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Can free energy be transduced from electric noise?

(free energy transduction/bioelectrochemistry/noise/localized chemiosmotic coupling/active transport)

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ABSTRACT **Recently, it was shown that free energy can be transduced from a regularly oscillating electric field to do chemical or transport work when coupled through an enzyme with appropriate electrical characteristics. Here we report that randomly pulsed electric fields can also lead to work being done, giving rise to speculation as to whether appropriately designed enzymes can extract and convert free energy from the inherent fluctuations in their environment. The paradox is resolved by showing that equilibrium electrical noise resulting from the environment around an enzyme cannot be completely random but is correlated to the state that the enzyme is in. If the noise has the appropriate reciprocal interaction with the enzyme, its potential to serve as a free-energy source disappears. This is shown by Monte Carlo and other numerical calculations and is proven analytically by use of the diagram method. This method also is used to provide an explicit equation showing that, under a range of conditions, our model enzyme will be induced by uncorrelated ("autonomous") noise to undergo net cyclic flux. That work can be transduced from the "random" noise is demonstrated by using numerical methods.**

Recently, it was demonstrated (1, 2) that an oscillating electric field is competent to do chemical work when coupled through an enzyme with differences in macroscopic polarization and basic free energy between its conformational states. These results might well account for the observation that the Na^+/K^+-ATPase mediates active transport when subjected to an oscillating electric field (1, 3, 4).

In vivo, fluctuating electric fields have been observed around cells (reviewed in ref. 5), and, certainly, large potential fluctuations must occur in the vicinity of ion channels upon opening or closing. This has been used (1, 6) as the basis for a model of ATP synthesis via the F_0/F_1-ATPase, in which coupling factor F_0 serves as a field-modulating channel, the opening and closing of which is linked to the binding and release of ligands in F_1. Also, it was suggested that the electric field around H^+-transporting ATPase in free energy-transducing membranes might oscillate because of turnover of neighboring electron-transfer chains, and that these oscillations might contain the free energy often missing in free energy balances (2).

In preliminary calculations, we found that totally random noise, when applied to the system described previously (1, 2), led to work being done. This result suggests that many (indeed most) forms of field fluctuations can do work. Yet we must realize that, in keeping with the laws of thermodynamics, internal noise arising in a system at equilibrium certainly cannot do work.

Although the effects of field fluctuations have been studied before for both noncyclic (7) and cyclic (8) systems, our results demonstrate that energy can be transduced from a randomly fluctuating field, allowing an enzyme to do work. In a subsequent paper (9), the general asymmetry requirements for a four-state enzyme to work will be studied in greater detail.

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MODEL AND CALCULATIONS

The four-state cycle in Fig. 1*A* describes an enzyme that catalyzes the translocation of substance S across the membrane where states 1 and 2 have the S binding site on the right-hand side (see figure 2 of ref. 2). The electrically important feature is that the transitions $1 \rightarrow 4$ and $3 \rightarrow 2$ involve the movement of a negatively charged arm of the protein across the membrane. Since S is uncharged, any interaction between a transmembrane electric field and the driven active transport is mediated solely by the protein.

In the present work, we shall consider what happens to the system (to be called "translocator") of Fig. 1*A* when it is subjected to random fluctuations in the transmembrane electric field. This can be done from two points of view. The first is where the fluctuation amplitude and/or mean relaxation time is assigned randomly, and the resulting set of differential equations is integrated as in ref. 2, with the procedure being repeated many times to obtain the net cyclic flux. The other possibility relies on the combination of the system of Fig. 1*A* with an intrinsic field generator, G^- {e.g., a charged carrier molecule that can go back and forth between the two sides [left (G_l^-) or right (G_r^-)] of the membrane independent of the translocator enzyme E^-}, such as that shown in Fig. 1*B*.

For the computations we shall use the same parameter values as in ref. 2, except that the field was allowed to fluctuate at random in the case of the calculation of the effect of an external field. The pseudo-unimolecular rate coefficients were:

$$\alpha_{12} = b;\ \alpha_{21} = 1/\rho;\ \alpha_{23} = b/\phi;\ \alpha_{32} = b^2\cdot\phi;$$

$$\alpha_{34} = b\cdot\rho;\ \alpha_{43} = 1;\ \alpha_{14} = b^2/\phi;\ \alpha_{41} = b\cdot\phi. \qquad [1]$$

ρ^2 is the concentration ratio of S across the membrane; ϕ is the potential-dependent factor, $\phi = \exp[F\Delta\psi/(2RT)]$, in the rate coefficients; and b is the "bias" factor that defines the system asymmetry (ref. 2; for other possibilities, see ref. 9). Unless stated otherwise, $b = 500$, $\phi = 16$ ($\Delta\psi = 143$ mV), and $\rho = 0.13$ [output free energy, $\Delta G_{out} = 10$ kJ/mol (2)].

We considered three cases. The first had the electric field alternate between 120 mV and −120 mV such that the duration of each phase was random. By using the method of ref. 2, the differential equations describing the system over a period t, where t was obtained with a random-number generator, were integrated analytically. The sign of the field was then inverted, and the procedure was repeated. This process was done a number (typically 50) of times, and the net

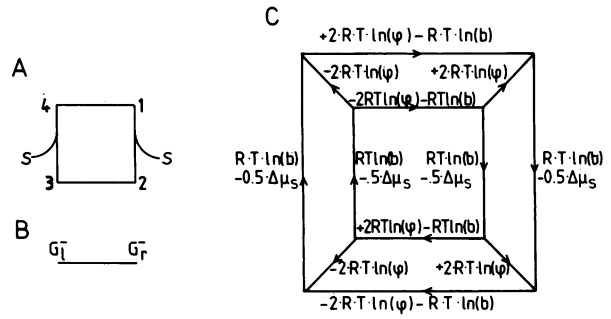

FIG. 1. Diagrams for the enzyme cycles discussed. (*A*) Cyclic diagram for the translocating enzyme that catalyzes the equilibration of S across a membrane as defined by figure 2 of ref. 2. (*B*) A "generator" charge that can move back and forth within the membrane, the electric field of which influences the transitions of *A*. (*C*) Diagrammatic combination of *A* and *B*, where the outer (inner) box represents the case with the generator on the left (right), and the diagonal lines represent generator (*B*) transitions from left to right. The basic free energy decrease for "endogenous" noise is given for each transition in the direction of the arrow. Those for "autonomous" noise would be the same, but with the values for the diagonal transitions being zero.

number of direct transitions from state 1 to state 4 was obtained. The second case used an identical duration for consecutive fluctuations but made the magnitude of their electric potential, $\Delta\psi$, random. The distribution of these magnitudes was taken to be Gaussian around zero, with a standard deviation (σ) of 120 mV, as indicated. The $\Delta\psi$ values were determined from:

$$\text{erf}[\Delta\psi/(\sigma\sqrt{2})] = R, \qquad [2]$$

where R was a random number between 0 and 1, and erf is the standard error function (10). In the third case, both amplitude and duration were treated as random.

In the Monte Carlo calculations (11) of Table 1, we explicitly considered that the system could be in any of the four states of Fig. 1*A* when G^- was on either the left or right. Transition probabilities were assigned to the individual steps, where $\Delta\psi$ (and hence ϕ) was determined by the location of G^-. For transitions with G^- on the left, the rate constants were assigned according to Eq. 1, and with G^- on the right, the rate constants were taken to be the same but with each ϕ exchanged for $1/\phi$. For the case of an "autonomous" noise generator, $\alpha_{il,ir}$ and $\alpha_{ir,il}$ (for i = 1, 2, 3, and 4) can be considered equal to k, which was assumed to be independent of the translocator state. For the case of the "endogenous" noise generator, the transition probabilities were taken to be subject to reciprocal electrical interactions—i.e., $\alpha_{1r,1l} = \alpha_{2r,2l} = \alpha_{3l,3r} = \alpha_{4l,4r} = k\phi$; and $\alpha_{1l,1r} = \alpha_{2l,2r} = \alpha_{3r,3l} = \alpha_{4r,4l} = k/\phi$. The standard magnitude for k was taken to be 7.407.

The steady-state flux, J_κ, around any cycle, as well as the individual state probabilities, for a diagram such as shown in Fig. 1*C*, can be evaluated by the diagram method (12–14):

$$J_\kappa = N\Pi_\kappa\text{-}[\exp(X_\kappa/RT) - 1]\Sigma_\kappa/\Sigma, \qquad [3]$$

where the symbols take on the meanings given in ref. 12. X_κ, the thermodynamic force around any cycle, κ, at steady state, is:

$$X_\kappa = RT\ln(\Pi_{\kappa^+}/\Pi_{\kappa^-}). \qquad [4]$$

In the matrix inversion method, we used the conservation condition that the sum of all probabilities must be equal to 1 to reduce the eight equations to seven linearly independent ones, wrote them in matrix form, and solved for the steady-state probabilities by matrix inversion (see ref. 2). Matrix inversion was also the method by which we obtained the fluxes for a 16-state diagram resulting from the combination of an S translocator with a translocator for a substance P.

RESULTS

Randomly Fluctuating Electric Fields Can Drive an Enzyme to Do Work. If the overall lifetimes for the positive and negative periods of a transmembrane electric field were random, the switching from positive to negative might be a Poisson process (it would be if the switch consisted of the

Table 1. Performance of the system depicted in Fig. 1*A* with the generator charge (Fig. 1*B*) as an autonomous or endogenous fluctuator

	Standard case		Level flow		
	Autonomous	Endogenous	Autonomous	Endogenous	SD
Net 4 to 1 transitions					
Number	1258.0	−1943.0	5842.0	57.0	28.0
Rate	2.04	−0.50	3.29	0.007	0.004
Generator transitions					
Number	2215.0	3550.0	6485.0	3588.0	21.0
Rate	3.59	0.92	3.65	0.459	0.004
Total time*	617.0	3872.0	1776.0	7814.0	43.0
P_{1l}	0.012	0.003	0.008	0.001	0.000
P_{2l}	0.448	0.284	0.471	0.488	0.003
P_{3l}	0.000	0.000	0.000	0.000	0.000
P_{4l}	0.024	0.006	0.015	0.002	0.000
P_{1r}	0.000	0.000	0.000	0.000	0.000
P_{2r}	0.073	0.005	0.015	0.002	0.000
P_{3r}	0.037	0.003	0.008	0.001	0.000
P_{4r}	0.406	0.698	0.483	0.506	0.008
$P_{1r} + P_{2r} + P_{3r} + P_{4r}$	0.516	0.706	0.506	0.509	0.003

Data are from the Monte Carlo calculations. One million iterations were performed using the standard parameter values, b = 500, ϕ = 16, and ρ = 0.13 (except that ρ = 1 was used in the level flow case.) The sixth column gives the standard deviation (i.e., the square root of the variance estimated from 17 calculations) for the values in the fifth column. P_i represents the probability to find the system in state i; $P_{1r} + P_{2r} + P_{3r} + P_{4r}$ is the probability of finding the negative generator charge on the right (see Fig. 1).

*Total time is relative (in arbitrary units).

autonomous translocation of a charge between symmetrically positioned sites) (15) constituting random telegraph noise. Another possible form of random electric noise could occur if the fluctuation lifetime were constant, with the amplitude distributed around zero according to a Gaussian distribution [a so-called Wiener process (15)]. Also, these two could be combined, providing for both random lifetimes and random amplitudes. In sample calculations for these three cases, the net number of $1 \rightarrow 4$ transitions exceeded unity after a few iterations (Fig. 2), showing that work had been done. Our noise distributions were all Lorentzian, as opposed to white noise, which would be featureless. However, biologically relevant noise tends to be Lorentzian rather than white (17).

Consistency with the Second Law of Thermodynamics. Up to this point we have considered externally defined, randomly oscillating electric fields and have shown that these can be used as a source of free energy. Since apparently random, oscillating local fields can be generated by a system at equilibrium, this may seem to indicate that free energy could be harvested from an equilibrium system through electrical noise. This would amount to a *perpetuum mobile* of the second kind and would be in conflict with the second law of thermodynamics.

We therefore questioned whether the random noise used in our calculation is indeed characteristic for the noise generated by an equilibrium system in the vicinity of the enzyme. For this purpose we considered an electric charge that may oscillate between two binding sites on different sides of the membrane in the vicinity of the translocator (see Fig. 1*B*). We first supposed that the transition probabilities for this charge would be independent of any influence. Thus, this charge would be an autonomous generator of a fluctuating electric field. The transition probabilities of the translocator were taken to depend on the electric potential generated by the generator charge in the same manner as they had been taken to depend on the transmembrane electric potential in the earlier calculations. The second column in Table 1 gives the result of a Monte Carlo calculation for such "autonomous" noise in the presence of a 59-fold concentration ratio of the neutral substance S, highest on the inside, across the membrane. Again, in this case there are many net transitions in the clockwise direction, implying uphill transport of S and, hence, free energy transduction from the fluctuating electric field (as generated by the single generator charge) to the chemical potential difference of S. Thus, even this type of noisy field must contain some free energy and cannot be characteristic for an equilibrium system in the vicinity of the translocator.

What then is unrealistic about our electric charge that, by fluctuating between its two binding sites, generates an oscillating electric field? Up to this point we have left out of consideration that the translocator, in order to be influenced by the generator, must carry electric charge and, hence, must itself generate an electric field. Coulomb's law is reciprocal (18); therefore, one should expect a reciprocal interaction between translocator and generator. Thus, in a second set of Monte Carlo calculations, we made the transition rate constants of the generator charge dependent on the electric potential generated by the translocator and, thus, on the state the translocator was in. As a consequence, the rate constants for the transition from state 1l to state 1r (and 2l to 2r) differed by the factor $\exp[F\Delta\psi/(RT)]$ from the transition rate constant between states 4l and 4r (and 3l to 3r), where 1, 2, 3, and 4 refer to states of the translocator (Fig. 1*A*) and l and r to states of the generator. When the calculations were repeated in this manner, no thermodynamically uphill transport of S was found (column 3 of Table 1). Instead the transition number was negative—i.e., the cycle was driven counterclockwise towards equilibrium by the gradient of S.

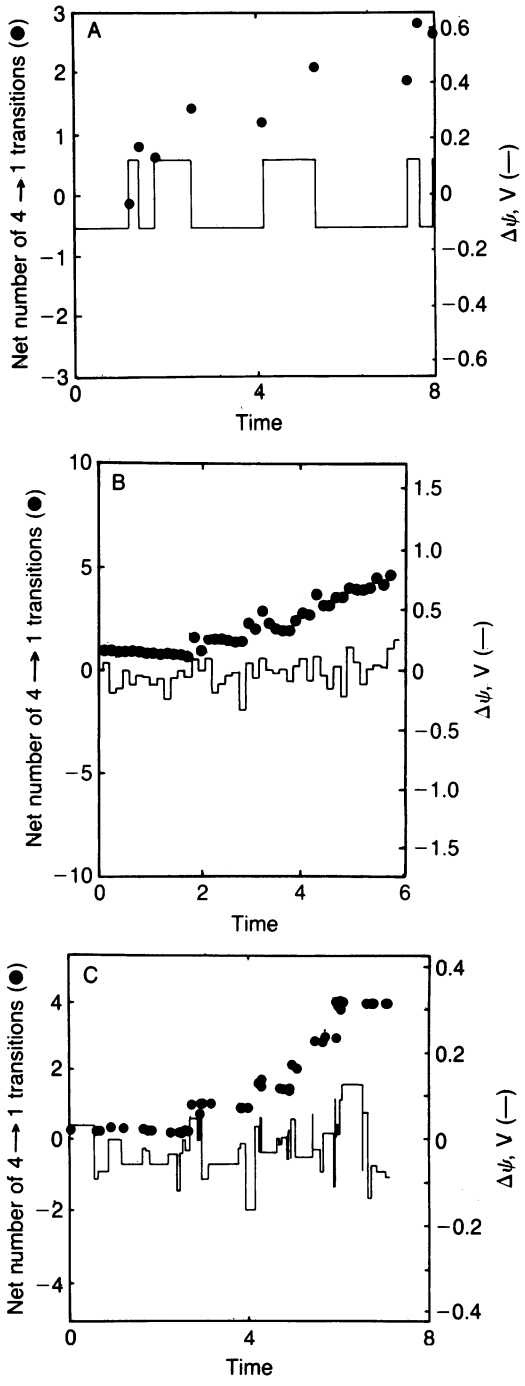

FIG. 2. Results of computations showing that random noise can do work ($b = 500$ and $\rho = 0.13$ for all cases). (*A*) The net number of direct $1 \rightarrow 4$ transitions induced by 120-mV or −120-mV electric pulses with random lifetimes given by $t = -\tau \cdot \ln(R)$ (16) in which R is a random number between 0 and 1 (17) and τ is the average relative lifetime (we used $\tau = 0.135$). (*B*) The net number of direct $1 \rightarrow 4$ transitions induced by random-amplitude electric pulses of constant-fluctuation lifetime (1/7.4 unit of time). The random amplitudes were assigned according to $\text{erf}[\Delta\psi/(\sigma\sqrt{2})] = R$, in which erf is the standard error function (13), σ is an assigned standard deviation, and R is a random number between 0 and 1. We used $\sigma = 120$ mV. (*C*) Case with both random time ($\tau = 0.135$) and amplitude ($\sigma = 60$ mV). Once again, >1 net transitions ($1 \rightarrow 4$) show that work has been done.

The bottom elements of columns 2 and 3 in Table 1 allow us to compare the distribution of the generator charge over its two states in the two types of calculations. In the case of the autonomous generator, the generator was equally distributed over its two binding sites, but in the calculation for the

endogenous fluctuations (column 3 in Table 1), the distribution of the generator charge turned out to be strongly affected by the translocator (i.e., $\Sigma_{i=1}^{4} P_{il} \neq \Sigma_{i=1}^{4} P_{ir}$, where P_i is the probability of finding the system in state i). Thus, we see that, in the endogenous noise system, the equilibrium fluctuations in the electric field generated by this charge are strongly influenced by the translocator and that the noise then is not random but is biased according to the translocator state.

Analytical Demonstration That Endogenous Noise Cannot and Autonomous Noise May Drive the Translocator into Doing Work. In the Monte Carlo calculations, we considered the generator charge and the translocator as separate elements. Thus, the system could be either in one of the four states with G^- on the left or in one of those with G^- on the right. Possible transitions were those of the translocator with G^- stationary or those between G_l^- and G_r^- with the translocator stationary. Fig. 1*C*, where the outer square corresponds to the case with the generator on the left and the inner square to that with G^- on the right, contains precisely the same transitions. Using this diagram, for the cases of Table 1, Monte Carlo and matrix inversion calculations yielded the same results.

Our present interest lies in understanding why random, autonomous noise may provide the free energy necessary for driving the translocator into doing transport work and why endogenous noise cannot. We have written down in Fig. 1*C* the basic free energy difference for each transition for the endogenous case. The driving force for any closed cycle is now obtained by summing the basic free energy differences along its branches. Performing this summation for any cycle describing transport with endogenous noise reveals that in no case is there a ϕ ($\Delta\psi$)-dependent cycle, and hence endogenous ("equilibrium") electrical noise can never perform work. The latter conclusion does not depend on the catalytic mechanisms (i.e., the diagrams) of the generator and the translocator and is independent of the magnitudes and signs of the charges.

In the case of autonomous noise, the diagonal terms $2RT\cdot\ln(\phi)$ in Fig. 1*C* are replaced with zeros. Consequently, eight cycles have ϕ-dependent driving forces: four have $4RT\ln(\phi)$, and four have $-4RT\ln(\phi)$. Thus, even though some cycles could have appreciable driving forces in the clockwise direction, other cycles could offset this, resulting in no transport, depending on the unnormalized cycle probabilities, Σ_κ. For the special case of $\Delta\mu_S = 0$ ($\rho = 1$), which represents the level flow case, we can obtain by appropriate algebraic manipulations a simple expression relating the total unnormalized net transport flux, $J_S\cdot\Sigma$, to ϕ and b (for other cases, equations are given in ref. 9):

$$J_S\cdot\Sigma/(b^5\cdot k^2) = (b-1)\cdot(\phi^2-\phi^{-2})^2\cdot[b\cdot(b+1) + 2\cdot(b+2k+1)/(\phi+\phi^{-1})], \quad [5]$$

where Σ, k, ϕ, and b are always positive. If $\phi \neq 1$, we find two possibilities for steady-state cycling. For $b = 1$, $J_S = 0$; and for $b \neq 1$, J_S must be nonzero. This equation proves analytically that autonomous noise can induce flux if $b \neq 1$ and $\rho = 1$. Of course when $\rho = 1$, there can be no free energy transduction (13). Our numerical calculations for $\rho \neq 1$ provide the proof that free energy transduction is possible for autonomous noise.

How Realistic Is Autonomous Noise? The above driving forces contain the terms $4RT\ln(\phi) = 2F\Delta\psi$. This implies that there must be a free energy source worth at least $2F\Delta\psi$ (14). In other words, some "external" reaction must drive the generator charge in order for it to respond autonomously relative to the electric influence of the translocator. One possibility for such a situation to exist would have our translocator located near a random, nonelectrically gated, ion-specific channel, across which a large ion electrochemical gradient had been established. Then every time the channel would open, the local potential would change, and upon closing, would be restored to its original value. Here, the required free energy would come from the movement of ions down their electrochemical gradient each time the channel would open.

Another possibility that we have investigated quantitatively is the case in which the fluctuations in the position of the generator charge were driven by the translocation of a substance, P, from the right-hand to the left-hand compartment (13, 14, 19). Fig. 3 shows how in this system the translocation rate of S would vary with the input free energy difference ($\Delta G_{in} = \Delta\mu_P$) for the "standard" 59-fold gradient of [S] (full line) and for the case of level flow (dashed line). In the former case, the fluctuations in the electric field caused by the activity of the translocator of P could drive the translocator of S to do uphill transport (i.e., positive J_S), provided that the gradient of P delivered sufficient free energy. For the case with $\Delta\mu_S = RT\ln(59) = 10$ kJ/mol (Fig. 3), the static head force ratio is >80%, even though we have considered here only Coulombic forces acting through the membrane as the "intermediate" in energy coupling between the translocation of S and the translocation of P. The ϕ value that was used in the calculation ($\phi = 16$) would be obtained if the charge on the P translocator were 10 Å from that on the S translocator when both were on the same side of the membrane (for an effective, relative dielectric constant of the membrane, $\varepsilon_r = 6$). Again, in the equilibrium case (endogenous noise), where there was not external free energy input ($\Delta G_{in} = \Delta\mu_P = 0$), no uphill transport of S was obtained.

DISCUSSION

Our results demonstrate that an enzyme can be made to cycle in a direction away from "equilibrium" by the input of energy in the form of random electric pulses. However, equilibrium noise cannot be used to do work, since in this case the probability of a local fluctuation of the "environment" would be intimately correlated to the immediate state of the enzyme in such a way that no net cyclic transitions would be

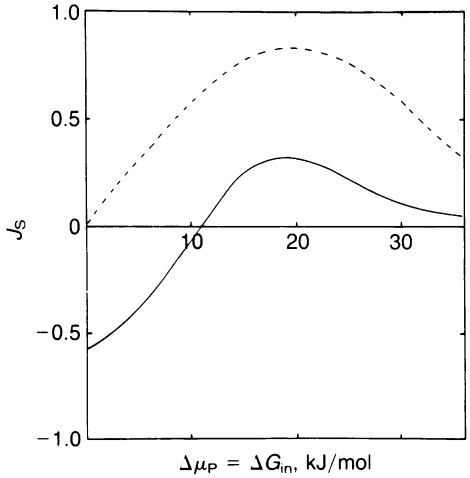

FIG. 3. The transport flux of S as a function of $\Delta\mu_P$ calculated for an S translocator coupled to a P translocator ($b = 500$; $\phi = 100$). The calculations were based solely on Coulombic coupling, where the electrical characteristics of both the S and P translocator were as shown in figure 2 of ref. 2. Two cases were considered. The first case ("level flow") was based on $\rho_S = 1$ ($\Delta\mu_S = 0$) (------). In the second case ("standard"), we held $\rho_S = 0.13$ ($\Delta\mu_S = \Delta G_{out} = 10$ kJ/mol (—). The static head force ratio, $\Delta G_{out}/\Delta G_{in}$, is seen to be >80%. The maximum efficiency was found to be ≈35%. In the case used, two univalent charges would be ≈10 Å apart when on the same side of the membrane (taking a relative dielectric constant of 6).

produced. Nonequilibrium "noise" can lead to free energy absorption and transduction. In this case, of course, there must be an ultimate, more classical source of the free energy. In Fig. 3 this was the transmembrane concentration gradient of P.

In accord with the previously mentioned optimal oscillation frequency with respect to transport or synthesis rate (1, 2), an optimal fluctuation lifetime was also demonstrated in the case of random electric pulses (9, 13, 14, 19). To enable an enzyme to absorb and transduce free energy from a fluctuating electric field, it is sufficient (for other possibilities, see ref. 9) that the enzyme exist in two different conformational states with different electric moments, allowing it to absorb energy from the field, and that there be a stability bias (we have used b to denote this) in the rate constants in favor of certain states (here states 2 and 4) (2). As discussed by Oosawa and Masai (8), an enzyme exposed to fluctuations, such as those of our autonomous generator, would display fluctuations asymmetric with respect to time reversal—i.e., the enzyme would apparently violate the principle of microscopic reversibility. We have resolved this paradox, showing why equilibrium noise would not be random and that true "random" noise contains free energy, thus leaving equilibrium microscopic reversibility inviolate.

That autonomous electric field noise (around an average of zero) could be shown to drive our translocator enzyme into doing work must reflect some nonlinear (and even an asymmetrical) response of the enzyme's turnover to variations in the electric field. The origin of this nonlinearity cannot solely be the exponential dependence of the rate constants on $\Delta\psi$ because a (construed) linear dependence allowed the translocator to be driven by an oscillating electric field (2). Rather it stems from the asymmetry in the basic free energies (12) of the four enzyme states. If factor b exceeds 1, states 4 and 2 are lower in basic free energy than are states 3 and 1 (Fig. 1). Consequently, at zero-field equilibrium, the former states are more densely populated than the latter. If, starting from this equilibrium, we would apply (*i*) an electric field from left to right and then (*ii*) the same field of opposite orientation for an equal, substantial period of time, net movement to the right in the upper branch [this net movement could be as great as $(P_4)_{eq,\Delta\psi=0} - (P_1)_{eq,\Delta\psi=0}$] and net movement to the left in the lower branch will occur. In ref. 9, other possibilities concerning the required kinetic asymmetry are discussed.

Since a macromolecule such as a protein can be treated as a thermodynamic system (for a discussion of the thermodynamics of small systems, see ref. 20 and references therein), an enzyme can be considered to be subject to asymmetric noise in any of its thermodynamic parameters. A nonequilibrium fluctuation in any of these is in principle sufficient to drive the system to do work.

The results and concepts presented here may account for observations of ATP synthesis by F_0/F_1-ATP synthase under circumstances where the apparent proton electrochemical gradient is either zero or very low (ref. 21; for reviews, see refs. 22–26). This has been briefly discussed by Westerhoff (25), even in the context of simultaneous local oscillations in $\Delta\psi$ and ΔpH such that $\Delta\mu_{H^+}$ is always zero. Also possible is a direct coupling between the F_0/F_1-ATPase and the cyclic electron transfer mediated by the electron-transfer chain (2, 13, 24, 25).

In summary, we have shown that random electric noise generated by a free energy-dissipating process can do work. We have tested many different forms of noise for this ability and found that, as long as the probability of the onset of a fluctuation is independent of the enzyme state, work is done. However, equilibrium noise is strongly state-dependent and consequently does not lead to work.

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