×10^{-9}	3.1×10^{-10}	7.4×10^{-19}	2.4×10^{-11}	2×10^{-8}	1.0	5.5×10^8	8.3×10^2	8.2×10^{-4}

$$\mathcal{T}_E\{\omega\}=\frac{2\Omega/\pi}{\Omega^2+\omega^2},\quad \mathcal{T}_{n_s}\{\omega\}=\frac{2\eta\Omega/\pi}{(\eta\Omega)^2+\omega^2}, \tag{2.27}$$

$$\mathcal{C}_E\{t'\}=\exp(-\Omega t'),\quad \mathcal{C}_{n_s}\{t'\}=\exp(-\eta\Omega t'). \tag{2.28}$$

For the solute fluctuations, the bandwidth of the frequency spectrum ($\sim\eta\Omega$) is much less than that for the electric field fluctuations ($\sim\Omega$), and the corresponding correlation time ($[\eta\Omega]^{-1}$) is much longer.

For the general case in which $\alpha\neq0$, the fluxes of charge and solute are coupled and the Langevin equation takes the form

$$\left(\frac{d^2}{dt^2}+\Omega(1+\eta)\frac{d}{dt}+\eta\Omega^2(1-\alpha^2)\right)\Delta\psi=\Delta\Psi. \tag{2.29}$$

The normalized frequency spectrum and correlation function, identical for both electric field and ionic number density, are

$$\mathcal{T}\{\omega\}=\frac{(2/\pi)\eta(1+\eta)(1-\alpha^2)\Omega^3}{(\omega^2+\omega_1^2)(\omega^2+\omega_2^2)}, \tag{2.30}$$

$$\mathcal{C}\{t'\}=\frac{\omega_1\omega_2}{\omega_2-\omega_1}\left(\frac{\exp(-\omega_1t')}{\omega_1}-\frac{\exp(-\omega_2t')}{\omega_2}\right), \tag{2.31}$$

where

$$\omega_1=\frac{\Omega}{2}[(1+\eta)+\sqrt{(1-\eta)^2+4\alpha^2\eta}],$$

$$\omega_2=\frac{\Omega}{2}[(1+\eta)-\sqrt{(1-\eta)^2+4\alpha^2\eta}]. \tag{2.32}$$

Because $\eta\ll1$, we may approximate the relations (2.30)–(2.32) by neglecting terms of order η^2 compared to unity, finding

$$\omega_1\simeq\Omega(1+\alpha^2\eta), \tag{2.33}$$

$$\omega_2\simeq\Omega\eta(1-\alpha^2), \tag{2.34}$$

$$\mathcal{T}\{\omega\}\simeq\frac{(2/\pi)\eta(1-\alpha^2)\Omega}{\omega^2+[\eta(1-\alpha^2)\Omega]^2}, \tag{2.35}$$

$$\mathcal{C}\{t'\}\simeq\exp[-\Omega\eta(1-\alpha^2)t'], \tag{2.36}$$

provided that $\alpha^2\gg\eta$. It is clear that the coupled frequency spectrum and correlation function are dominated by the slow mode of solute transport whose decay time is $\sim[\Omega\eta(1-\alpha^2)]^{-1}$, and that the fast mode of electric current transport makes a negligible contribution to the power spectrum and time correlation function. In cell membranes $\mu_-\ll\mu_+$ [9] so that the factor $(1-\alpha^2)$ in Eqs. (2.33)–(2.36) equals $4\mu_-/\mu_+\ll1$, making the correlation time constant much longer than $(\eta\Omega)^{-1}$.

If the cell membrane were impervious to anions ($\mu_-=0$), there would be but one degree of freedom, for the cations, Eq. (2.13) would become $\mathbf{j}=\sigma\mathbf{E}$, and the frequency spectrum $\mathcal{T}_E\{\omega\}$ and correlation function $\mathcal{C}_E\{t'\}$ would be those of Eqs. (2.27) and (2.28). In this degenerate case, there would be no fluctuations in the solute density.

III. FLUCTUATIONS IN A UNIFORM ELECTROLYTE

In contrast to the cell as a capacitor, having fluctuations in the extensive properties Q and N_s, we now consider an electrolyte of infinite extent for which the intensive properties E and n_s will fluctuate about the mean values of 0 and $\overline{n_s}$, respectively. We might expect that the relationships of Eqs. (2.7) and (2.8) would apply if we choose for the characteristic volume V the appropriate microscopic volume within which these fluctuating quantities would be correlated. Unlike the extensive volume V, these microscopic volumes depend upon intensive properties. For electric charge fluctuations, the characteristic volume would be κ^{-3} so that

$$\langle(\Delta E)^2\rangle\sim\frac{k_BT\kappa^3}{\epsilon} \tag{3.1}$$

while the appropriate volume for solute fluctuations would be the volume per solute molecule, $(\overline{n_s})^{-1}$,

$$\langle(\Delta n_s)^2\rangle\sim\overline{n_s}/(\overline{n_s})^{-1}\sim\overline{n_s^2}. \tag{3.2}$$

The exact proportionalities of Eqs. (3.1) and (3.2) need to be determined from thermodynamical or statistical mechanical arguments.

Before proceeding, we recognize that the fluctuations of the electric field and solute concentration will be correlated in both space and time. Denoting the normalized spectral density of these fluctuations in wave number (magnitude k) and frequency space by $\mathcal{S}_E\{k,\omega\}$, we may expect the form of Eq. (3.1), for example, to be

$$\langle(\Delta E)^2\rangle=\langle(\Delta E)^2\rangle_{\rm th}\int_0^\infty\int_0^\infty\mathcal{S}_E\{k,\omega\}dkd\omega, \tag{3.3}$$

where $\langle(\Delta E)^2\rangle_{\rm th}$ is the exact value of $\langle(\Delta E)^2\rangle$ determined from thermodynamic considerations, which we expect to be of order $k_BT\kappa^3/\epsilon$, and the double integral has the value of unity. If the double integral is first integrated on ω, the resulting integrand is a function of k denoted by $\mathcal{K}_E\{k\}$:

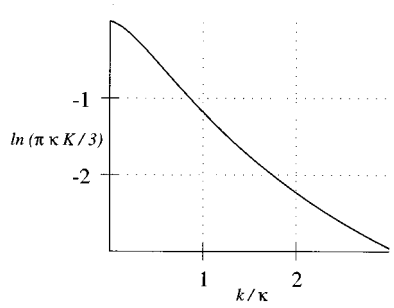

FIG. 2. A plot of the normalized wave number spectrum $\mathcal{K}_E\{k\}$ of the electric field as a function of k/κ.

$$\int_0^\infty \int_0^\infty \mathcal{S}_E\{k,\omega\}dk\,d\omega \equiv \int_0^\infty \mathcal{K}_E\{k\}dk. \tag{3.4}$$

Because the integration on ω is equivalent to ensemble averaging, the normalized wave number spectral density $\mathcal{K}_E\{k\}$ is a themodynamic quantity and not dependent upon any dissipative property of the electrolyte.

We begin first with the fluctuations of the electric field. We adopt the technique of Chandler and Anderson [7], who determined the electrical component of the free energy per unit volume a of an electrolyte as a rapidly converging series of terms corresponding to cluster integrals. For the particular case of zero hard core ion radius, and employing only the first term of the series, the absolute value of a is $k_B T\kappa^3/12\pi$. Setting this equal to the electric field energy per unit volume, $\epsilon\langle(\Delta E)^2\rangle/2$, we have

$$\langle(\Delta E)^2\rangle = \frac{k_B T\kappa^3}{6\pi\epsilon}\int_0^\infty \mathcal{K}_E\{k\}dk, \tag{3.5}$$

$$\mathcal{K}_E\{k\} = (3/\pi\kappa)\left(1-\frac{k^2}{\kappa^2}\ln\left[1+\frac{\kappa^2}{k^2}\right]\right). \tag{3.6}$$

The wave number spectrum $\mathcal{K}_E\{k\}$ of Chandler and Anderson, Eq. (3.6), is plotted in Fig. 2. Note that most of the energy is contained within the small wave number region of the spectrum, $k \ll \kappa$. This is in contrast to the spectrum of Oosawa [4], for which $\mathcal{K}_E \propto k^2/\kappa^2$ for small wave number, compared with $\mathcal{K}_E \propto 1-k^2/\kappa^2$ in Eq. (3.6) and Fig. 2.

The spatial correlation function of the electric field may be found from the transform of $\mathcal{K}_E\{k\}$. To simplify this calculation, we approximate the wave number spectrum of Fig. 2 by a simple exponential:

$$\mathcal{K}_E\{k\} \simeq (3/\pi\kappa)\exp(-(3/\pi)[k/\kappa]) \tag{3.7}$$

that differs very little from Eq. (3.6) (see Fig. 2). The corresponding normalized spatial correlation function is

$$\mathcal{C}_E\{r'\} \simeq \frac{1}{1+(\pi\kappa r'/3)^2}. \tag{3.8}$$

This geometric decline of $\mathcal{C}_E$ with $\kappa r'$ is slower than the exponential decline of Oosawa [4].

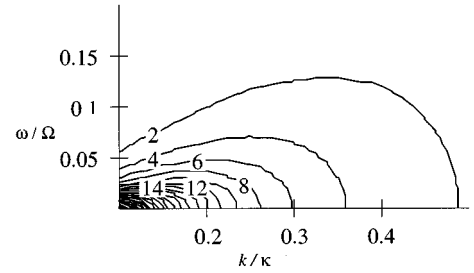

FIG. 3. Contours of the normalized wave-number–frequency spectrum $(\pi\kappa\Omega/3)\,\mathcal{S}_E\{\omega,\kappa\}$ as a function of the reduced frequency ω/Ω and wave number k/κ for $\alpha^2 \ll 1$.

The Langevin equation for the fluctuating variables E and n_s may be derived by applying the conservation equations for electric and solute charge:

$$\nabla\cdot\mathbf{j} + \frac{\partial(\epsilon\nabla\cdot\mathbf{E})}{\partial t} = 0,$$

$$\nabla\cdot\mathbf{j}_s + \frac{\partial(2Zen_s)}{\partial t} = 0,$$

to the transport equations (2.13) and (2.14). The resulting Langevin equation has the form of Eq. (2.29) with $\eta \equiv k^2/\kappa^2$. The normalized wave-number–frequency spectrum $\mathcal{S}_E\{k,\omega\}$ of Eq. (3.3) becomes [see Eq. (2.30)]

$$\mathcal{S}_E\{k,\omega\} = \mathcal{K}_E\{k\}\left(\frac{(2/\pi)(k^2/\kappa^2)[1+(k^2/\kappa^2)](1-\alpha^2)\Omega^3}{(\omega^2+\omega_1^2)(\omega^2+\omega_2^2)}\right), \tag{3.9}$$

where

$$\omega_1 = \frac{\Omega}{2}\{[1+(k^2/\kappa^2)] + \sqrt{[1-(k^2/\kappa^2)]^2+4\alpha^2(k^2/\kappa^2)}\},$$

$$\omega_2 = \frac{\Omega}{2}\{[1+(k^2/\kappa^2)] - \sqrt{[1-(k^2/\kappa^2)]^2+4\alpha^2(k^2/\kappa^2)}\}. \tag{3.10}$$

Contours of the wave-number–frequency spectrum $\mathcal{S}_E\{k,\omega\}$ are plotted in Fig. 3 for the case of weak coupling, $\alpha^2 \ll 1$; i.e., nearly equal ion mobilities. The spectral intensity is greatest for small values of ω/Ω and k/κ.

For the case of $\alpha^2 \ll 1$, we may determine the time correlation function $\mathcal{C}_E\{t'\}$ by noting that $\omega_1 = \Omega$ and $\omega_2 = (k/\kappa)^2\Omega$ and that as a consequence of Eq. (2.31) the time transform of $\mathcal{S}_E\{k,\omega\}$ is

$$\int_0^\infty \mathcal{S}_E\{k,\omega\}\cos\omega t'\,d\omega \simeq (3/\pi\kappa)\exp[-(3/\pi)(k/\kappa)] \times \exp[-(k/\kappa)^2\Omega t'], \tag{3.11}$$

where we have used the approximation of Eq. (3.7). Integrating on the wave number k we find the time correlation

$$\mathcal{C}_E\{t'\} \simeq \int_0^\infty \int_0^\infty \mathcal{S}_E\{k,\omega\} \cos\,\omega t' d\omega dk$$

$$\simeq \frac{3}{2\sqrt{\pi\Omega t'}} \exp\left(\left[\frac{3}{2\pi\sqrt{\Omega t'}} \right]^2 \right) \operatorname{erfc}\left(\frac{3}{2\pi\sqrt{\Omega t'}} \right) \tag{3.12}$$

$$\simeq 1-(2\pi^2/9)\Omega t' \text{ if } \Omega t' \ll 1$$

$$\simeq \frac{3}{2\sqrt{\pi\Omega t'}} \text{ if } \Omega t' \gg 1. \tag{3.13}$$

Note that the time correlation function of the electric field decays algebraically as $(t')^{-1/2}$ rather than exponentially, as does the spatial correlation function [Eq. (3.8)].

The mean square fluctuation of the solute density, $\langle (\Delta n_s)^2 \rangle$, is determined by evaluating the contributions to the change in free energy density a from perturbations to the number density n_i of ions in the ion configuration space. We assume a small perturbation $\xi = \Delta n_i / n_i$ that will be expanded as a Fourier series in configuration space. Considering the solute ions as a perfect solution [8], the free energy per unit volume is increased by the perturbation

$$a\{\xi\} = n_i(1+\xi)k_BT[\ln n_i(1+\xi) - f\{T\}] = a\{0\} + n_i k_B T \xi^2 \tag{3.14}$$

since the mean value of ξ is zero.

In expanding the perturbation in a Fourier series in configuration space, we must limit the maximum wave number k_m to a value such that $n_i k_m^3 \gg 1$, so as to ensure that the occupation number of a cell of volume k_m^{-3} is large, as required by the Boltzmann statistics we use for the perfect solution. We shall call this volume ℓ^3, and note that it is necessarily much larger than the volume per solute molecule. Excluding a volume ℓ^3 from the configuration space of each molecule makes an additive contribution to the free energy density of a perfect system of $n^2 k_B T \ell^3$, as in the case of a perfect gas where ℓ^3 would be the second virial coefficient [8]. For our ionic solution, the increment in free energy density is therefore

$$\Delta a = n_i^2 k_B T \ell^3 \xi^2. \tag{3.15}$$

Comparing with Eq. (2.4), we can solve for the mean value of ξ^2:

$$\langle \xi^2 \rangle = 1/n_s \ell^3,$$

$$\langle (\Delta n_s)^2 \rangle = n_s/\ell^3, \tag{3.16}$$

where we have used $n_i = 2n_s$. The condition that $n_s \ell^3 \gg 1$ ensures that $\xi \ll 1$.

We now construct a simple wave number spectrum $\mathcal{K}_s\{k\}$ of $\langle (\Delta n_s)^2 \rangle$ by requiring that $\mathcal{K}_s$ be proportional to k^2 for $k\ell \ll 1$ so that each mode contributes equally to the spectral energy density, but that $\mathcal{K}_s\{k\} \to 0$ rapidly for $k\ell \gg 1$. A suitable normalized spectrum would be

$$\mathcal{K}_s\{k\} = (4\ell^3/\sqrt{\pi}) k^2 \exp(-k^2\ell^2) \tag{3.17}$$

from which we obtain the normalized spatial correlation function $\mathcal{C}_s\{r'\}$ from the transform of $\mathcal{K}_s\{k\}$:

$$\mathcal{C}_s\{r'\} = [1-2(r')^2/\ell^2] \exp(-[r']^2/4\ell^2). \tag{3.18}$$

Repeating the steps that led to Eq. (3.12), we find the time correlation function for the solute density fluctuations:

$$\mathcal{C}_s\{t'\} = \left(1 + \frac{\Omega t'}{\kappa^2 \ell^2} \right)^{-3/2}. \tag{3.19}$$

Like the correlation function of the electric field [Eq. (3.13)], $\mathcal{C}_s\{t'\}$ decays algebraically, as $(t')^{-3/2}$.

IV. ELECTRICAL PROPERTIES OF THE CYTOPLASM AND CELL MEMBRANE

Two electrical properties that affect the fluctuations in electric field and solute density of a cell are the electrical conductivity σ and the electric permittivity ϵ (or the relative permittivity $\epsilon_{\rm rel} \equiv \epsilon/\epsilon_0$, where ϵ_0 is the vacuum permittivity). A summary of the empirical values of σ and $\epsilon_{\rm rel}$ measured in bulk samples of muscle, lung, liver, fat, bone, and whole blood, as a function of frequency $f \equiv \omega/2\pi$ over the range 10 Hz $\leqslant f \leqslant$ 10 MHz, is given by Foster and Schwan [10].

For all of these samples, the electrical conductivity varies only slightly with f, having values between $\sim 10^{-2}$ S/m for bone and 0.7 S/m for blood. The blood conductivity is about the same as that of an electrolyte having a $K^+ + Na^+$ ion density of 100 μmol/l, a typical value for cytoplasm and extracellular fluid. Lower values for other samples reflect their more complex structure but indicate that the origin of the conductivity is the presence of an electrolyte suffusing the sample. The insensitivity to frequency in the measured range also indicates the electrolytic nature of the conduction process.

On the other hand, the relative permittivity $\epsilon_{\rm rel}$ shows a marked dependency upon f, declining from $\sim 10^7$ at 10 Hz to $\sim 10^3 - 10^4$ at 10 MHz, but remaining unchanging at higher frequencies in some cases. These large values of $\epsilon_{\rm rel}$ at low frequencies are the result of heterogeneities in the tissue structure and the presence of cell membranes of very high electrical resistance, giving rise to a dielectric loss (called the Maxwell Wagner loss) in bulk tissue samples [11]. On the scale of a single cell, however, the electric permittivity and conductivity are independent of frequency, over the range of frequency of consequence to the evaluation of the correlation function.

Measurement of some eukaryotic cell membrane properties listed by Pethig [11] gives a median membrane capacitance of $C/A = 1\ \mu$F/cm^2 and resistance of $RA = 1.2 \times 10^3\ \Omega$ cm^2. Their product, RC, is the time constant $\epsilon_m/\sigma_m = 1.2 \times 10^{-3}$ s. (This value is comparable to the response time of the cell potential to large disturbances, as in an action potential [5].) The relative permittivity of a membrane should be about the same as that of protein, its principal constituent, or $(\epsilon_{\rm rel})_m = 2.7$ [11]. The corresponding values of membrane permittivity and conductivity are thus $\epsilon_m = 2.4 \times 10^{-11}$ F/m and $\sigma_m = 2 \times 10^{-8}$ S/m, and the membrane thickness $h = \epsilon_m A/C = 2.4$ nm.

For the cell cytoplasm, we will use a blood conductivity

TABLE II. RMS electric field values.

	$(k_BT/\epsilon V)^{1/2}$ (V/m)	$(k_bT\kappa^3/6\pi\epsilon)^{1/2}$ (V/m)	$(k_bT\kappa^3/6\pi\epsilon)^{1/2}(3/\pi\kappa V^{1/3})$ (V/m)
Cytoplasm	1.1×10^2	1.8×10^7	2.2×10^3
Membrane	1.6×10^4	4.0×10^7	7.6×10^4

of $\sigma_c=1.1$ S/m. Even though the cytoplasm structure is not homogeneous, the low proportion of low $\epsilon_{\rm rel}$ protein justifies the use of a relative permittivity of water $\epsilon_{\rm rel}=78$ for the cytoplasm, or $\epsilon_c=6.9\times10^{-10}$ F/m. The corresponding time constant is $\epsilon_c/\sigma_c=6.3\times10^{-10}$ s, much smaller than that for the membrane.

A typical solute density in the cytoplasm is $n_s=100$ mol/m^3. At a temperature of 310 K the corresponding cytoplasm Debye length is $\kappa_c^{-1}=1.0$ nm, which is much less than a typical cell diameter d of 10 μm. Assuming that the conduction channels of the membrane constitute 1% of the membrane area, as they do in gap junctions [12], the average membrane ion density is about $n_s=1$ mol/m^3 and the membrane Debye length is $\kappa_m^{-1}=1.8$ nm, comparable to the membrane thickness.

If we assume that the cell is a sphere of diameter 10 μm, then the cell volume $V_c=5.2\times10^{-16}$ m^2 and the membrane area $A=3.1\times10^{-10}$ m^2.

These typical values of cell properties are summarized in Table I, together with the characteristic frequency Ω and the parameter η of Eqs. (2.25) and (2.26). The constraint that applies to Eqs. (2.33)–(2.36) is amply satisfied by the value of η listed in Table I.

In Table II we list several values of the RMS electric field for the membrane and cytoplasm. In the first column, we use the value for a capacitor of volume V, Eq. (2.7), applied to both cytoplasm and membrane. In the second column, the electrolyte value of Eq. (3.5) is used. In the third column, we calculate the RMS value of the electric field correlation function evaluated for the distance $r'=V^{1/3}$, the maximum dimension of the cytoplasm or the membrane, as determined by Eq. (3.8).

Considering the cytoplasm or membrane as a uniform electrolyte, the value of $\langle(\Delta n_s)^2\rangle$ depends upon the choice of the length scale ℓ needed to ensure the applicability of Boltzmann's statistics. If we choose $n_s\ell^3=10$, then $\sqrt{\langle(\Delta n_s)^2\rangle}=n_s/10$ for both cytoplasm and membrane. This is much greater than the classical value of $\sqrt{n_s/V}$ for fluctuations averaged over the entire volume V, as given in Eq. (2.8). The characteristic frequency $\Omega/(\kappa\ell)^2$ for the time correlation function of Eq. (3.19) is calculated to be 1.54×10^{-3} Ω and 2.36×10^{-4} Ω for the cytoplasm and membrane, respectively.

V. DISCUSSION

The capacitor-resistor model of the cell membrane is widely used and the RMS electric field of Eq. (2.7), estimated as 1.6×10^4 V/m in Table II, is securely based. What is different about the analysis of Sec. II is the incorporation of the solute fluctuations in the cytoplasm due to the movement of ion pairs across the membrane, which affects the frequency spectrum of the electric field but not its RMS value. This solute motion is much slower than the exchange of charge since the anions are less mobile than the cations within the membrane. The ions respond both to the electric field and the chemical potential difference across the membrane. The resulting electric field frequency spectrum and time correlation function, Eqs. (2.35) and (2.36), are dominated by this slower process, having a characteristic frequency of the order of $\eta\Omega_m\sim1$ s^{-1}.

Other treatments of the frequency spectrum, such as that by Procopio and Fornes [3], assume zero anion mobility, and find a spectrum characterized by the frequency Ω_m, as in Eq. (2.27). While this may be a physiologically interesting portion of the spectrum, there is little energy content in this region as long as the anion mobility is nonzero.

The model of Sec. II assumes that the electric potential and solute density are uniform within the cytoplasm and in the extracellular environment, differences in these quantities occurring only across the membrane. For uniformity of n_s in the cytoplasm, it is necessary that the time for ion pairs to diffuse throughout the cytoplasm, $V_c^{2/3}/\mathcal{D}$ (where $\mathcal{D}=\Omega_c/\kappa_c^2$ is the solute diffusivity), is much shorter than the characteristic time $(\eta\Omega_m)^{-1}$. Employing the values of Table I, the dimensionless time ratio, $\eta(\Omega_m/\Omega_c)\kappa_c^2V_c^{2/3}=3\times10^{-2}$, satisfies this condition.

The membrane electric field and the cytoplasm solute fluctuations each possess a time-averaged free energy of $k_BT/2$. The RMS solute concentration fluctuations, $\sqrt{\langle(\Delta n_s)^2\rangle}/\overline{n_s}=1/\sqrt{\overline{n_s}V_c}$, calculated from the values of Table I, is 2.3×10^{-7}. The ratio of the membrane RMS electric field to that of the resting potential of ~100 mV/h is 4×10^{-4}. Thus the fluctuating quantities are small compared to their equilibrium state values.

In the uniform electrolyte of the cytoplasm, the RMS electric field of Eq. (3.5) has the estimated value of 1.8×10^7 V/m (see Table II), much greater than the value for the membrane, but comparable to the resting electric field in the membrane. The average electric field energy is $k_BT/2$ in each volume $3\pi\kappa^{-3}$ of the cytoplasm. If this energy were spread over the entire volume of the cytoplasm, the RMS field would be considerably less (see column one of Table II). But the surprising result is that the RMS value of the spatial correlation function of the cytoplasm electric field for a separation distance $V_c^{1/3}$, the dimension of the cytoplasm, is estimated in Table II to be 2.2×10^3 V/m. Thus there is substantial correlation of the electric field fluctuations throughout the cytoplasm, a testimony to the effect of the long range Coulomb forces acting on the ions.

We have noted that the correlation function of the electric field, as derived by Oosawa [4], decays exponentially as $\exp\{-\kappa r'\}$, in contrast to the algebraic decay of Eq. (3.8). This difference stems from the form of the wave number

spectrum $\mathcal{K}_e\{k\}$, which in Sec. III is a declining function of k/κ (see Fig. 2) as given by Chandler and Anderson [7], rather than the increasing function assumed by Oosawa. In the latter case, this leads to an infinite value for $\langle E^2 \rangle$.

Assuming comparable ion mobilities in the cytoplasm electrolyte, the frequency spectrum and time correlation function of the electric field are characterized by the frequency $\Omega_c \sim 1 \times 10^9 \text{ s}^{-1}$.

The solute density fluctuations are substantial within a volume ℓ^3, which we assume to be an order of magnitude larger than the volume per solute molecule. But these fluctuations are essentially uncorrelated over larger distances because the solute density correlation function decays exponentially. The time correlation function of these solute density fluctuations, which decays algebraically, is characterized by the frequency $\Omega_c / \kappa_c^2 \ell^2 = 5.3 \times 10^7 \text{ s}^{-1}$.

The relations discussed above and treated in earlier sections of this assume that the cytoplasm and membrane have uniform, isotropic properties (σ, ϵ, κ, etc.). While this is clearly not the case for the membrane, it is reasonably so for the cytoplasm. Nevertheless, for the guidance of the reader, we have listed the uniform-property values of the electric field for both membrane and cytoplasm in Table II, for the two models of capacitor-resistor and uniform electrolyte, even where they perhaps do not apply reliably.

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