HOW TO EVALUATE THE ELECTRIC NOISE IN A CELL MEMBRANE?*

Martin Bier

Dept. of Physics, East Carolina University
Greenville, NC 27858, USA
bierm@mail.ecu.edu

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Dedicated to Professor Peter Talkner on the occasion of his 60th birthday

There has been considerable public anxiety about possible health effects of electromagnetic radiation emitted by high voltage power lines. Power frequencies (60 Hz in the US, 50 Hz in many other countries) are sufficiently slow for the associated electric fields to distribute themselves across the highly resistive cell membranes. To assess the ambient power frequency fields, researchers have compared the voltage that these fields induce across cell membranes to the strength of the electric noise that the membranes generate themselves through Brownian motion. However, there has been disagreement among researchers on how to evaluate this equilibrium membrane electric noise. I will review the different approaches and present an *ab initio* modeling of membrane electric fields. I will show that different manifestations of Brownian noise lead to an electric noise intensity that is many times larger than what conventional estimates have yielded. Next, the legitimacy of gauging a nonequilibrium external signal against internal equilibrium noise is questioned and a more meaningful criterion is proposed. Finally, an estimate will be derived of the nonequilibrium noise intensity due to the driven ion traffic through randomly opening and closing ion channels.

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1. Introduction

Electrical appliances that are powered by an AC source all emit some electromagnetic radiation of the frequency of the AC source. From everyday gadgets like computers, electric blankets, electric razors, *etc.* a person can be exposed to a field with an amplitude of about 500 V/m [1]. This should be rather harmless. There is, for instance, already an electric field of about

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100 V/m between the earth and the sky [2]. The equipotential surfaces associated with that field are generally not horizontal. So ever since the dawn of human evolution, man has already been exposing himself to a slowly fluctuating field of about 100 V/m as he is moving around objects.

With power lines, however, we are in a completely different ballpark. In almost every country in the world a network of high voltage power lines, suspended from imposing Eiffel Tower-like structures, crisscrosses the landscape. These lines can carry up to half a million Volt and when standing right under a power line a person can be exposed to about 10 kV/m [1].

There has been a lot of debate and public anxiety about possible health effects that the long term exposure to such fields may have. Epidemiological studies have been somewhat inconclusive. Many data have been gathered, analyzed, and reanalyzed over the last quarter century [1, 3]. One problem is that the diseases that have raised the most concern are, fortunately, very rare. Childhood leukemia, for instance, occurs on average in only one out of every ten thousand children. Large populations are necessary in order to measure a slightly enhanced rate of occurrence in an exposed population. Because it is hard to accurately assess the exposure of each subject in a survey to power frequency radiation and to other cancer causing factors, the epidemiological studies have considerable margins of error.

The epidemiological inconclusiveness all the more justifies a biophysical approach. Where and how does an power frequency field interact with a living organism? Can we come up with some thresholds that have to be exceeded before a physiological effect can occur? Below I will briefly review some of the major results of the last few decades. I will propose some new approaches and I will suggest some directions for future investigations.

Electromagnetic radiation has an electric and a magnetic component. My focus will be on a possible physiological effect of the electric component. It is for brevity's sake and not for the lack of lively debate and remarkable research results that I will exclude magnetoreception [4–10].

2. The distribution of an electric field inside an organism

The intracellular and extracellular medium are very ionic and conduct well. So when an electric field is imposed on a piece of living tissue, the ions move and, within a microsecond, compensate for the field inside the liquid. The cell membrane is very resistive and this means that, once a steady state is reached, all of the voltage drop occurs across the cell membranes. The electromagnetic (EM) radiation frequency window between 0 and 300 Hz is generally characterized as Extremely Low Frequency (ELF). In this regime the field changes sufficiently slowly, relative to the aforementioned microsecond, for the field to remain distributed over just the membranes.

Two "conversions" occur when an ambient ELF field distributes itself across cell membranes in living tissue. Living tissue, first of all, has an average resistivity that is much smaller than that of the surrounding air. Consequently, inside the organism an electric field is partly canceled out by the compensating displacement of charged particles. The resulting field attenuation is described by the following formula [7, 11]:

$$\frac{E_i}{E_0} \approx \epsilon_0 \omega \rho \,. \tag{1}$$

Here ϵ_0 is the dielectric permittivity of a vacuum (8.8×10^{-12} C^2/N.m^2), ω is the angular frequency ($\omega = 2\pi f$), and ρ represents the resistivity of the tissue (1–2 Ωm at about 100 Hz). For living tissue in a power frequency field this ratio is found to be at most 10^{-7}. Reference [11] by Foster and Schwan contains a rigorous derivation of Eq. (1). It is not hard, however, to intuit this formula. When an organism is exposed to a field, charge relocation takes place to compensate for this field. The slower the change of the field, the easier it is for this internal compensation to keep up. This is how the frequency dependence arises. Furthermore, for lower resistivity the internal compensation will be easier.

Once inside the tissue, the field is effectively amplified as all of the potential difference along the diameter of a cell (about $d = 10\mu$m) gets focused on the width of the cell membrane (about $h = 5$ nm). With $E_{\rm mem}/E_i \approx d/h$ we find an amplification of about 10^3. For a longer cell, however, this number may be larger. For the net conversion factor we thus derive a factor of about 10^{-4}. For an external field of $E_0 \approx 10$ kV/m, the membrane field is found to be a Volt per meter. This leads to about 5 nanovolt across a membrane of 5 nm width.

The 5 nanovolt may seem negligibly small relative to, for instance, the physiological transmembrane potential of about 100 millivolt. If the ELF field is to have an effect it is through interference with the catalytic cycle of membrane proteins. Proteins are generally very polar molecules and external electric fields can affect energy levels of conformational states and activation barriers.

3. The membrane as a Johnson–Nyquist resistor

The significance of an added nanovolt-order ELF oscillation across a cell membrane was first approached with rigorous quantitative physics in 1990 by Weaver and Astumian (WA). In a *Science* paper they compared the ELF voltage to the voltage due to thermal noise [12]. Because of the Brownian motion of the charge carriers, there is always a small fluctuating voltage between the two ends of a resistor. This voltage was first measured [13] and

then explained [14] in 1928. The so-called Johnson–Nyquist (JN) noise is white and in a frequency window Δf the average square voltage is expressed as

$$\langle \Delta V^2 \rangle = 4k_{\mathrm{B}} T R(\Delta f). \tag{2}$$

Here k_{B} is the Boltzmann constant, T is the absolute temperature, and R is the resistance. The cell membrane can be conceived of as a resistor. The interfaces of the membrane with the intracellular and extracellular fluid effectively act like capacitor plates that are 5 nm apart. In the WA view the transmembrane noise can be evaluated as the noise between the capacitor plates in an RC circuit (Fig. 1). The AC response of an RC circuit is part of any basic physics textbook. For the high frequencies there is not enough time for the voltage to build up across the capacitor. For the low frequencies there is enough time. So in the WA picture only low frequency JN noise manifests itself across the membrane. The cutoff between the low and high frequency regime is the RC time of the membrane. This RC time is independent of size and shape of the membrane and amounts to about a millisecond for a living cell. The 50 or 60 Hz power frequencies are thus well within the low frequency regime. Upon quantitative assessment Weaver and Astumian find a noise intensity that far overwhelms the signal due to a 10 kV/m ELF field. They then point out that, because of the noise, a membrane protein would never even be able to detect such an ELF field, let alone that the ELF field could have a physiological effect.

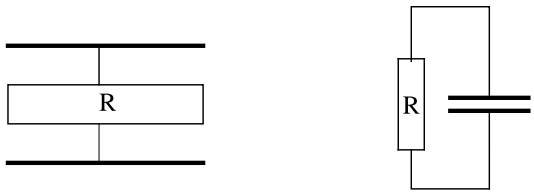

Fig. 1. The electrical structure of the cell membrane is shown in (a). The interior of the membrane operates as a resistor with a high resistance. In our context the resistor is also a white noise generator that follows Eq. (2). On both sides of the membrane the interface with the ionic solution acts like a capacitor plate. In the WA model [12] the electric potential between the two solutions is evaluated. This is equivalent to the potential between the capacitor plates in (b). Later models [15,16] focused on the electric field inside the resistor. Because of the sheet-like nature of the membrane the resistor R should then actually be conceived of as N parallel resistors that each have a resistance NR, where N is a very large number.

In 2002, W.T. Kaune put forward that, as a membrane protein is embedded in the cell membrane, it should, in the context of Fig. 1(b), be imagined to be *inside* the resistor [15]. Inside the resistor a protein should be subject to the electric fields that presumably cause the JN-voltage of Eq. (2). Moving the protein from between the capacitor plates to inside the resistor in Fig. 1(b) effectively inverts the WA picture. As was mentioned before, at low frequency the voltage on the capacitor follows and equals the voltage generated by the resistor. This means that at low frequency the field inside the resistor gets balanced out by the countervoltage from the capacitor. At high frequency the capacitor cannot follow. So eventually the protein will only "feel" the fast oscillations with periods below the RC time. In such a model there would be a possibility for the power frequency radiation to be "stick out" above the noise spectrum.

However, if we are imagining the membrane protein to be inside the resistor, Fig. 1 is no longer the appropriate setup for calculations. A real cell membrane is about 5 nm thick and many billions of square nanometers in surface area. So the resistor in Fig. 1 is actually a very thin sheet. As the lateral conductivity of a membrane is small, the sheet should be modeled as an array of many parallel resistors. Taking, in that case, N parallel resistors of resistance NR leads to the same net resistance R. The amount of noise, however, increases very fast with N. And not only does the number of "noise making resistors" increase when N is increased, the amount of noise per resistor also grows with N as each individual resistors generates a voltage that follows $\langle \Delta V^2 \rangle = 4k_{\mathrm{B}}TNR(\Delta f)$. At each frequency in the spectrum the resistors oscillate *incoherently*, *i.e.* the oscillations have random phase differences relative to each other. This being out of phase leads to the resistors pushing and pulling current in and out of each other. The capacitor is not involved in this "pulling and pushing". This "pulling and pushing" of current constitutes the *intramembrane noise*. It can be easily intuited that the intramembrane noise increases with N and that, for large N, the effect of the capacitor becomes more and more negligible. A exact mathematical solution for any value of N was first formulated by Vincze, Szasz, and Szasz [16]. A simpler derivation of the same result is found in [17]. When cutting up the membrane into the aforementioned individual resistors, a logical choice is taking the elementary resistor as a cube of 5 nm $\times$ 5 nm $\times$ 5 nm [7]. For an ordinary cell this leads to a value of N of the order of millions. The noise that a membrane protein "feels" in this case is almost all intramembrane, it is many times larger than what WA would predict, and the spectrum is effectively white [16, 17].

4. The membrane as a barrier to ions

The results from the previous section were rigorously derived. However, it makes sense to step back and reexamine the legitimacy of some of the basic premises. The basic idea behind Nyquist's $\langle \Delta V^2 \rangle = 4k_{\mathrm{B}}TR(\Delta f)$ is in the Brownian motion of the charge carriers *inside* the resistor. A cell membrane, however, consists for the most part of a lipid bilayer with no mobile charges inside. The transmembrane voltage emerges because of penetrations of the membrane by ions from the aqueous solution on either side of the membrane. These penetrations are random and left-to-right penetrations are not necessarily balanced out by right-to-left penetrations. At equilibrium a transmembrane potential thus arises as a consequence of *2-sided shot noise*.

It is easy and straightforward to take a membrane separating two identical ionic solutions. Given the membrane's permeability and the ionic concentrations, the penetration rates can be evaluated. The voltage that develops between the two sides is essentially an effect of the elementary charge being finite. It is through Fick's Law and Nernst's Law [18] that one can go from concentrations and permeabilities to currents, voltages and resistances. Remarkably, one then arrives again at Nyquist's $\langle \Delta V^2 \rangle = 4k_{\mathrm{B}}TR(\Delta f)$ [17].

The result appears surprising as nothing in Nyquist's original 1928 proof seems to suggest that the case of 2-sided shot noise is included. Nyquist's proof is a proof from the absurd that involves resistors, capacitors, and inductors and it uses the Equipartition Theorem (which says that at equilibrium every degree of freedom takes on $\frac{1}{2}k_{\mathrm{B}}T$ of thermal energy) as a starting point. A simpler form of Nyquist's proof is found in the reference by Feynman, Leighton, and Sands [2]. The peculiarity was also noticed by Sarpeshkar, Delbrück, and Mead [19]. In their 1993 paper these authors eventually argue that the 2-sided shot is the basic phenomenon that underlies JN noise.

A real membrane is also a capacitor. So any charge imbalance leads to a finite ΔV and a force, proportional to ΔV, that drives ΔV back to zero. This leads to an Ornstein–Uhlenbeck process (*i.e.* a random walk in a parabolic potential, see, for instance, the textbook by Van Kampen [20]) for the variations over time of ΔV. Substituting the ionic strengths of physiological solutions (which is about the same as that of sea water) and the cell membrane's RC time one derives a $\langle |\Delta V| \rangle$ that corresponds to about 3 monovalent ions per square micrometer [17]. These ions are not fixed at one position on the membrane-liquid interface. They move over the surface with a speed that can be estimated from $\frac{1}{2}mv^2 \approx k_{\mathrm{B}}T$ and comes out to be between 10^2 and 10^3 m/s. The dimensions that we took in the previous section for an elementary resistor (5 nm $\times$ 5 nm $\times$ 5nm) are also

realistic for a membrane protein. Whenever an ion, on its trajectory on the membrane, crosses over such a protein, the protein feels a delta function-like electric pulse. Given the 3 ions per square micrometer and the speed of these ions, the noise intensity that a membrane protein is subjected to due to the membrane-parallel random trajectories can be evaluated [17]. This noise comes out be be many orders of magnitude larger that the noise intensity due to the membrane transverse penetrations.

Early in this section we noticed that the random membrane penetrations, *i.e.* 2-sided shot noise instead of JN noise, brings us back to the same old Nyquist formula and the ensuing WA estimate. It is tempting to hypothesize that the membrane parallel trajectories are equivalent to the intramembrane noise that we discussed in the previous section in the context of JN resistors. The numbers appear to correspond. But a rigorous proof to that effect is not available.

5. A criterion for possible physiological effects

In this section we again start out with stepping back and reexamining the basic premises of what we have done. In the previous two sections we evaluated the strength of equilibrium noise and compared it against the strength of an ELF field. Ultimately this may be like comparing apples and oranges. An external field can do work. That is how an electromotor works. Equilibrium noise cannot do work. A rock at the bottom of a lake cannot take the energy from Brownian motion of water molecules and propel itself out of the water as the lake cools down. The Second Law of Thermodynamics does not allow it.

To clarify these matters further, consider the example in Fig. 2. A transporter enzyme is able to take a molecule S and carry it to the other side of the membrane. We can imagine the transport cycle as a two step process. As the enzyme goes from state E to state E^*S, it picks up an S. As it drops off the molecule S, it goes back to E. A cycle with net transport occurs when the pick-up and the drop-off are on different sides of the membrane. With the reaction $S_{in} \rightleftharpoons S_{out}$ at equilibrium, no energy input into the enzyme, a zero transmembrane voltage, and the two baths on either side of the membrane being of identical composition, there will be no net transport. This is most easily concluded by invoking the so-called Principle of Detailed Balance. This principle is a consequence of the Second Law of Thermodynamics [21,22] and states: *No system in thermal equilibrium in an environment at constant temperature spontaneously and of itself arrives in such a condition that any of the processes taking place in the system by which energy may be extracted, run in a preferred direction, without a compensating reverse process.* In the context of Fig. 2(b), Detailed Balance asserts

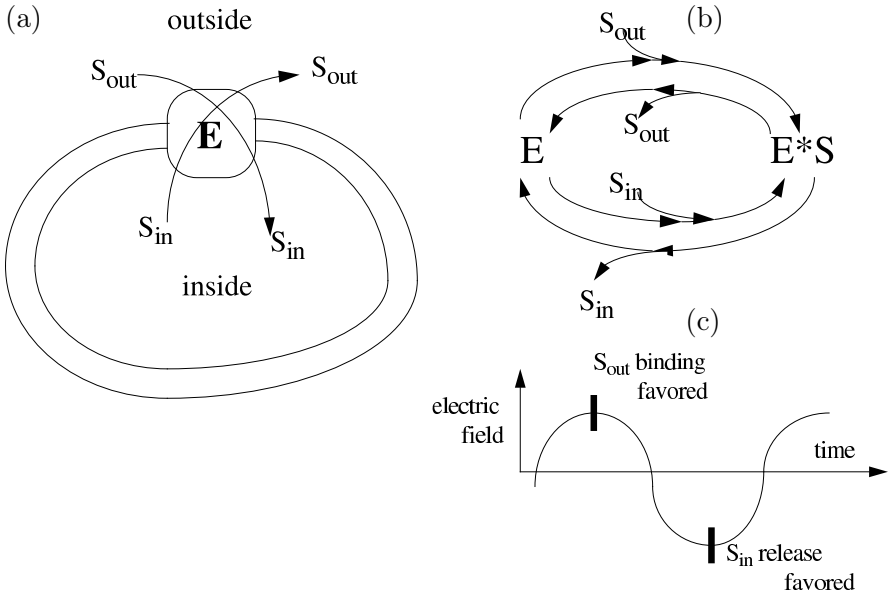

Fig. 2. An enzyme E operates as a transmembrane carrier for a molecule S (a). No net transport occurs when concentrations of S are the same on each side. In the context of the kinetic scheme in (b), this means equal traffic along the top two transitions (S_{out} binding and S_{out} release) and equal traffic along the bottom two transitions (S_{in} binding and S_{in} release). With an imposed AC electric field (c) it is possible to modulate energy levels such that net cycling in (b) can occur. Such net cycling results in net crossmembrane transport of S.

that, for both the S_{out} reaction and the S_{in} reaction, the forward and the backward arrow will carry an equal amount of traffic. So, on average, no net cycling and no ensuing net transport of S will occur.

It is possible to drive transport of S by subjecting the transporter to a zero-average, oscillating or fluctuating electric field. If E, E*S, and the transition states have different dipoles, than the energy levels of these states, and thus the transition rates between these states will vary as the field varies. Imagine a situation where a positive-direction electric field (see Fig. 2(c)) lowers the energy level of E*S and the energy level of the transition state for S binding on the outside. Next an electric field in the negative direction lowers the energy level of E and the energy level of the activation barrier for S release on the inside. The oscillation in time as depicted in Fig. 2(c) will entrain the chemical kinetics and bring about a net cycling in the clockwise direction in Fig. 2(b). Such cycling will result in net transport of S. This AC powering has actually been shown to work for Na,K-ATPase. Under

physiological conditions Na,K-ATPase takes its energy from the hydrolysis of ATP (adenosine triphosphate) and uses that energy to pump three sodium ions to outside the cell and bring two potassium ions to inside the cell [23]. *In vivo* the reaction ATP $\rightarrow$ ADP + P (where ADP stands for adenosine diphosphate and P represents an inorganic phosphate) releases about 22 $k_{\mathrm{B}}T$ units of energy. In the absence of an ATP–ADP chemical gradient, but subjected to an oscillating electric field, this ion pump has been shown to operate [24]. Straightforward chemical kinetics is able to accurately account for the frequency dependence of the transport rate [25].

At equilibrium there will be no net cycling *on average*. However, the transitions are random events. If there are N transitions between E and $\mathrm{E}^*\mathrm{S}$, then there will be an average number of net cycles that is proportional to $\sqrt{N}$. This is for the same reason that after N coin tosses, there is an average difference between the number of heads and the number of tails that is proportional to $\sqrt{N}$. Technically, it is only in the thermodynamic limit, *i.e.* $N \rightarrow \infty$, that $\sqrt{N}$ becomes negligible relative to N and that Detailed Balance applies. So as time evolves, ($\mathrm{S_{in}}$–$\mathrm{S_{out}}$) performs a random walk. At equilibrium and in the course of a time t, a net number of S molecules of $\Delta \mathrm{S_{eq}} \propto \sqrt{t}$ is thus carried across the membrane. This is like a diffusive effect, as also for a diffusing particle we find an average displacement due to diffusion that is proportional to $\sqrt{t}$ [20]. The AC field induced transport that we discussed in the previous paragraph is obviously proportional to t, *i.e.* $\Delta \mathrm{S_{AC}} \propto t$.

It is obvious that at $t \rightarrow 0$, we have $\Delta S_{\mathrm{eq}} \gg \Delta S_{\mathrm{AC}}$ and diffusive effects that overwhelm the AC pumping. However, there will always come a time $t = t_*$ at which $\Delta \mathrm{S_{eq}} = \Delta \mathrm{S_{AC}}$. Only when $t > t_*$ will the pumping effect start to "stick out" above the diffusive effects and will it, in principle, become detectable. A common approach has been to take the power in an ELF signal and compare it to the power of the equilibrium membrane electric noise in a certain bandwidth around that ELF frequency. But, as was mentioned at the beginning of this section, this is not a meaningful comparison since the power in equilibrium noise, unlike, the power in an ELF signal, is not able to do work. A better criterion is the time t_* after which *detectable molecular change* can occur [26]. It is only for $t > t_*$ that an ELF signal can have a physiological effect. I am aware of only one instance in the literature where a t_* has been estimated: in 1995 Astumian, Weaver, and Adair derived a nice and simple formula for the relation between t_* and the external field. It is easy to check that according to their formulae measurable effects of 10 kV/m ELF exposure will arise at time scales larger than a human life span [27].

6. Nonequilibrium noise

Detailed Balance is obviously broken when an external source radiates an ELF signal into an organism. There is, after all, no feedback from the organism back to the ELF source. So the source brings energy into the organism. Inside the organism this energy is, subsequently, partly converted and partly dissipated.

Imagine that, in the close proximity of the enzyme E that we discussed in the previous section, there is another enzyme E′. Imagine next that E′ is changing its dipole as it is going through its ATP driven catalytic cycle. The flipping dipole will create a fluctuating electric field around E′. The enzyme E will "feel" this fluctuating field. The fluctuating electric field can, in principle, drive transport cycles in the enzyme E.

The situation with the enzymes E and E′ is similar to the one with an external ELF source. Detailed Balance is obviously broken when E′ is driven through its catalytic cycle by the hydrolysis of ATP. Eventually, the chemical energy in ATP is, via the nonequilibrium fluctuations that constitute the signal from E′ to E, partly converted into a chemical potential between S_{in} and S_{out}.

When describing equilibrium noise, the analysis is greatly aided by the Equipartition Theorem and by Detailed Balance. The analysis of nonequilibrium noise is much harder. *In vivo*, an enzyme like the one in Fig. 2 is subject to many nonequilibrium fluctuations. Not just fluctuating electric fields, but also incoming light, temperature variations in space and in time [28], nonequilibrium fluctuations in space and in time of concentrations of chemicals, *etc.* can do work on the enzyme E and can, in principle, drive transport of S.

Living systems operate far from equilibrium and many energy conversions are taking place all the time. The organized maintenance of the far-from-equilibrium condition and the continuous transduction and dissipation of energy are some of the main characteristics of being "alive". Enzymes are the most prominent conduits for this dissipation and conversion of energy.

A complete accounting of all the energy transduction in a cell and the ensuing nonequilibrium noise is beyond our present means. However, the driven transmembrane electric currents [29] and the associated noise [30,31] have been measured. This is a part of the nonequilibrium picture that we can actually quantitatively assess.

We saw earlier that the transmembrane voltage fluctuations due to 2-sided shot noise at equilibrium were given by Eq. (2). This leads to a current power spectral density of $S_I^{\mathrm{eq}} = 4k_{\mathrm{B}}T/R$ [32]. The current power spectral density gives the mean square current per unit of bandwidth (*i.e.* Hz). The noise power in a certain frequency window is obtained by mul-

tiplying the power spectral density with the resistance and integrating over the frequency window. The intensity of equilibrium noise is generally taken to be frequency independent. This "white noise" assumption is reasonable when working in a sub-MHz regime [17, 32]. The flat frequency spectrum makes for a straightforward and easy analysis of equilibrium noise.

The nonequilibrium noise that "streams" from E′ to E is able to do work just like an external ELF signal can do work. Therefore the comparison between the power spectral density of nonequilibrium noise and the power of an ELF signal is actually fair and meaningful.

We will not look at the intramembrane noise. We will simply, as in the WA model, look at the electric fluctuations between the reservoirs on either side of the membrane. In previous sections we studied the equilibrium fluctuations. Below we will evaluate the nonequilibrium fluctuations.

For a living cell there is a continuous cycling of ions across the membrane. For each type of ion at steady state the same current I goes in-to-out as well as out-to-in (see Fig. 3). Pumps drive ions through the membrane against the electrochemical gradient. This active transport requires energy and is commonly powered by the hydrolysis of ATP. Ion channels allow ions to flow with the electrochemical gradient.

Pumps transport ions one-by-one. When the actual membrane passage time of an ion is negligible compared to the time between subsequent passages, we can think of these passages as delta function-like pulses. We then

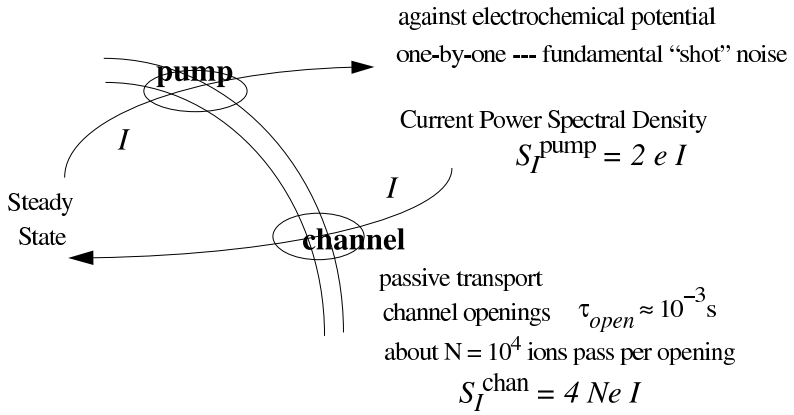

Fig. 3. A living cell maintains electric currents across its membrane. Pumps drive ions against the electrochemical potential and channels let ions flow back. Transport through pumps is active and one-by-one. Channels let about 10^4 ions pass during an average channel opening. The randomness of the channel openings is the main contributor to nonequilibrium noise.

face ordinary shot noise. The noise is white and the current power spectral density is easily evaluated as $S_I^{\text{pump}} = 2eI$ [32]. Here I represents the current referred to in the last paragraph and e is the elementary charge.

For a channel the equivalent of the pump's elementary charge is the amount of charge that passes during a channel opening. For a sodium channel, for instance, the average channel open time is about $\tau_{\text{open}} = 10^{-3}$ s. The current that flows during an average channel opening is of picoampere magnitude. A picoampere current corresponds to about 10^7 elementary charges per second. So during an average channel opening about $N = 10^4$ ions flow. We thus find $S_I^{\text{chan}} \approx 4NeI$ for the current power spectral density due to channel activity. There is a prefactor 4 instead of a prefactor 2 because the open time of a millisecond is an average of an exponential distribution. The extra stochasticity about doubles the current power spectral density [33]. It is obvious that the channel noise is larger than the pump noise by a factor of about ten thousand. This is basically because pumps transport charge in larger units. So we have $S^{\text{noneq}} \approx S^{\text{chan}}$.

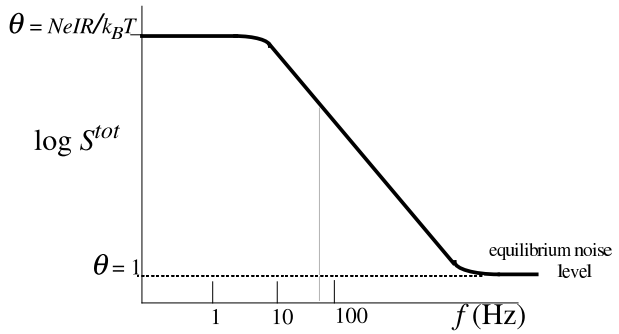

Fig. 4. The measured power spectral density of noise across a cell membrane behaves like $1/f$ between about 10 Hz and about 10^4 Hz. Above 10^4 Hz the level of the white equilibrium noise starts to exceed the nonequilibrium noise. The measured plateau where f is smaller than about 10 Hz corresponds well with our estimate from Eq. (3). At the power frequencies the nonequilibrium noise is about 100 times as intense as the equilibrium noise.

$S_I^{\text{noneq}} \approx 4NeI$ is a valid approximation as long as one looks at frequencies smaller than the channel's inverse average open time. At frequencies higher than $1/\tau_{\text{open}}$, the correlations on timescales shorter than τ_{open} make for a smaller noise amplitude. When one type of channel is involved, the eventual spectrum $S_I^{\text{noneq}}(\omega)$ is a sigmoid; a so-called Lorentzian spectrum that drops down from $4NeI$ to zero at about $\omega = 1/\tau_{\text{open}}$.

The power spectral density of actual cell membranes was first recorded in the 1960s by Verveen and Derksen [30, 34]. More accuarate recordings

have been made since [31]. Fig. 3 depicts the general shape of such spectra. The plateau that runs from zero Hz to somewhere between 1 and 10 Hz represents the level $S_I^{\mathrm{noneq}} \approx 4NeI$ that we just calculated. Verveen and Derksen already noticed that this level was many times larger than what just equilibrium noise would predict. For the dimensionless ratio between nonequilibrium and equilibrium noise we derive

$$\theta = \frac{S^{\mathrm{noneq}}}{S^{\mathrm{eq}}} \approx \frac{4NeI}{4k_{\mathrm{B}}T/R} = N\frac{e}{k_{\mathrm{B}}T}IR\,. \tag{3}$$

For the current power spectral density of the equilibrium noise we ignore the intramembrane noise and took the WA estimate. Substituting realistic values for the resistance of a cell membrane (about 10^3 $\Omega\mathrm{cm}^2$, see, for instance, page 254 of [35]) and transmembrane currents (10 $\mu\mathrm{A/cm}^2$, [29]) we find for θ a value of about 1000. To the right of the plateau the power spectral density drops off roughly like $1/\omega$. The apparent $1/f$-noise can be explained by the fact that, in a real cell membrane, there are many types of channels with different τ_{open}'s and different ensuing values of N. The $1/f$ pattern can thus emerge as a superposition of a number of Lorentzians. It has been argued that channels may exhibit $1/f$ noise in and of themselves [36], but these ideas are still controversial.

At the power frequency we still have a ratio $S^{\mathrm{noneq}}/S^{\mathrm{eq}}$ of about one hundred. Experimental observations affirm this [30,31]. As the S^{eq} according to the WA model already overwhelms the possible response to a 10 kV/m signal from a power line, including the nonequilibrium noise in the description only renders ambient ELF radiation more inconsequential.

7. Conclusions and discussion

The very end of this paper is an appropriate place to again step back and reconsider the basic premises and the results. As was shown with the E–E*S example and its interaction with the enzyme E′, nonequilibrium noise can be an agent in the conversion of energy. So some nonequilibrium noise may not just be noise, but actually a signal. This is most obvious with a signal going through a nerve cell. In that case a signal propagates as the opening of sodium channels triggers the opening of nearby sodium channels. These channel openings are regulated and no longer random; they no longer constitute noise, but, instead, make up a signal that moves information. Much of what we take for nonequilibrium noise may therefore actually be signal. It would be wrong to take all of the S^{chan} that we evaluated and put it in the denominator of a signal-to-noise ratio. With nonequilibrium noise in living systems we face a gray area between signal and noise.

For living systems there is evolutionary pressure towards sensitive and efficient signal detection. Sharks, skates, and rays, for instance, are able to detect microvolt-per-meter magnitude electric fields in seawater. Picking up such fields is easier in seawater than it is in air as the attenuation ratio of Eq. (1) becomes about one. Sharks, skates, and rays use their electric sense to pinpoint their prey when they move in closely and smell becomes inaccurate. The electric field-sensing organs have been thoroughly researched [37–41] and it appears that the equilibrium $k_{\mathrm{B}}T$-limit accounts for the noise in signal-to-noise ratios. Nonequilibrium contributions to the noise have apparently been almost eliminated in this case. One should realize, however, that these electric field-sensing organs are highly specialized multicellular structures that have evolved over hundreds of millions of years in response to conditions that existed for hundreds of millions of years. ELF radiation, on the other hand, is a fairly new phenomenon in the environment. There is, furthermore, no obvious selective advantage for an organism in picking up such fields and, even if it were so, specialized detection structures are unlikely to evolve in just decades.

All in all, from a biophysical perspective it seems very unlikely that any land based organism could pick up the electric component of a 10 kV/m ELF field. Noise levels appear prohibitively large.

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