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Gauging the Strength of Power Frequency Fields Against Membrane Electrical Noise

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The possible physiological effect of power frequency fields (60 Hz in the US, 50 Hz in most other countries) is still a hotly debated issue. These relatively slow fields distribute themselves across cell membranes and a common approach has been to compare the strength of these fields to the strength of the electric noise that the membrane generates itself through Brownian motion. However, there has been disagreement among researchers on how to evaluate the membrane electric noise. In the first part of this article three major models are discussed. In the second part an ab initio modeling of membrane electric fields finds that different manifestations of Brownian noise lead to an electric noise intensity that is many times larger than what conventional estimates have yielded. Finally, the legitimacy of gauging a nonequilibrium external signal against internal equilibrium noise is questioned. Bioelectromagnetics 26:595–609, 2005.

Key words: noise; transmembrane voltage fluctuations; ELF; Weaver–Astumian model; Kaune model

INTRODUCTION

Power frequency sources (60 Hz in the US, 50 Hz in the rest of the world) of electromagnetic (EM) radiation are ubiquitous in modern industrial society. Household appliances like electric razors and electric blankets can expose the consumer to an electric field of about 500 V/m. Such fields are fairly insignificant. There is, for instance, already a stationary field of about 100 V/m between the earth's surface and the sky. But high voltage power lines can carry up to about 500 000 V. Right near a power line the field can be as strong as 12 kV/m. In the close vicinity of a high voltage distribution station fields of 16 kV/m may be present. Much public anxiety has focused on high voltage power lines.

The frequency range between 30 and 300 Hz is known as the extremely low frequency (ELF) regime. The photons associated with the ELF regime, unlike ultraviolet light, do not have enough energy to ionize or otherwise disrupt biomolecules. Commonly present ELF fields, furthermore, do not carry enough energy to cause heating. EM radiation can only be directed if the emitting equipment has dimensions that are comparable to the wavelength of the signal. Power frequency radiation has wavelengths of many thousands of miles. So Coulomb's Law, which is valid for a stationary field, can also be applied to evaluate the field strength in the vicinity of power frequency sources. The human body has a higher conductivity than the surrounding air. Electric fields are therefore compensated by internal charge movement and turn out much smaller inside the body than outside. This effect is stronger at lower frequencies. In the ELF regime, the attenuation is 7 to 8 orders of magnitude [Foster and Schwan, 1989; Adair, 1991]. The liquid inside and outside of the cells that make up the human body is very much like salt water. It has many dissolved ions and these ions can flow towards the membrane and compensate for an external field within microseconds. At microwave frequencies (i.e., GHz), the water molecules inside and outside of a cell are rapidly oscillated and can heat up tissue. But at power frequencies, all of the imposed field gets effectively distributed across the cell membranes. For the identification of a possible physiological ELF effect, the focus has therefore been on what may happen when, on top of the normal transmembrane potential of a living cell, there is a small low frequency modulation. Such a modulation may affect the catalytic action of membrane proteins.

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Epidemiological studies on the effect of prolonged ELF exposure have been largely inconclusive [NIEHS, 1999; IARC, 2002]. Many studies have been conducted, but, so far, the occurrence of most ailments appears to not be demonstrably correlated to prolonged ELF exposure. Much public attention has centered on a possibly increased risk of childhood leukemia. Wertheimer and Leeper [1979] reported such increased risk. But the magnitude of the alleged ELF effect was close to the margin of error of the study. In the subsequent quarter century many thorough studies have been conducted without the issue becoming decisively settled. The inconclusiveness of long-term epidemiological studies is in large part due to the big margin of error, which, in turn, is due to the fact that it is hard to assess the subjects' long-term exposure to ELF as well as the subjects' long-term exposure to other cancer causing factors. The involved ailments, moreover, are rare and large sample populations are required to get to statistically significant results.

There has also been a fair amount of confusion in the discussion of a biophysical mechanism that could possibly account for an ELF effect. Weaver and Astumian [1990] claimed in a 1990 *Science* paper that the Brownian motion of charges in and around the cell membrane creates a thermal noiseband that far exceeds the magnitude of the modulation by an external power frequency field. They argued that no physiological effect can occur if there is no way for a membrane to even ''feel'' the ELF modulation. Kaune [2002] presented a different model for the thermal noise in a cell membrane. In the ELF regime his noiseband vanished and thus allowed for the ''detection'' of typical power frequency fields by the cell membrane. Very recently, however, Vincze et al. [2005] suggested revisions to Kaune's model. With these revisions the thermal noise power becomes larger and effectively white, that is, noise strength is independent of frequency. In the model of Vincze et al. [2005], ELF fields would once again be drowned out by thermal noise.

In the next section of this article it will be pointed out what the different assumptions are on which the three competing models are based. In a subsequent section, we will attempt to develop a correct picture of membrane electricity by going through an ab initio modeling. In a final Discussion section, the legitimacy of comparing nonequilibrium, externally imposed noise to internal equilibrium noise is questioned.

WEAVER–ASTUMIAN VERSUS KAUNE VERSUS VINCZE–SZASZ–SZASZ

When a small particle or large molecule is immersed in a fluid, the random collisions with molecules from the medium cause Brownian motion. Brownian motion is responsible for diffusion. Diffusion is described by $\langle x^2(t)\rangle = 2Dt$, where x is the displacement from the $t=0$ position. $\langle x^2(t)\rangle$ represent the average square of the displacement. When a force F is pulling the small particle through the fluid with a speed v, the same random collisions that cause diffusion are responsible for the friction β in $F=\beta v$. Diffusion and friction are thus connected. Quantitatively the connection is expressed by Einstein's fluctuation-dissipation theorem, that is $D=kT/\beta$. Here k represents the Boltzmann constant and T is the absolute temperature; kT is roughly the average energy present in the Brownian motion of one particle.

In an electrical resistor it is again random collisions that cause the resistance that a flowing electron ''feels.'' As in the hydrodynamic case, these random collisions also cause random fluctuations between the two ends of a resistor [Feynman et al., 1966]. On a timescale larger than the average time between collisions, the amount of charge that accumulates in the infinite reservoir A in Figure 1 is given by $\langle q^2(t)\rangle = 2(kT/R)t$. Obviously the resistance R is playing the role that the friction β plays in fluid dynamics.

More well known than the above formula for $\langle q^2(t)\rangle$ is the related formula for the average of the

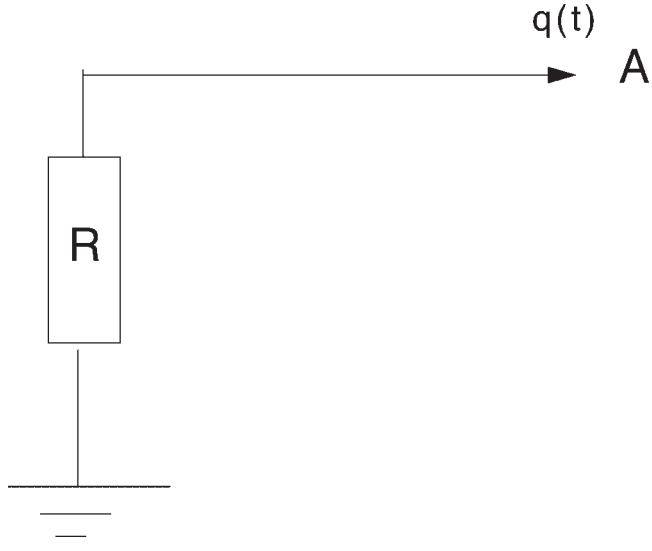

Fig. 1. A resistor is connected to the ground and to another infinite reservoir A. The net voltage between the reservoirs remains zero. Due to Brownian motion of electrons in the conduction band there is a zero average fluctuating current through the resistor. The net charge accumulating in the reservoir is the result of these fluctuations in the same way that diffusive displacement is the result of random Brownian kicks. We have $\langle q^2(t)\rangle = 2(kT/R)t$ for the average square charge accumulation in time t.

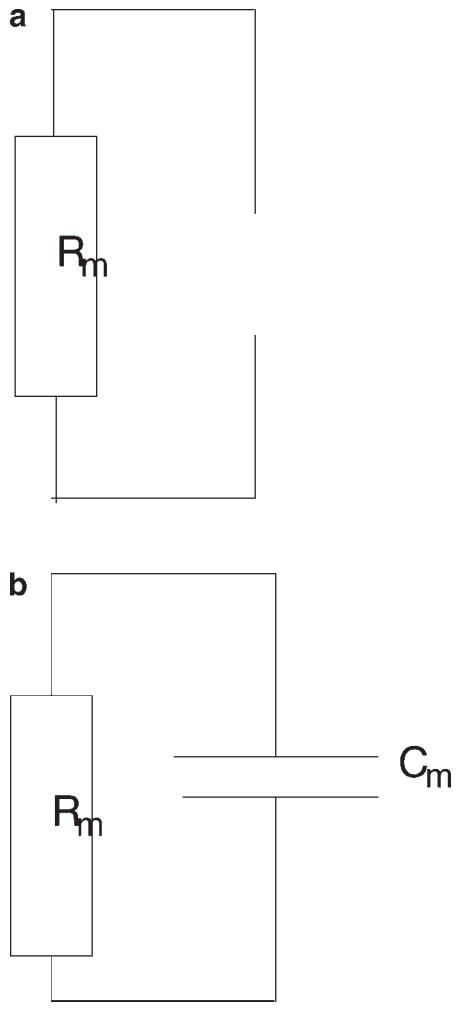

Fig. 2. **a**: Between the two ends of a linear resistor there is a zero average fluctuating noise voltage ξ. The noise spectrum is white. Within a frequency band Δf we have $\langle \xi^2 \rangle = 4kTR\Delta f$. **b**: When capacitor plates are present it is at high frequency that V_m, the voltage across the capacitor, cannot keep up with the voltage ξ coming from the resistor. The cutoff occurs at $1/\tau_m$, where τ_m is the characteristic time of the circuit $\tau_m = R_m C_m$.

square of the voltage ξ across a resistance R, cf. Figure 2a, in a frequency window Δf:

$$\langle \xi^2 \rangle = 4kTR(\Delta f). \tag{1}$$

The noise spectrum of "fluctuation-dissipation noise" is white when you consider time scales larger than the average time between collisions. This means that each frequency in the spectrum contributes with an equal amplitude. So the frequency itself does not figure in Equation 1. Equation 1 was first derived by Nyquist [Nyquist, 1928; Feynman et al., 1966] to explain noise that had been observed by Johnson [Johnson, 1928].

Now consider Figure 2b and go to Fourier space. In Fourier space there is a harmonic oscillation at each frequency ω. The resistor generates noise with a flat spectrum. For large frequencies, the oscillation is too fast for the charge on the capacitor to keep up. At high ω the oscillating voltage V_m across the capacitor will therefore be smaller than the oscillating voltage ξ across the resistor. There will, furthermore, be a phase lag, that is, the voltage across the capacitor will follow the resistor voltage with some delay. We have

$$V_m = \frac{\xi}{1 + i\omega\tau_m}. \tag{2}$$

Here $\tau_m = R_m C_m$ represents the characteristic time of the RC circuit. We have used the subscripts "m" because the RC circuit of Figure 2b is indeed how the cell membrane is generally modeled (cf. Fig. 3).

In a first analysis it makes sense to look at the basic equilibrium behavior of the membrane, that is, the behavior that the membrane would exhibit if it separated two identical solutions. The equilibrium fluctuations constitute an omnipresent noiseband. Nonequilibrium noises from opening and closing ion channels and from operating ion pumps only add to the basic thermal noise. We will discuss such nonequilibrium contributions in

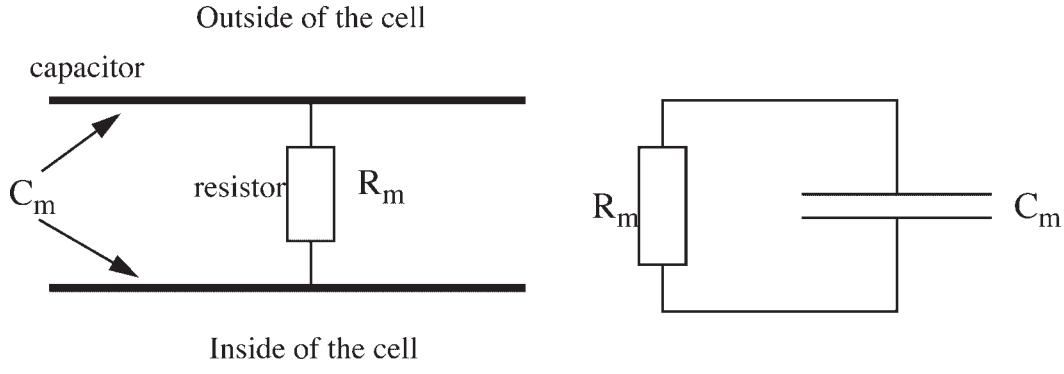

Fig. 3. The standard way to model the membrane as an electrical circuit is shown on the left. R_m and C_m are the resistance and capacitance between the inside and outside of the cell. The resistor also provides a thermal electromotive force. The equivalent circuit is shown on the right.

the Discussion section. Weaver and Astumian [1990] argue that what a membrane protein "feels" is the transmembrane potential V_m. They take the R_m of typical cells. They observe that in the ELF regime $\|i\omega\tau_m\|$ is much smaller than 1 and thus effectively negligible (cf. Eq. 2). They apply Equation 1 to calculate $\langle V_m^2 \rangle$. For the frequency bandwidth they take $\Delta f = 10$ Hz and $\Delta f = 100$ Hz. They thus find that the thermal noise generally exceeds the transmembrane effect of reasonable power frequency fields by several orders of magnitude.

Kaune proposes a revision of the Weaver–Astumian model [Kaune, 2002]. Kaune argues that the accumulated surface charge on the membrane is only part of the noise picture. Random Brownian motion of charges inside the membrane causes inhomogeneous charge distributions. These inhomogeneous charge distributions, in turn, cause fields. Ultimately it is these thermal intramembrane electric fields together with the, also thermally created, fluctuations in the transmembrane field that drive charge movement, that is, cause current. This net field is what the all important membrane proteins eventually "feel." The membrane is like a thin sheet (about 5 nm thick and 10^9 nm^2 in surface area for a cell with a 10 μm radius). There is a lot of variation in the intramembrane thermal electric field from one location to another on the membrane surface. It is therefore essential in the Kaune model that the membrane is modeled with a large number of parallel resistors (cf. Fig. 4) instead of the one R_m-resistor of Weaver and Astumian.

One resistor with a resistance R_m is equivalent to N parallel resistors that each have a resistance NR_m (cf. Fig. 4). This is obviously true for the net resistance. It is still somewhat of a nontrivial exercise to prove that the N parallel NR_m resistors in Figure 4 generate the same noise across the capacitor as one R_m resistor. At frequency ω each of the N resistors generates a harmonic oscillation with the same amplitude $\|\xi^0\|$. The phases, however, are random, that is, each oscillation comes with a factor $\exp[2\pi ip] = \cos 2\pi p + i \sin 2\pi p$, where p is a random number between 0 and 1. Adding oscillations with the same amplitude but different phases is like adding 2-dimensional vectors with equal norm and different directions. In Appendix 1 it is shown that, for large N, adding N randomly phased 2D-vectors with the same norm $\|\xi^0\|$ leads to a vector of norm $\sqrt{N}\|\xi^0\|$. The eventual voltage generated by all parallel resistors together will be the average of all the voltages of the individual resistors. If we let $\|\xi_\mu\|$ be the amplitude of the ω-oscillation in the μ-th resistor, then we have for the amplitude of the net voltage

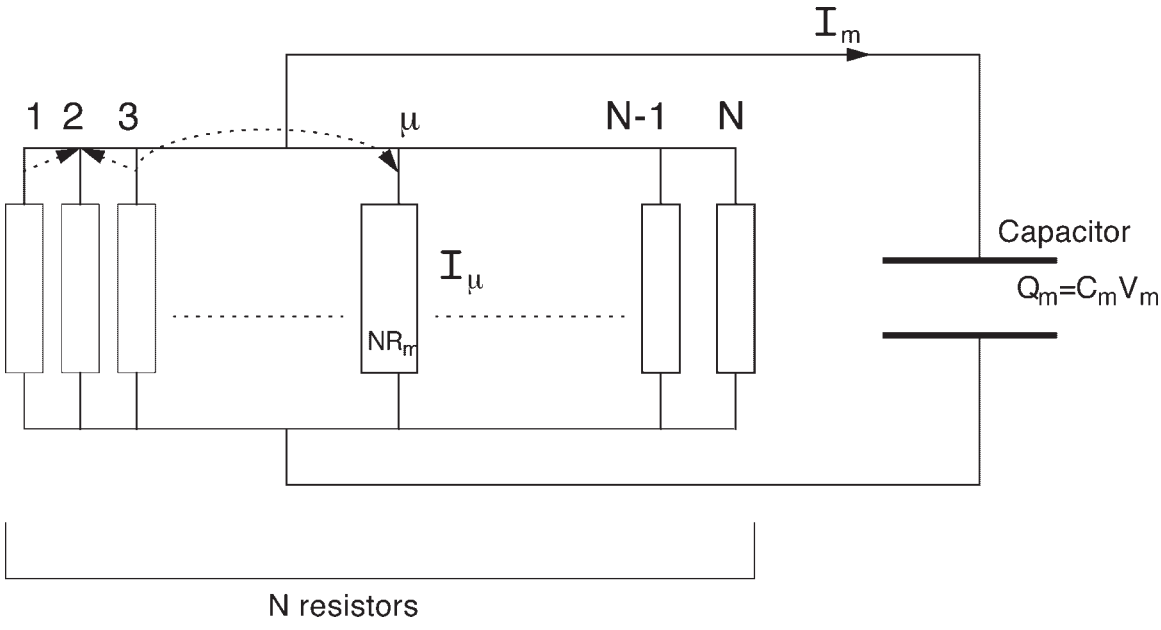

Fig. 4. The membrane of a living cell is best thought of as a film. Transmembrane currents can flow anywhere in the membrane, but lateral conductivity is very small. Rather than with the circuit in Figure 3 (with one R_m resistor), the membrane is therefore best modeled with N parallel resistors that each have a resistance NR_m. Going from one resistor to N parallel resistors does not affect the transmembrane noise strength in the Weaver–Astumian model [Weaver and Astumian, 1990]. But the handling of the N parallel resistors is of crucial importance in the models of Kaune [2002] and Vincze et al. [2005].

that eventually "powers" the oscillation across the capacitor: $\|\xi_m\| = (1/N)\|\sum_{\mu=1}^{N} \xi_\mu\| = \|\xi^0\|/\sqrt{N}$. Each individual resistor has a resistance NR_m. From $\langle\|\xi^0\|^2\rangle = 8kT(NR_m)\,\Delta f$ (the factor 4 in Eq. 1 becomes 8 when we work with the amplitude instead of the average), we infer $\|\xi^0\| \propto \sqrt{N}$. This means that the eventual ξ_m that generates the oscillation across the capacitor is independent of N and only depends on the net resistance R_m. One is therefore free to conceive of the membrane as carved up into any number of identical parallel segments. Such a partition does not affect the generated V_m across the capacitor.

Focusing, once again, on one frequency ω in Fourier space, Kaune gives the following equation for the current I_μ through the μ-th resistor (cf. Fig. 4):

$$I_\mu = \frac{1}{NR_m}\left[\left\{\xi_\mu - \frac{1}{N}\sum_{\nu=1}^{N}\xi_\nu\right\} + \frac{i\omega\tau_m}{1+i\omega\tau_m}\left\{\frac{1}{N}\sum_{\nu=1}^{N}\xi_\nu\right\}\right]. \tag{3}$$

Here ξ_μ represents the amplitude of the ω-oscillation generated in the μ-th resistor. The ξ_μ and ξ_ν now include the random phase factors. To obtain the net voltage through the μ-th resistor one has to take the self generated voltage and subtract the voltage due to the other parallel resistors. The result has to be divided by NR_m to obtain the current. Each ξ_μ comes with its own random phase factor. It is actually because the resistors oscillate out of phase that they "force" current in and out of each other. The first term in curly brackets thus describes current between resistor μ and all the other resistors (dotted arrows in Fig. 4). Physically, this term describes the thermal currents inside the membrane, that is, the intramembrane noise. The second term describes the currents due to the capacitor. The $i\omega\tau_m$ in the numerator appears because the current to and from the capacitor is the time derivative of the charge on the capacitor (which is proportional to the capacitor voltage, $Q_m = C_m V_m$). The amplitude $\xi_m = \sum_{\nu=1}^{N}\xi_\nu/N$ of the net voltage generated by all resistors together has to be multiplied by $(1+i\omega\tau_m)^{-1}$ to obtain the voltage across the capacitor (cf. Eq. 2). The capacitor contribution is obviously the same for each of the N resistors.

Because of the random phase factors, applying the summation $\sum_{\mu=1}^{N}$ averages out all the intramembrane thermal noise currents. With $I_m = \sum_{\mu=1}^{N} I_\mu$ being the net transmembrane current, we have:

$$I_m R_m = \frac{i\omega\tau_m}{1+i\omega\tau_m}\xi_m. \tag{4}$$

Here $\xi_m = (1/N)\sum_{\mu=1}^{N}\xi_\mu$ is the amplitude of the net voltage generated by all of the N parallel resistors collectively. Equation 4 is what Kaune eventually goes with. He takes the left hand side of Equation 4 and then takes $E_m = (I_m R_m)/d_m$, where d_m represents the membrane thickness, as the net noise generated electric field in the membrane. For the power spectrum of the noise he ends up with $E_m^2 \propto \omega^2\tau_m^2/(1+\omega^2\tau_m^2)$. This is the result that one would have obtained using $N=1$ (cf. Fig. 4). Kaune assumes that the intramembrane noise involves an amount of power that is negligible in comparison to power associated with the I_m-current and he thus essentially comes back to the $N=1$ case.

We consider the setup in Figure 4 and focus on one frequency ω. The charge on the capacitor follows $Q(t) = Q_m \exp[i\omega t]$. For the voltage between the plates we have $V(t) = V_m \exp[i\omega t] = (1/C_m)Q_m \exp[i\omega t]$. For Weaver and Astumian, the ultimate field is $E_m = V_m/d_m$, where d_m is the width of the membrane. Kaune describes the field as associated with the net transmembrane current. The current is the time derivative of the charge. So $I(t) = \frac{dQ(t)}{dt} = i\omega Q_m \exp[i\omega t] = i\omega V_m C_m \exp[i\omega t]$. It is thus that Kaune gets an extra ω in the numerator. As was pointed out in the previous paragraph, this ω becomes an ω^2 in the power density.

For each frequency ω in Figures 3 and 4, the AC potential that generates the current is the net result of the white noise potential (cf. Eq. 1) and the voltage on the capacitor. Looking at the left side picture in Figure 3 it is easy to see that at low frequencies the charge and voltage can accumulate on the capacitor and push against the thermally generated voltage. At high frequency, that is, faster than $\tau_m = R_m C_m$, the capacitor has no time to charge up and voltage and current in the resistor will look as if the capacitor is not there at all. So where Weaver and Astumian end up with a maximal noise amplitude at low frequency and an asymptotic approach to zero at high frequency, Kaune ends up with the reverse result. Kaune's noise amplitude goes to zero when the frequency approaches zero and asymptotically reaches the white noise level at high frequency. Power frequencies are low and, if Kaune's picture is correct, commonly present power line field levels would not be drowned out by thermal noise.

It is clear from Figure 4 that if the ω-oscillations of the N resistors are all out of phase, they will force current to and from each other. Obviously, there will then be fluctuation-dissipation noise that will not be reflected in an effect on the net current I_m. Kaune is aware that the power involved in this intramembrane noise is hard to evaluate and that the aforementioned summation takes all this noise out of the picture. He eventually assumes that the power dissipation due to the intramembrane noise, that is, the incoherence, is negligible compared to the power dissipated by the current I_m that goes to and from the capacitor. In

dropping intramembrane currents from consideration, Kaune de facto assumes a model in which the N parallel resistors in Figure 4 exchange no currents. This would imply that the N resistors oscillate coherently. Kaune's coherence assumption is troubling. In the context of some of our previous calculations, ''coherence'' means that there are no random phase factors and that all N parallel resistors in Figure 4 oscillate in phase. The coherence assumption thus eliminates intramembrane noise. The math that we did with the random phase factors would no longer apply in this case and we would simply have $\xi_{\mathrm{m}} = \xi^0$, that is, the net potential generated by the parallel resistors equals the potential generated in each resistor individually. We saw before that the net potential ξ_{m} should be independent of N. Equation 1, however, dictates $\|\xi^0\| = \sqrt{N}\|\xi_{\mathrm{m}}\|$. It is impossible to carry through the coherence assumption without running into absurdities. There is no reason for separate resistors to oscillate coherently. The physics should dictate incoherence. The work by Vincze et al. [2005] was motivated by such considerations.

The *Bioelectromagnetics* paper of Vincze et al. [2005] shows a way to mathematically deal with incoherent noise. These authors present a matrix formalism that eventually leads them to an estimate of the noise power spectral density that includes the intramembrane noise. By taking into account the intramembrane thermal electromotive activity that Kaune leaves out, they derive a much bigger noiseband. Appendix 2 shows a shorter derivation of the main result of Vincze et al. [2005].

The main result of the analysis of Vincze et al. [2005] is the formula

$$\frac{1}{2}\sum_{\mu=1}^{N} N R_{\mathrm{m}} I_{\mu} I_{\mu}^{*} = 4\left\{N - \frac{1}{(1+\omega^2\tau_{\mathrm{m}}^2)}\right\} kT\Delta f. \quad (5)$$

This formula expresses how the total generated fluctuation-dissipation power in a bandwidth Δf in all resistors together ($\Pi_{\mathrm{tot}} = 4NkT\Delta f$) is distributed over the intramembrane noise ($\Pi_{I_\mu} = \frac{1}{2}\sum_{\mu=1}^{N} N R_{\mathrm{m}} I_{\mu} I_{\mu}^{*}$) and the $R_{\mathrm{m}}C_{\mathrm{m}}$-oscillation ($\Pi_{R_{\mathrm{m}}C_{\mathrm{m}}} = 4kT\Delta f/(1+\omega^2\tau_{\mathrm{m}}^2)$). With Kaune's ''coherent noise'' all parallel resistors in Figure 4 oscillate in phase with each other. With coherent noise, the resistors are not ''pushing'' any current into each other. Coherent noise therefore essentially boils down to taking the $N = 1$ case. For Kaune, the thermal electric storm is in the power that does not go toward the transmembrane field and is dissipated in the membrane. He thus comes to $\Pi_{I_\mu} \propto \omega^2\tau_{\mathrm{m}}^2/(1+\omega^2\tau_{\mathrm{m}}^2)$. It is obvious from Equation 5 that the ω-dependent $\Pi_{R_{\mathrm{m}}C_{\mathrm{m}}}$ becomes negligible relative to Π_{tot} and Π_{I_μ} if N takes on order 10^1 values or higher. In other words, for high N the intramembrane noise dominates and appears effectively white.

Adair [1991] has suggested partitioning a cell membrane into little $5 \times 5 \times 5$ nm units and taking each such cube as a separate resistor. This is a logical step, since the membrane is already 5 nm thick. For even the smallest cells such a partition implies an N of order 10^7. A large value of N leads to a noise spectrum that is essentially white (cf. Fig. 5). It can be easily intuited why this happens. Larger N means more resistors (N) with larger resistance (NR_m). Larger resistance means more thermal noise and more resistors also means more thermal noise. For large N, the power in the $R_{\mathrm{m}}C_{\mathrm{m}}$ oscillator (which is independent of N) becomes negligible in comparison to the power in the intramembrane noise. Kaune [2002], Adair [1991], and Vincze et al. [2005] point out that by picking the fundamental units too small one could end up with thermal noise that is sufficiently large to trigger action potentials. Such an absurdity puts an obvious upper limit on the estimate of N.

EQUILIBRIUM ELECTRIC NOISE ACROSS AND ON A MEMBRANE

In discussing mathematical intricacies, as we did in the previous section, it is easy to be led away from some of the basic underlying physics. The simple truth is that a lipid bilayer differs from an ordinary resistor in some important aspects. A traditional linear resistor has a conduction band that contains a large number of electrons. Thermal motion of such electrons causes the fluctuating currents and voltages discussed in the previous section. But transmembrane currents are carried by small ions (Na^+, K^+, Cl^-) from the electrolyte solution on either side. The membrane itself consists for the most part of a bilayer of phospholipid molecules and does not contain such ions. It is through Brownian motion that ions can occasionally pass from one side of this thin (about 5 nm) membrane to another. Such passages are almost instantaneous. A membrane that separates two reservoirs of electrolyte solution thus effectively acts as a resistor. Even though it is only two molecular layers thick, the lipid bilayer of a cell membrane sets up a very high activation barrier for the passage of the aforementioned small ions [Hille, 1992].

The electrical noise across a cell membrane is therefore a form of shot noise [Schottky, 1918], that is, delta function-like electrical pulses occurring at random times. Shot noise was first discovered and reported in the nonequilibrium context of saturated vacuum tubes. Recent progress in nanofabrication technology has revived the interest in shot noise, particularly since nanostructures and ''mesoscopic''

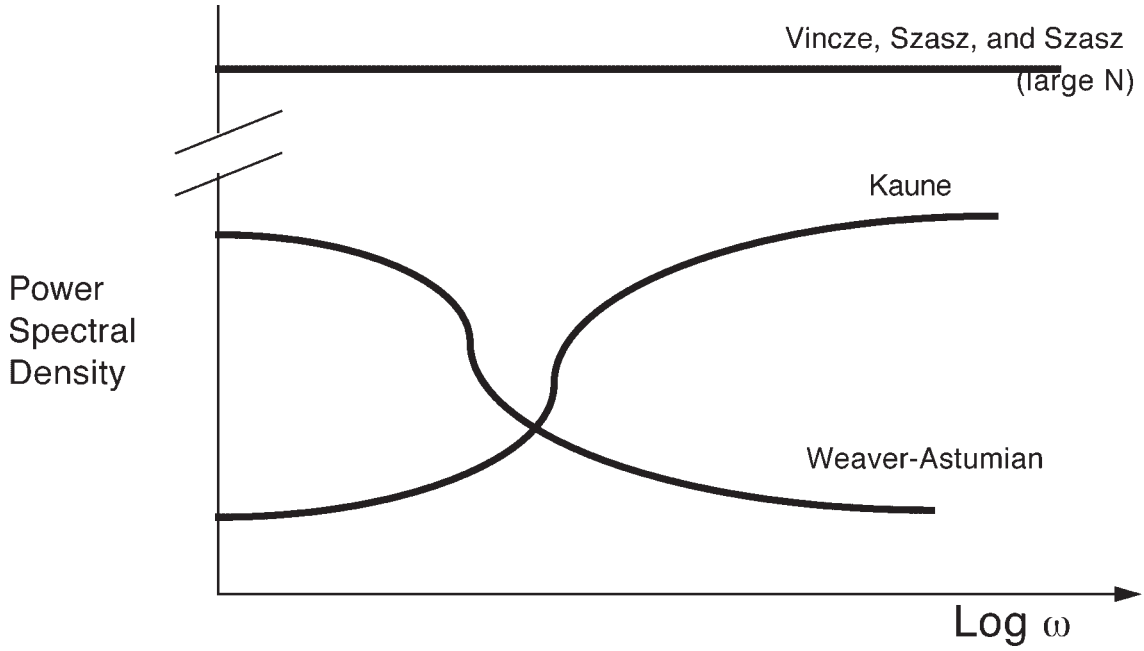

Fig. 5. The noise spectrum experienced by a membrane protein according to each of the three different models discussed in this section. Weaver and Astumian [1990] focus on the transmembrane voltage and find a downward sigmoid. Kaune [2002] focuses on the on the field associated with the transmembrane current and finds an upward sigmoid. Vincze et al. [2005] share Kaune's focus but work with a large number of incoherently operating resistors. For a large number of resistors they essentially end up with white noise far above the levels of Weaver–Astumian and Kaune. Fifty and 60 Hz fields operate at the left end of the graph. Working with Kaune's model, the power of common ELF fields is found to be comparable to that of the noise. In the other two models, the noise drowns out any realistic ELF fields.

resistors allow measurements on previously inaccessible scales [Sarpeshkar et al., 1993; Schoelkopf et al., 1997; Gomila et al., 2004]. Below I will first show that the equilibrium, 2-sided shot noise across a lipid bilayer eventually leads again to Equations 1 and 2.

The textbook by Stryer [1995] gives values for the lipid bilayer membrane permeabilities of the most common ions: $P_{Na} = 10^{-12}$ cm/s, $P_K = 5 \times 10^{-12}$ cm/s, and $P_{Cl} = 10^{-10}$ cm/s. In such listings the permeability is usually defined as the number of moles that cross a square centimeter of membrane in 1 s when the transmembrane concentration difference of the ion involved is 1M. Below we will not work in moles per liter, but simply use the particle density. The membrane permeability of a monovalent ion S involves both the diffusion coefficient D_s of the particular ion S inside the membrane and the width d_m of the membrane: $P_S = D_S/d_m$. The formula for the transmembrane particle current $j = P_S \Delta C$, where ΔC denotes the transmembrane concentration difference, is thus a form of Fick's Law [Moore, 1972].

In this section, we will ignore noise that is associated with the driven nonequilibrium transport through channels, transporters, and pumps. But even in an equilibrium situation, without driven transport, the presence of channels in a lipid bilayer can significantly increase the permeability. The validity of the approach shown below, however, is not affected by such a presence. When there are channels in the lipid bilayer membrane, we simply have to work with higher ion permeabilities than the ones listed in the previous paragraph.

It is through Nernst's Law, that is, $V_m = (kT/e)[\ln(C_1/C_2)]$ [Moore, 1972], that concentrations and permeabilities can be translated into voltages and electrical currents. In this formula, e represents one elementary charge and C_1 and C_2 are the concentrations on the two sides of the membrane. Eventually, we will be interested in equilibrium noise. Close to equilibrium means $C_1/C_2 \approx 1$. For small values of ε we have $\ln(1+\varepsilon) \approx \varepsilon$. With $C_1 \approx C_2 = C$ and $\Delta C = C_1 - C_2$ we get from Nernst's Law a proportionality between V_m and ΔC: $\Delta C = (Ce/kT)\, V_m$. If the particle current is $j = P_S \Delta C$, then the electrical current is $I = eP_S \Delta C$. Substitution of the expression for ΔC yields a form of Ohm's Law: $I = (eP_S C/kT)\, V_m$. So we find that a unit area of membrane has an electrical conductance of $g_m = \left(e^2 P_S C/kT\right)$ or, equivalently, a resistance of $R_m = \left(kT/e^2 P_S C\right)$.

With a concentration C for the ion S on each side of the membrane, we have a particle current per unit area of P_sC going both from side 1 to side 2 and from side 2 to side 1. The passage of ions (i.e., electrical current) through the membrane is a Poisson process [Feller, 1957; DeFelice, 1981]. In a small time interval, Δt, there is a probability $2P_S C\Delta t$ that a unit area of membrane will be permeated by an ion.

So $2P_S C$ is the average rate at which the ions pass through a unit area. These passages are pulse like. The process is similar to a sequence of coin tosses, where head versus tail corresponds to $1 \rightarrow 2$ passage versus $2 \rightarrow 1$ passage. There is a 50-50 distribution on average, leading to a net flow of $\langle j \rangle = 0$. But for a Poisson process, the variance σ^2 (the variance is the square of the standard deviation) equals the number of passages. We thus have after time T: $\sigma^2/T = 2P_S C$. When we look at time steps Δt that are significantly larger (about an order of magnitude or more) than the average time between two pulses, that is, $\Delta t \gg (2P_S C)^{-1}$ we face the cumulative effect of a number of Poisson pulses within Δt. The central limit theorem [Van Kampen, 1992] then becomes applicable. This theorem tells us that the number of ions that passes through the membrane during Δt will be almost Gaussian distributed with a zero average and a standard deviation of $\sqrt{2P_S C\Delta t}$. For the number of ions passing during the i-th timestep, we have $\Delta n(t_i) = \sqrt{2P_S C}\,\xi(t_i)\,\Delta t$. Here $\xi(t_i) = \theta_i/\sqrt{\Delta t}$, where θ_i are numbers drawn randomly from a zero average Gaussian distribution with a standard deviation of one. We see that $n(t_i)$ follows a classical random walk that can be described with a Langevin type equation $\dot{n} = \sqrt{2P_S C}\,\xi(t)$.

By scaling with a factor e, the charge of the monovalent ion, we can go from particle traffic to charge traffic, that is, electrical current. We then get a Langevin type stochastic differential equation for the transmembrane electrical current

$$\dot{q}_m = \sqrt{2e^2 P_S C}\,\xi(t). \tag{6}$$

For the average square charge transfer Δq in time t we have:

$$\left\langle \Delta q_m^2(t) \right\rangle = 2e^2 P_S C t. \tag{7}$$

Equations 6 and 7 are analogous to the equations that describe the random walk of an overdamped Brownian particle, $\dot{x} = \sqrt{2D}\,\xi(t)$, and the diffusion equation, $\left\langle \Delta x^2(t) \right\rangle = 2Dt$ where D denotes the diffusion coefficient. In stochastic dynamics, the diffusion coefficient D and the friction coefficient β are related by Einstein's well known Fluctuation-Dissipation Theorem: $D = kT/\beta$. Our equivalent of the diffusion coefficient is $D_q = e^2 P_S C$. From the resistance formula that we derived from the Nernst equation, we can infer an electrical equivalent of Einstein's Fluctuation-Dissipation Theorem:

$$D_q = e^2 P_S C = \frac{kT}{R_m}. \tag{8}$$

We see from this equation that, in the electro-chemical context, R_m plays the role of the friction coefficient β.

After substituting Equation 8 in Equation 6 it is possible to retrieve Nyquist's Equation 1. Nyquist's derivation [Nyquist, 1928] applies to a Brownian "gas" of charge carriers in a resistor. That derivation, furthermore, involves inductances and the equipartition theorem. It is not a priori obvious that the same formula results when dealing with the 2-sided shot noise through a membrane. Apparently it does and it seems like Nyquist put the finger on a particular manifestation of something much more general [Sarpeshkar et al., 1993].

Equations 6 and 7 would provide an accurate description of membrane currents if all passing current were immediately carried off to infinity and no potential difference were to develop, that is, the situation depicted in Figure 1. However, the net charge that accumulates inside a cell will "stick" to the membrane and charge it up like a capacitor (cf. Fig. 3). If q_m is the accumulated charge on a unit area of membrane, then the voltage V_m across the membrane follows $q_m = C_m V_m$. Here C_m denotes the capacitance of a unit area of membrane. We have $C_m = \varepsilon_0 \varepsilon_r / d_m$, where $\varepsilon_0 = 8.8 \times 10^{-12}$ $\mathrm{Nm^2/C^2}$ represents the dielectric permittivity of a vacuum, ε_r is the relative dielectric permittivity of the bilayer, and d_m is the bilayer width. For a lipid bilayer, we have $\varepsilon_r \approx 2$. The width equals about 5 nm. The bilayer is thus found to have a capacitance of about 1 $\mu\mathrm{F/cm^2}$.

The induced transmembrane potential V_m will provide a force to bias the charge permeation. This force will drive V_m back to zero again. Taking this force into account the stochastic differential equation turns into:

$$\dot{q}_m(t) = -\frac{q_m(t)}{R_m C_m} + \sqrt{2D_q}\,\xi(t). \tag{9}$$

The quotient q_m/C_m represents the potential V_m that drives $q_m(t)$ back to zero. R_m represents the resistance to the current. So it is obvious that $-q_m(t)/(R_m C_m)$ describes a current that drives $q_m(t)$ back to zero. For $V_m(t)$ we have:

$$\frac{dV_m(t)}{dt} = -\frac{V_m(t)}{R_m C_m} + \frac{1}{C_m}\sqrt{\frac{2kT}{R_m}}\,\xi(t). \tag{10}$$

Equations 9 and 10 describe a so-called Ornstein–Uhlenbeck process. Most authoritative textbooks on

stochastic processes include a section on the Ornstein–Uhlenbeck process [Feller, 1957; Van Kampen, 1992]. In its archetypal form the Ornstein–Uhlenbeck equation describes the motion of an overdamped Brownian particle in a quadratic potential well.

The ordinary differential Equations 9 and 10 are hard to handle because of the stochastic term $\xi(t)$. In many cases we therefore turn to an equivalent description in terms of a partial differential equation that describes the time evolution of the probability density $P = P(V_m, t)$:

$$\partial_t P = \frac{1}{R_m C_m}\partial_{V_m}(V_m P) + \frac{kT}{C_m^2 R_m}\partial_{V_m}^2 P. \qquad (11)$$

In this equation $P(V_m, t)\, d(V_m)$ represents the probability that at time t the transmembrane voltage is between V_m and $V_m + d(V_m)$. A similar equation can be set up for $q_m(t)$. By setting the left hand side of Equation 10 equal to zero and solving the remaining ordinary differential equation, a stationary distribution can be derived. This stationary distribution is found to be a zero-average Gaussian with a standard deviation $\langle V_m^2 \rangle = kT/C_m$.

Let's turn back to the system without capacitance, that is, Equations 6 and 7. The Fourier transform of $I(t)$ is $\bar{I}(f) = \int_{-\infty}^{\infty} I(t) e^{i\omega t}\, dt$. The passage of an ion through a lipid bilayer takes about $\tau = 10^{-7}$ s. Relative to the timescales we will be working with, the current associated with such a passage can be conceived of as a delta function, $e\delta(t)$. The Fourier transform of $\delta(t)$ is a flat spectrum, that is, $\bar{\delta}(f) = 1$. For any real signal $I(t)$, $|\bar{I}(f)|$ is a symmetric function, that is, $|\bar{I}(f)| = |\bar{I}(-f)|$. The quantity $(2/T)|\bar{I}(f)|^2$, where T is the time over which the signal $I(t)$ was recorded, is defined as the power spectral density $S(f)$ of the signal $I(t)$. $S(f)\Delta f$ is proportional to the amount of power that the signal $I(t)$ carries in the frequency window between f and $f + \Delta f$. If $I(t)$ has the form of N delta like passages of monovalent ions, then we have for the Fourier transform $\bar{I}(f) = eN$ and for the power spectral density $S_{I_m}(f) = (2/T)e^2 N$. For $T \to \infty$, the number of pulses will equal $N = 2P_S CT$. So we derive $S_{I_m}(f) = 4e^2 P_S C$. The textbook by DeFelice [1981] provides a more rigorous review of the theory that is presented in this paragraph.

With $S_{I_m}(f) = 4e^2 P_S C$ we have a flat power spectrum. The area $\int_{f=0}^{\infty} S_{I_m}(f)\, df$ represents the total power in the signal. With the flat spectrum this appears to be infinite. Nyquist already derived that quantum mechanics leads to a cutoff at $hf \approx kT$, where $h = 6.63 \times 10^{-34}$ Js represents Planck's constant. At $T \approx 300$ K, the associated cutoff frequency is about 6×10^{12} Hz. However, the passage time $\tau \approx 10^{-7}$ s gives our delta functions a finite width that results in a cutoff at $f \approx 10^7$ Hz.

The average permeation rate $2P_s C$ leads to a characteristic timescale of the setup we are looking at. When we take a realistic value for a lipid bilayer like $P_s = 10^{-11}$ cm/s and $C = 0.15$ mol/liter, we find that there is about one ion passage per second through one square micrometer of bilayer. A lipid bilayer sphere with a diameter of about 10 μm has a surface area of about 300 μm^2 and this implies about 300 transmembrane ion passages per second for the entire cell.

We thus see that between the ion passage rate $(2P_s C)$ and the inverse duration of one passage $(1/\tau)$ there can be several decades along the frequency axis where the noise is white (a flat spectrum), but does not have a Gaussian amplitude distribution. In many contexts white noise is thermal noise and consists of a small signal that changes much faster than any other characteristic timescale of a system. In our case, however, on a timescale between $\Delta t = \tau$ and $\Delta t = 1/(2P_S C)$, we have a noise amplitude distribution that is symmetric around zero and has two sharp peaks (one for $1 \to 2$ passage and one for $2 \to 1$ passage). In the realm $\tau < \Delta t < 1/(2P_S C)$ ion passage is rare, but the flatness of the power spectrum comes about because ion passage gives a very sharp pulselike signal.

Taking the capacitor properties of the membrane into account and analyzing the resulting Ornstein–Uhlenbeck process, we are led to yet another characteristic time: $\tau_m = R_m C_m$. The resistance of a patch of membrane is inversely proportional to the area and the capacitance is proportional to the area. The time $\tau_m = R_m C_m$ is therefore a quantity that depends not on cell size, but solely on the width of the membrane and the material that it is made of. In the resulting RC circuit, the frequencies higher than $1/R_m C_m$ are too fast to build up across the capacitor. This leads to another cutoff in the spectrum [Van Kampen, 1992]:

$$S_{V_m}(f) = \frac{4kTR_m}{1 + \omega^2\tau_m^2} = \frac{4\tau_m}{1 + \omega^2\tau_m^2}\langle V_m^2 \rangle. \qquad (12)$$

where ω represents the angular velocity $\omega = 2\pi f$. Likewise we have for the electric field:

$$S_{E_m}(f) = \frac{4\tau_m}{1 + \omega^2\tau_m^2}\langle E_m^2 \rangle. \qquad (13)$$

A lipid bilayer and a cell membrane both have a capacitance of about 1 $\mu F/cm^2$. As was mentioned in the previous paragraph, the electrical resistance between the inside and outside of the cell is inversely proportional to the magnitude A of the cell's surface area. It, therefore, makes sense to take the resistance of a fixed unit area as a membrane property and obtain the

resistance of the entire cell through division by A. The resistance has very different values for a real cell membrane (about $10^3\ \Omega\,\mathrm{cm}^2$) and a pure lipid bilayer (about 10^6–$10^9\ \Omega\,\mathrm{cm}^2$). So for a real cell membrane the RC time amounts to about a millisecond. For a pure lipid bilayer, the RC time can be of the order of minutes.

An actual cell membrane contains many specialized channels to regulate the traffic of different kinds of ions. As was pointed out above, it is mostly the presence of these channels that makes the conductance of a cell membrane higher than the conductance of a pure lipid bilayer by several orders of magnitude. Channels are complicated in that they can open or close in response to ion concentrations and/or ligand concentrations. Many channels also open and close in response to the transmembrane voltage. Such voltage sensitive channels can bring about a resistance that depends on the transmembrane voltage, that is, they can rectify. However, equilibrium noise cannot be rectified [Brillouin, 1950] and the rectification properties do therefore not interfere with equilibrium noise. The cell membrane, furthermore, contains pumps that employ energetically downhill processes, like ATP hydrolysis, to power ion transport against the electrochemical gradient. Channel rectification and ion pumps should definitely be part of the picture when nonequilibrium noise is being studied.

In this study, however, we focus on the more fundamental problem of *equilibrium* noise across a membrane. From $R_\mathrm{m} = kT/(2e^2 P_\mathrm{S} C)$ it is obvious that the resistance of a membrane depends on what kind of ions are present and in what concentration they are present in the electrolyte solution. The high estimate of $10^9\ \Omega\,\mathrm{cm}^2$ corresponds to a pure lipid bilayer in a solution with about 0.1 mol/liter of sodium. The formula $S_{V_\mathrm{m}}(f) = 4kTR_\mathrm{m}$ shows that a higher resistance implies larger voltage fluctuations. Current fluctuations, however, obey $S_{I_\mathrm{m}}(f) = 4kT/R_\mathrm{m}$, so these will be smaller at higher R_m.

To get a complete picture, there are some other fluctuations to consider. We will see shortly that a membrane protein is subject to more noise than just that from transmembrane ion traffic. Across a capacitor in an RC circuit, the variance of the voltage fluctuations equals $\langle V_\mathrm{m}^2\rangle = kT/C_\mathrm{tot}$, where C_tot represents the capacitance of the entire membrane. This formula is actually a manifestation of the equipartition theorem [Van Kampen, 1992; Sarpeshkar et al., 1993] since the energy, $(1/2)C_\mathrm{tot}V_\mathrm{m}^2$, amounts to the $(1/2)kT$ of thermal energy that every degree of freedom takes on when there is thermal equilibrium. So a cell with a surface area A_tot has a transmembrane voltage due to thermal noise that is Gaussian distributed, has a zero average, and a root mean square voltage of $\sqrt{\langle V_\mathrm{m}^2\rangle} = \sqrt{kT/(C_\mathrm{m}A_\mathrm{tot})}$.

For a zero-average Gaussian distribution with standard deviation σ, that is, $P(x) = (1/\sigma\sqrt{2\pi})\exp[-x/2\sigma^2]$, the average absolute value can be easily evaluated as $\langle|x|\rangle = 2\int_0^\infty |x|P(x)\,\mathrm{d}x = (2/2\pi)\sigma$. The variance around this average is readily evaluated as $(1-(2/\pi))\sigma^2$. A cell with a surface area A_tot thus has, on the average $\langle|q_\mathrm{tot}|\rangle = C_\mathrm{tot}\langle|V_\mathrm{m}|\rangle = (2/\sqrt{2\pi})\sqrt{kTC_\mathrm{m}A_\mathrm{tot}}$ of charge on the membrane (positive on one side and negative on the opposite side). Assuming that the positive ions on the one side of the membrane and the corresponding negative ions on the other side of the membrane are both monovalent and of equal mobility, we see that a square unit of membrane has on average $\langle n\rangle = (2/e\sqrt{2\pi})\sqrt{kTC_\mathrm{m}/A_\mathrm{tot}}$ ions on each side. Substituting the numbers, we find that for a spherical cell with a diameter of about 10 μm, that is, a surface area of about 300 $\mu\mathrm{m}^2$, the average thermal transmembrane voltage equals about $\langle|V_\mathrm{m}|\rangle = 4\times10^{-5}$ V. This amounts to only about three ions per square micrometer of membrane. The average thermal velocity of ions on the membrane surface can be estimated with $(1/2)mv^2 \approx kT$. At 300 K this average thermal velocity is found to be about 5×10^2 m/s. This means that a micrometer is, on average, traversed in less than 10^{-8} s. So the random fluctuations in the number n of ions on a square unit of membrane, which has a standard deviation of $\sqrt{\langle n\rangle}$, are generally faster than other timescales of the system.

The membrane area per monovalent ion is:

$$a_e = \frac{e}{2}\sqrt{\frac{2\pi A_\mathrm{tot}}{kTC_\mathrm{m}}}. \tag{14}$$

The area a_e is also characteristic in that it has an average number of ions that equals the standard deviation. On areas smaller than a_e, the standard deviation in the number of ions exceeds the average number of ions. Robert Adair has proposed a $5\times5\times5$ nm cube of membrane as a fundamental electrical unit [Adair, 1991]. This is also the approximate size of an average membrane protein, and since the effect of noise on protein operation is what we ultimately want to assess, it is an important scale to consider. Under physiological conditions, the Debye screening length [Moore, 1972] also amounts to about a nanometer. So only when an ion actually "hits" the 5×5 nm protein surface do we get a "pulse." We will refer to the 5×5 nm area as an "Adair segment" of area $a_\mathrm{Ad} = 25\ \mathrm{nm}^2$. What proteins "feel" is the electric field, that is, $E_\mathrm{m} = V_\mathrm{m}/d_\mathrm{m}$, where $d_\mathrm{m} = 5$ nm represents the width of the membrane. So, in what follows, we will consider the transmembrane electric field instead of the transmembrane voltage.

It is obvious that on a 5×5 nm area of membrane there will be an ion for a fraction of time that amounts to $\varepsilon = a_{\mathrm{Ad}}/a_e$. The ratio ε will be of the order 10^{-4}. The pulse-like passages of ions will again constitute a Poisson process. We, once more, face a form of shot noise in the sense that the noise is due to the elementary charge being finite. The shot noise dealt with so far was transmembrane. In this paragraph the noise parallel to the membrane is evaluated. When an instantaneous measurement is performed, there is a probability ε that an ion is found in a particular segment of area a_{Ad}. In order for the average absolute field to amount to $\langle|E_{\mathrm{m}}|\rangle$ the field with an ion on a_{Ad} must equal $\langle|E_{\mathrm{m}}|\rangle/\varepsilon$. The variance equals $\sigma^2 = (\langle|E_{\mathrm{m}}|\rangle/\varepsilon)^2\varepsilon - \langle|E_{\mathrm{m}}|\rangle^2$. For small ε the second term can be neglected and we derive a standard deviation of the electric field that is a factor $1/\sqrt{\varepsilon}$ larger than the average electric field. Finally, if there are ν ion passages over our a_{Ad} segment per unit of time, we have a flat noise spectrum and a power spectral density of $S_{E_{\mathrm{m}}}(f) = 2\langle|E_{\mathrm{m}}|\rangle^2\nu$. The rate ν is easily estimated. As we saw before, the thermal velocity of an ion in solution at 300 K is about 5×10^2 m/s. This means an ion can traverse about 10^{11} Adair segments per second. The aforementioned cell with a surface area of 300 μm^2 measures about 10^7 Adair segments. With about a thousand ions on the entire cell surface, the rate μ is expected to be on the order of $10^3 \cdot 10^{11-7} = 10^7$. What we have dealt with in this paragraph is actually a special case of Campbell's theorem [DeFelice, 1981; Van Kampen, 1992]. Obviously, because of the factor ν, the noise due to random motion of ions over the membrane ($S_{E_{\mathrm{m}}}(f) = 2\langle|E_{\mathrm{m}}|\rangle^2\nu$) will be much larger than the noise due to transmembrane ion traffic (cf. Eq. 13). A more thorough treatment of the theory that we applied can again be found in the textbook by DeFelice [1981].

It is unlikely that it is the same ions sliding on the membrane surface all the time. Ions can go from the membrane surface into the solution while, elsewhere at the same time, other ions go from the solution onto the membrane. Taking this effect into account would again add to the noise intensity.

DISCUSSION

Above we calculated the equilibrium noise across and on a membrane. We have assessed the electrical noise that a membrane protein would be subjected to. For any reasonable bandwidth (10–100 Hz) it appears that the equilibrium noise that a membrane protein experiences has much more energy than the power frequency electromagnetic radiation that it is subjected to from power lines and/or electrical appliances.

The picture of Weaver and Astumian [1990] is not complete; there are more ''noises'' operating on a motor protein than just the thermal fluctuations of the transmembrane potential. Analyzing the equivalent circuit, Kaune [2002] was correct in concluding that intramembrane noise that never reaches the membrane surface also contributes. After ridding Kaune's model of the implied and troubling hypothesis that all the intramembrane noise is ''coherent,'' Vincze et al. [2005] derived a noise power that is more than a million times that of Weaver and Astumian. Weaver and Astumian's incomplete account of the noise already leads to transmembrane fluctuations that far overwhelm those due to realistic power frequency fields. The approach of Vincze et al. [2005] only renders the power frequency fields more negligible by many orders of magnitude.

Intramembrane noise is hard to imagine when the resistor is a 5 nm thick membrane and when the current consists of pulse like ion passages through this membrane. However, the thermal motion of ions parallel to the membrane surface appears to act like a manifestation of the intramembrane noise. Taking this thermal motion into account leads to the same more than millionfold increase of noise intensity that Vincze et al. [2005] derived from a setup like Figure 4.

As was pointed out before, the membrane of a real living cell has a smaller resistance than a pure bilayer due to the presence of pumps, transporters, and channels. A smaller resistance leads to a smaller RC time, a larger thermal noise current, and a smaller thermal noise voltage. The latter, in turn, leads to a smaller thermal noise electric field. It is also important to realize that a living cell is very far from equilibrium. A living cell carries, for instance, a transmembrane voltage of about 80 mV. Channels and transporters conduct currents down the electrochemical potential and, in steady state, ion pumps maintain the same currents against the potential [Van Mil et al., 2003]. These ''guided'' nonequilibrium currents are much larger than the equilibrium currents that we have discussed. Nonequilibrium noise does not have a flat frequency spectrum. Instead, the noise strength is inversely proportional to the frequency and it is therefore generally called 1/*f*-noise. There are important qualitative differences between equilibrium and nonequilibrium noise that are not reflected in the spectrum or time correlation [Bier, 1997]. Equilibrium noise cannot power any process. Nonequilibrium noise, however, can drive energetically uphill processes. In any treatment of membrane proteins and the environment in which they operate it is important to keep these noises separate.

Consider the setup in Figure 6. The two nearby proteins E_1 and E_2 are coupled through their dipoles. Suppose that E_1 catalyzes the hydrolysis of ATP and

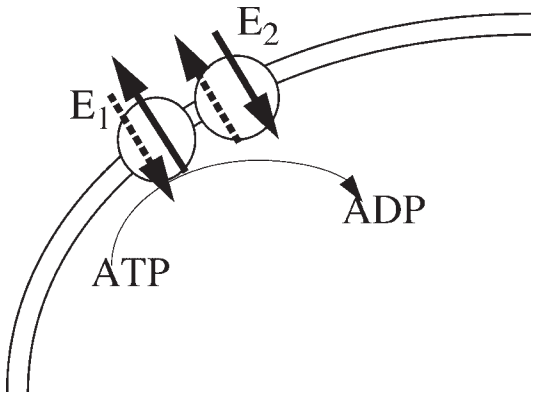

Fig. 6. A membrane protein E_1 carries a dipole whose orientation depends on the conformational state (ATP bound vs. ATP unbound) in the ATP hydrolyzing cycle. The dipole of membrane protein E_2 is coupled to the one of E_1 and follows the fluctuation of E_1. In the presence of an ATP-ADP chemical potential E_2 performs nonequilibrium energy dissipating fluctuations. In the absence of such a potential the fluctuations are Brownian, equilibrium fluctuations that do not dissipate any energy. There is no statistical criterion on the basis of which one can discriminate between equilibrium and nonequilibrium fluctuations.

that there are two possible orientations of the dipole. The orientation with ATP bound is reversed from what it is when ATP is not bound. Now suppose you are looking only at E_2. As E_1 is hydrolyzing ATP, E_2 will follow the imposed nonequilibrium fluctuation. If ATP and ADP are in a chemical equilibrium, there will still be Brownian fluctuations between the $\uparrow\downarrow$ and the $\downarrow\uparrow$ configurations of the E_1E_2-system. But in this case the flips are equilibrium and the distribution between $\uparrow\downarrow$ and $\downarrow\uparrow$ is a Boltzmann distribution. It is not possible to just measure E_2 dwelling times in different states and formulate a statistical criterion to discriminate between equilibrium and nonequilibrium noise. But there is a crucial physical difference between the equilibrium and the nonequilibrium situation. In the nonequilibrium case, E_1 can make E_2 do work via the dipole–dipole interaction. E_1 can, for instance, force E_2 through a transport cycle if E_2 is a pump. An external EM field works very much like the ATP hydrolysis in the above example [Astumian et al., 1987]. Unlike the Brownian motion of the system itself, such an EM field can do work. It brings new energy into the system. This energy can be dissipated and heat up the system. It is also possible for this energy to not be dissipated completely and to be partially converted into ''work'' on a metabolic chain. Metabolic flows can be affected and the effect can accumulate over time [Vaughan and Weaver, 2005].

The example in the previous paragraph shows that equilibrium and nonequilibrium noise are very different. Gauging the strength of an external EM field against the strength of the internal Brownian motion may be beside the point. It may be very much like comparing the available energy in a battery to the battery's heat capacity times the absolute temperature.

This article is not intended as a final assessment. If anything, it hopes to contribute to the impetus to get to a correct evaluation of the noises that a membrane protein is subject to. The transition from equilibrium to nonequilibrium noise is currently a hot topic in electronics and solid state physics [Schoelkopf et al., 1997; Gomila et al., 2004]. But in the context of cell membranes with embedded proteins this is still a largely unexplored territory. Perhaps equilibrium noise is not what the energy in 50 or 60 Hz EM radiation should be compared to. External power frequency fields are nonequilibrium sources. Gauging such fields against other nonequilibrium noises may be more reasonable. It is only after having come to a good and complete understanding of the noise environment of a membrane protein that responsible statements can be made about the possibility of physiological effects of 50 or 60 Hz EM radiation.

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APPENDIX 1

In this appendix, we will prove by mathematical induction that adding n vectors with norm $\|\xi^0\|$ and random phases will lead to a vector whose norm approaches $\sqrt{n}\|\xi^0\|$ in the large n limit.

First we take two vectors with the same norm. We scale this norm to unity. Without loss of generality we let one vector be the unit vector on the x-axis (cf. Fig. 7). Of course, it is only the difference in angle ϕ that matters for the eventual norm of the sum. The direction of the second vector is picked randomly from a flat distribution between $\phi = 0$ and $\phi = 2\pi$. Summing the x and y coordinate it is obvious from Figure 7 that we have $x_2 = 1 + \cos\phi$ and $y_2 = \sin\phi$. We thus have for the average square norm of the sum r_2^2:

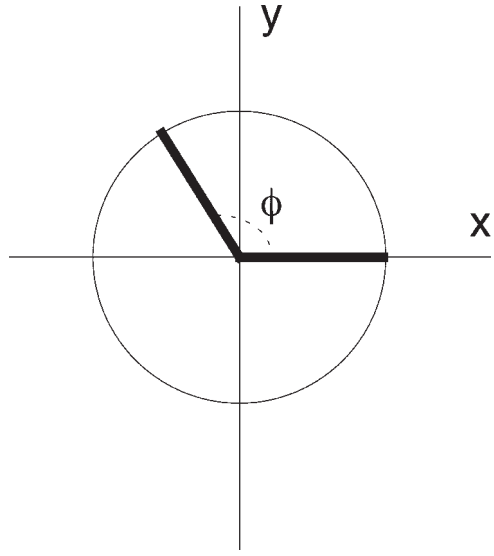

Fig. 7. The angle ϕ between two unit vectors is a random number from a flat distribution between 0 and 2π. The average length of the sum of the two vectors is $\sqrt{2}$. In this appendix it is, furthermore, shown that for n unit vectors with random directions, the average norm of the sum vector equals $\sqrt{n}$.

$$r_2^2 = \frac{1}{2\pi}\int_{\phi=0}^{2\pi}(x_2^2 + y_2^2)\,d\phi$$
$$= \frac{1}{2\pi}\int_{\phi=0}^{2\pi}\{(1+\cos\phi)^2 + sin^2\,\phi\}\,d\phi \qquad (15)$$
$$= \frac{1}{2\pi}\int_{\phi=0}^{2\pi}(2 + 2\cos 2\phi)\,d\phi = 2$$

And hence $r_2 = \sqrt{2}$.

To prove that $r_n = \sqrt{n}$ for the sum of n randomly phased unit vectors we need to prove that $r_{n-1} = \sqrt{n-1}$ implies $r_n = \sqrt{n}$. $r_n = \sqrt{n}$ for all n then follows by mathematical induction. Add a unit vector with a random direction ϕ to a vector $(x_{n-1}, y_{n-1}) = (\sqrt{n-1}, 0)$. This leads to:

$$r_n^2 = \frac{1}{2\pi}\int_{\phi=0}^{2\pi}\{(\sqrt{n-1} + \cos\phi)^2 + \sin^2\phi\}\,d\phi = n \qquad (16)$$

QED.

APPENDIX 2

In this appendix, a derivation of Equation 5 is shown. Equation 5 is also the main result of the recent

article by Vincze et al. [2005]. The derivation presented below, however, is significantly more concise.

Equation 3 can be rewritten as follows:

$$I_\mu = \frac{1}{NR_m}\left\{\xi_\mu - \frac{1}{1+i\omega\tau_m}\left(\frac{1}{N}\sum_{\nu=1}^{N}\xi_\nu\right)\right\}. \quad (17)$$

What this equation says is that, at a frequency ω, the AC voltage in each resistor in Figure 4 is the sum of the self-generated thermal voltage ξ_μ and a potential $(1/N)\sum_{\nu=1}^{N}\xi_\nu$ that is due to the other resistors and the capacitor. The $1/(1+i\omega\tau_m)$ comes about because of the RC delay. The average power dissipated in each resistor equals $(1/2)(N R_m) I_\mu I_\mu^*$. Here the superscript "*" denotes complex conjugation, that is $(a+bi)^* = a-bi$. With Equation 17 we write for the power dissipation in each resistor:

$$\frac{1}{2}NR_m I_\mu I_\mu^* = \frac{1}{2NR_m}\left[\xi_\mu - \frac{1}{1+i\omega\tau_m}\left(\frac{1}{N}\sum_{\nu=1}^{N}\xi_\nu\right)\right]\left[\xi_\mu^* - \left\{\frac{1}{1+i\omega\tau_m}\left(\frac{1}{N}\sum_{\nu=1}^{N}\xi_\nu\right)\right\}^*\right]. \quad (18)$$

After working out all the algebra (using $(z_1 z_2)^* = z_1^* z_2^*$, $(z_1/z_2)^* = z_1^*/z_2^*$, and $zz^* = \|z\|^2$), performing the summation $\sum_{\mu=1}^{N}$, and working out the algebra again, one finds for the total dissipated power:

$$\frac{1}{2}\sum_{\mu=1}^{N} NR_m I_\mu I_\mu^* = \frac{1}{2NR_m}\sum_{\mu=1}^{N}\|\xi_\mu\|^2 - \frac{1}{2R_m(1+\omega^2\tau_m^2)}\left\|\frac{1}{N}\sum_{\mu=1}^{N}\xi_\mu\right\|^2. \quad (19)$$

All resistors in Figure 4 have the same resistance NR_m. So for all resistors the noise amplitude has the same value $\|\xi^0\|$. Of course, there are still the random phase factors, that is, $\xi_\mu = \|\xi^0\|\exp[2\pi i p]$, where p is a random number between 0 and 1. So we have $\sum_{\mu=1}^{N}\|\xi_\mu\|^2 = N\|\xi^0\|^2$. When discussing the equivalency between one R_m resistor and N parallel NR_m resistors we already derived $\|(1/N)\sum_{\mu=1}^{N}\xi_\mu\|^2 = (1/N)\|\xi^0\|^2$. Appendix 1 contains a rigorous derivation of this identity. We are now led to a very powerful equation:

$$\frac{1}{2}\sum_{\mu=1}^{N} NR_m I_\mu I_\mu^* = \frac{\|\xi^0\|^2}{2R_m} - \frac{\|\xi^0\|^2}{2NR_m(1+\omega^2\tau_m^2)}. \quad (20)$$

This equation very nicely separates out all the energies that feature in the different competing models. The term $\|\xi^0\|^2/(2N R_m)$ represents the power generated in one resistor. So $\Pi_{tot} = \|\xi^0\|^2/(2R_m)$ is therefore the total noise power generated in all resistors together. Since $\|\xi^0\|^2 = 8kT N R_m \Delta f$ it increases with N (the 4 in Equation 1 for an average, becomes 8 when describing the amplitude $\|\xi^0\|$). So we have $\|\xi^0\|^2/(2R_m) = \Pi_{I_\mu} + \Pi_{R_m C_m}$. Here $\Pi_{R_m C_m} = \|\xi^0\|^2/\{2NR_m(1+\omega^2\tau^2)\}$

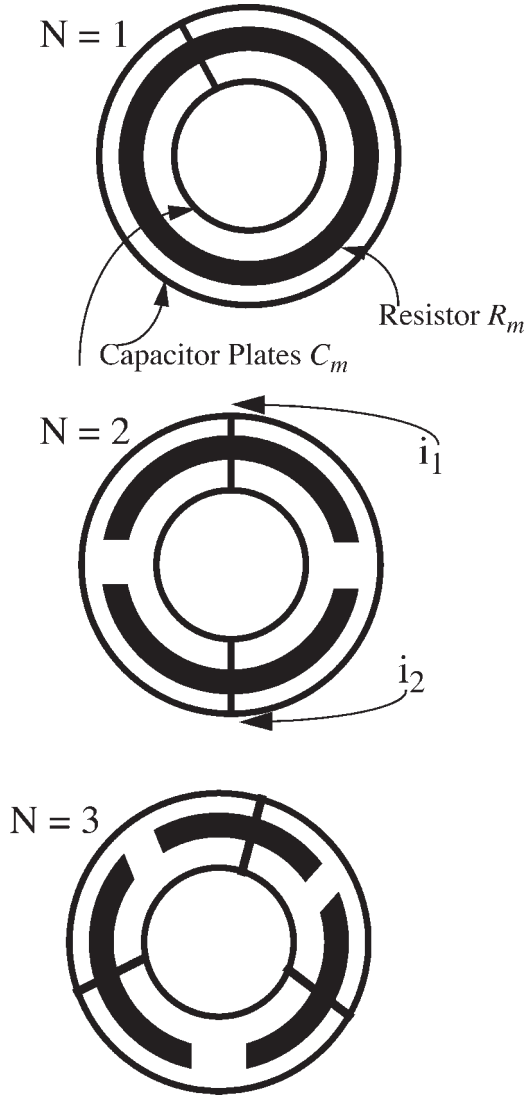

Fig. 8. Electrical cross-sections of a cell for $N=1$, $N=2$, and $N=3$. The inner and outer circle represent the inside and outside of the membrane and they operate like capacitor plates. The thick, black circle in the middle represents the resistor(s). In the article by Vincze et al. [2005], the zero mode is the net current through all the resistors together ($i_1 + i_2$ for $N=2$). The higher modes, such as $i_1 - i_2$, describe zero average spatial variations in the transmembrane current.

comes from the current I_m that is associated with the capacitor. $\Pi_{R_mC_m}$ thus denotes the part of the generated fluctuation-dissipation power that goes into the oscillation of the R_mC_m circuit. Π_{I_μ} represents the fluctuation-dissipation power in the intramembrane noise.

Using $\|\xi^0\|^2 = 8kTNR_m\Delta f$ one derives $\Pi_{R_mC_m} = \{4kT/(1+\omega^2\tau_m^2)\}\Delta f$. The expression $4kT/(1+\omega^2\tau_m^2)$ is well known; it is simply the power spectral density of thermal noise in an RC circuit. This is the energy that goes towards the generation of a field between the capacitor plates and, as such, it is the focus of the Weaver–Astumian approach. Obviously, it is independent of N. The Weaver–Astumian approach thus avoids the problem of coherence versus incoherence and the issue of parallel connectivity. For Weaver and Astumian the thermal-electric storm is in the field between the capacitor plates, they toss out Π_{I_μ} and obtain $\Pi_{tot} = \Pi_{R_mC_m} \propto 1/(1+\omega^2\tau_m^2)$. The term $\Pi_{I_\mu} = (1/2)\sum_{\mu=1}^{N} NR_mI_\mu I_\mu^*$ stands for the power that is fluctuated and dissipated by intramembrane currents. This is the intramembrane noise. None of the Π_{I_μ}-power goes towards charging up the capacitor. For larger N the resistors ''push'' more current into each other and the Π_{I_μ}-term is therefore dependent on N.

With $\left\|\xi^0\right\|^2 = 8kTNR_m\Delta f$ we can rewrite Equation 20 as:

$$\frac{1}{2}\sum_{\mu=1}^{N} NR_mI_\mu I_\mu^* = 4\left\{N - \frac{1}{(1+\omega^2\tau_m^2)}\right\}kT\Delta f,$$

which is Equation 5 of the main text. After some minor algebraic manipulation it is easy to see that this equation is essentially the same as Equation 30 in the article by Vincze et al. [2005].

Figure 8 shows schematic cross-sections of a spherical cell for $N=1$, $N=2$, and $N=3$. Consider the situation with $N=2$. Each resistor has its own current (i_1 and i_2 in the figure). When you add up these currents you obtain the net current going into the cell, that is $i_{sum} = i_1 + i_2$. The difference between i_1 and i_2, that is, $i_{diff} = i_1 - i_2$, constitutes the first mode. Going from (i_1, i_2) to (i_{sum}, i_{diff}), or back, is a 2×2-matrix operation. Clearly, the matrix will be $N\times N$ for the general case with N resistors. Instead of dealing with all the individual currents (and all the ensuing vectors and matrices), we took a shortcut and immediately went to the power (which is like a norm of a vector) with Equation 17. We thus got to Equation 5 without having to go through the complicated matrix algebra of Vincze et al. [2005].