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The adenylate kinase reaction acts as a frequency filter towards fluctuations of ATP utilization in the cell

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The buffering ability of the adenylate kinase reaction with respect to the phosphate potential and the efficiency of oxidative phosphorylation in the presence of a fluctuating load conductance were studied by computer simulations. Fluctuations of the load conductance, i.e., of the irreversible ATP-utilizing reactions in the cell, were generated by integrating an Ornstein-Uhlenbeck diffusion process. This real or colored noise was then injected into the set of differential equations describing the rate laws for the changes of the adenine nucleotide concentrations based on a simple nonequilibrium thermodynamic model of oxidative phosphorylation. Numerical integration of this system of stochastic differential equations allowed us to investigate the influence of different parameters on the performance of this energy converter. Probability density estimates revealed that the variance of the efficiency about its optimal value was significantly reduced by the adenylate kinase reaction. It was found that the buffering ability of this enzyme is restricted to a specific frequency domain of the fluctuations of the load conductance. This frequency filtering was confirmed by substituting the random fluctuations of the load conductance by simple sinusoidal perturbations. All these studies revealed that for each domain of frequencies of the load perturbations there exists an optimal activity of the adenylate kinase which minimizes deviations from optimal efficiency of oxidative phosphorylation.

1. Introduction

Within the realm of nonequilibrium thermodynamics oxidative phosphorylation can be considered as an energy converter where input and output flows are defined by the linear phenomenological relations [1,2]:

$$J_p = L_p X_p + L_{po} X_o \quad (1)$$

$$J_o = L_{po} X_p + L_o X_o \quad (2)$$

where J_p and J_o are the net rate of ATP production and oxygen consumption, respectively. L_p, L_{po} and L_o are the phenomenological Onsager coefficients summarizing the overall kinetic properties of this process [3]. The forces involved in eqs. 1 and 2 are X_o, the redox potential of the oxidizable substrate, and X_p, the phosphate potential defined by $X_p = -(\Delta G_p^0 + RT \ln([ATP]/[ADP][P_i]))$. Experimental results revealed that within the physiological range of the forces oxidative phosphorylation can be adequately described by these relations [2].

This phenomenological treatment permitted specification of the conditions for optimal efficiency of oxidative phosphorylation. The system can be driven to operate at optimal efficiency when a load flow

$$J_l = L_l X_p \quad (3)$$

is attached to the output of the energy converter. A necessary and sufficient condition for the operation of oxidative phosphorylation requires then

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that the load conductance L_l, summarizing all irreversible ATP-utilizing reactions in the cell, be matched to L_p according to $L_l/L_p = \sqrt{1-q^2}$ [2]. Here q is the degree of coupling of oxidative phosphorylation which is a dimensionless normalized measure of the cross-coupling coefficient $q = L_{po}/\sqrt{L_p L_o}$ introduced by Kedem and Caplan [4].

Assuming that L_p and q are not subject to short-term regulation (see also ref. 5) the natural fluctuations of the load conductance as they occur in a living cell would constantly endanger conductance matching from being fulfilled and oxidative phosphorylation could hardly ever operate at optimal efficiency. As has been shown in earlier studies, reversible ATP-utilizing reactions such as that catalyzed by adenylate kinase can compensate for deviations from conductance matching and consequently reduce the lowering of the efficiency beyond its optimal value through thermodynamic buffering [6].

The aim of this study is to provide insight into the buffering effects of the adenylate kinase reaction in the presence of a fluctuating load conductance L_l. It is difficult to tackle this problem on an experimental basis, since there is still no technical possibility available to follow instantaneously the intracellular variations of the efficiency of oxidative phosphorylation in a fluctuating environment. Therefore, we have chosen to investigate this problem by computer simulations of a realistic model of oxidative phosphorylation with a fluctuating load conductance in the absence and presence of adenylate kinase. Statistical analyses of these simulations revealed that adenylate kinase acts as a frequency filter with respect to the random perturbations of the load conductance. This finding was further corroborated by considering purely sinusoidal fluctuations of L_l. These studies complement and extend the investigations of thermodynamic buffering by adenylate kinase published in previous work [6,7].

2. Modelling of oxidative phosphorylation plus the adenylate kinase reaction in a fluctuating environment

The main processes determining the concentrations of the adenine nucleotides and thus also of the phosphate potential are depicted in fig. 1. In addition to the flows J_p and J_l defined above, the adenylate kinase reaction represented by the phenomenological relation

$$J_a = L_a X_a \tag{4}$$

has to be included in this scheme. Here L_a is the phenomenological conductance of the adenylate kinase reaction, or, in other words, a constant which is proportional to the activity of the adenylate kinase. The driving force for this reaction is the adenylate kinase potential defined as $X_a = -(\Delta G_a^0 + RT \ln([ATP][AMP]/[ADP]^2))$. The rate laws for the adenine nucleotide concentrations are then given by

$$[\dot{A}TP] = J_p + J_l + J_a = (L_p + L_l) X_p + L_{po} X_o + L_a X_a \tag{5}$$

$$[\dot{A}DP] = -J_p - J_l - 2J_a = -(L_p + L_l) X_p - L_{po} X_p - 2L_a X_a \tag{6}$$

$$[\dot{A}MP] = J_a = L_a X_a \tag{7}$$

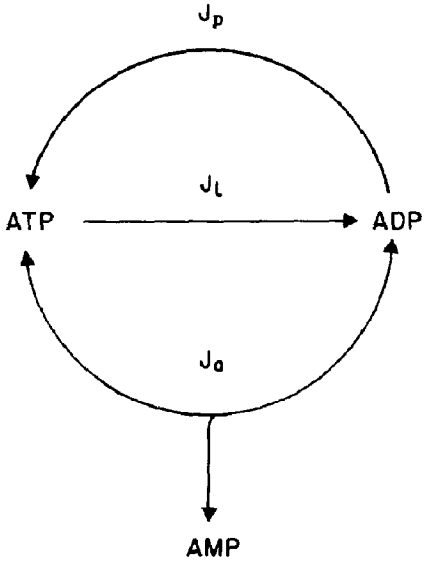

Fig. 1. Scheme of oxidative phosphorylation plus the adenylate kinase. This representation shows how the three different flows J_p (phosphorylation), J_l (load) and J_a (adenylate kinase reaction) affect the adenine nucleotide concentrations.

From these equations we note the conservation of the adenine nucleotides

$$[\dot{A}TP] + [\dot{A}DP] + [\dot{A}MP] = 0 \quad (8)$$

As shown earlier, these equations describe not only the steady-state situation of the system but also the transients from one state to another as was experimentally demonstrated with isolated mitochondria from rat liver [7]. These experiments therefore constitute the empirical justification for the validity of the linear relations between flows and forces assumed in eqs. 1–4. Thus, within the physiological range of the forces, the differential equations (eqs. 5–7) provide an adequate and realistic description of our system.

In a living cell, in contrast to mitochondrial incubations, L_1 can no longer be considered as a constant. In this study we have chosen to represent the time dependence of L_1 first as a stationary stochastic process

$$L_1 = L_1^m + \rho_t \quad (9)$$

where L_1^m is the value of the matched load conductance and a stationary colored or real noise ρ_t [8]. This noise can be interpreted as an Ornstein-Uhlenbeck process given by the Langevin equation of diffusion [9]

$$\dot{\rho}_t = -\gamma\rho_t + \sigma\xi_t \quad (10)$$

γ being the inverse correlation time of the noise and ξ_t a white noise with variance σ^2.

Hence, the time history of the colored noise can be calculated by integrating the associated Ito stochastic differential equation

$$d\rho_t = -\gamma\rho_t\, dt + \sigma\, dW_t \quad (11)$$

where W_t is the Wiener process, the derivative of which, in the sense of generalized functions, is white noise [10]. The process is normally distributed with $N(0,\sigma^2/2\gamma)$ and with covariance

$$E\rho_t\rho_s = \sigma^2/2\gamma \exp(-\gamma|t-s|) \quad (12)$$

where E denotes the mathematical expectation. This means that ρ_t is not delta-correlated and hence shows a frequency spectrum of a Lorentzian type which declines at higher frequencies [11]. It is important to note that this colored noise can be driven to the white noise limit by letting σ^2 and γ go to infinity with $\sigma^2/2\gamma = \text{constant}$. In other words, the frequency composition of the colored noise can be governed by manipulating the parameters γ and/or σ. This is illustrated in fig. 2 which depicts the time histories and the respective power spectral density estimates of the load conductance as defined in eq. 4 for colored noises with different correlation times. From this figure we note that the intensity of the high-frequency contributions is enhanced upon increasing γ, i.e., by choosing a shorter correlation time.

This fluctuating load conductance L_1 was then injected into the differential equations (eqs. 5–7) and, after a logarithmic transformation of the variables, these equations were numerically integrated with a fourth-order Runge-Kutta method with automatic step-size control [7]. Thus, the computer simulations of our model are realized by numerical integration of a set of nonlinear stochastic differential equations with parametric or multiplicative colored noise.

Note that such simulations may yield a probability density estimate of the adenine nucleotide concentrations and functions thereof, as for example X_p, by sampling the points of a trajectory over a very long time of integration. The basic assumption underlying such estimates is the validity of the ergodic hypothesis which states that the time average is identical to the ensemble average. It must be borne in mind, however, that probability density estimates based on an individual, albeit long, trajectory are always the result of a particular case with individual and specific initial conditions, sequence of random numbers, etc., and may, therefore, not reflect the true probability density. Another approach to this problem consists of solving a stationary Fokker-Planck equation which allows a direct calculation of the ensemble probability density [12]. In the light of the ergodic hypothesis, the solution of the Fokker-Planck equation is the dual problem to the long-term integration of an infinity of time integrations of the system. Unfortunately, the solution of the Fokker-Planck equation associated with our set of differential equations poses severe computational problems and is analytically not feasible, which may be taken as an illustration of the invariance

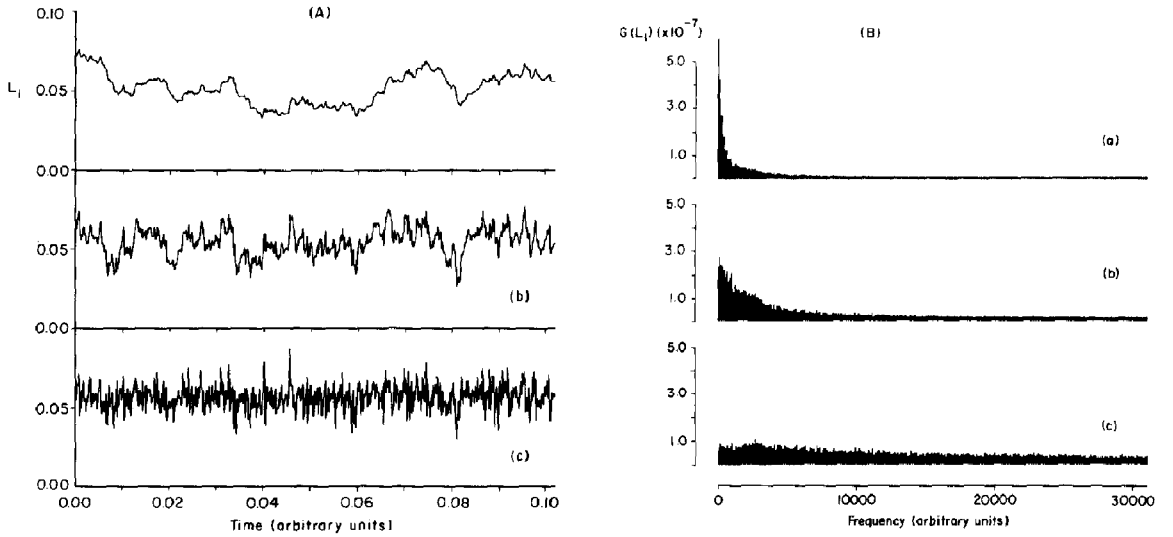

Fig. 2. Time histories of load conductance (A) and power spectra (B). Panels a–c depict the effect of different values of γ on fluctuations of the load conductance, viz., in frequency units: $\gamma = 100$ (a), $\gamma = 1000$ (b) and $\gamma = 10000$ (c). L_1 was calculated according to eq. 9 with a matched load conductance $L_1 = 0.0571$ and the initial value $\rho_\tau^0 = N(0,0.0001)$. ρ_τ was generated by numerical integration of eq. 10 at intervals of 0.0001 time units. Time and frequency are expressed in arbitrary units. For calculation of the power spectral power density estimates see fig. 5.

of the sum of difficulties. In fact, new numerical algorithms have to be sought to tackle this problem, an enterprise which is clearly beyond the scope of this paper.

3. Response of the system to random fluctuations of the load conductance

The response of oxidative phosphorylation plus the adenylate kinase reaction towards the fluctuating L_1 values was plotted on the adenylate kinase reaction simplex [7] in fig. 3. Here each point represents the state of the system's trajectories at a specific time. From this figure we observe that the frequency composition of the load conductance deeply influences the behaviour of the system. As γ increases, the adenine nucleotide concentrations tend to stay close to the state corresponding to optimal efficiency. This effect can be understood as a consequence of the inertia of the system with respect to rapid fluctuations of the load conductance since the adenine nucleotide pool itself acts as a buffer. In other words, due to its inherent kinetic inertia the system is blind towards very rapid fluctuations.

Increasing the activity of the adenylate kinase by increasing the conductance L_a contracts the trajectories near the loci corresponding to the thermodynamic equilibrium of the adenylate kinase reaction (fig. 3B). However, from this representation it is not clear how much the fluctuations of the adenine nucleotide concentrations are reduced by the adenylate kinase reaction.

To visualize the buffer effect of this enzyme more clearly we calculated the following functions of the adenine nucleotides: (1) the force ratio $x = ZX_p/X_o$ which is a measure of the phosphate potential normalized by the phenomenological stoichiometry $Z = \sqrt{L_p/L_o}$ [4] and (2) the efficiency $\eta = -J_p X_p / J_o X_o$. These functions allowed us to reduce the representation of the system's response towards a fluctuating load conductance to one dimension. Fig. 4 shows the probability density estimates of the force ratio and of the efficiency calculated with a noise with a short correlation time ($\gamma = 10000$). From this plot it is now evident that the dispersion of the values

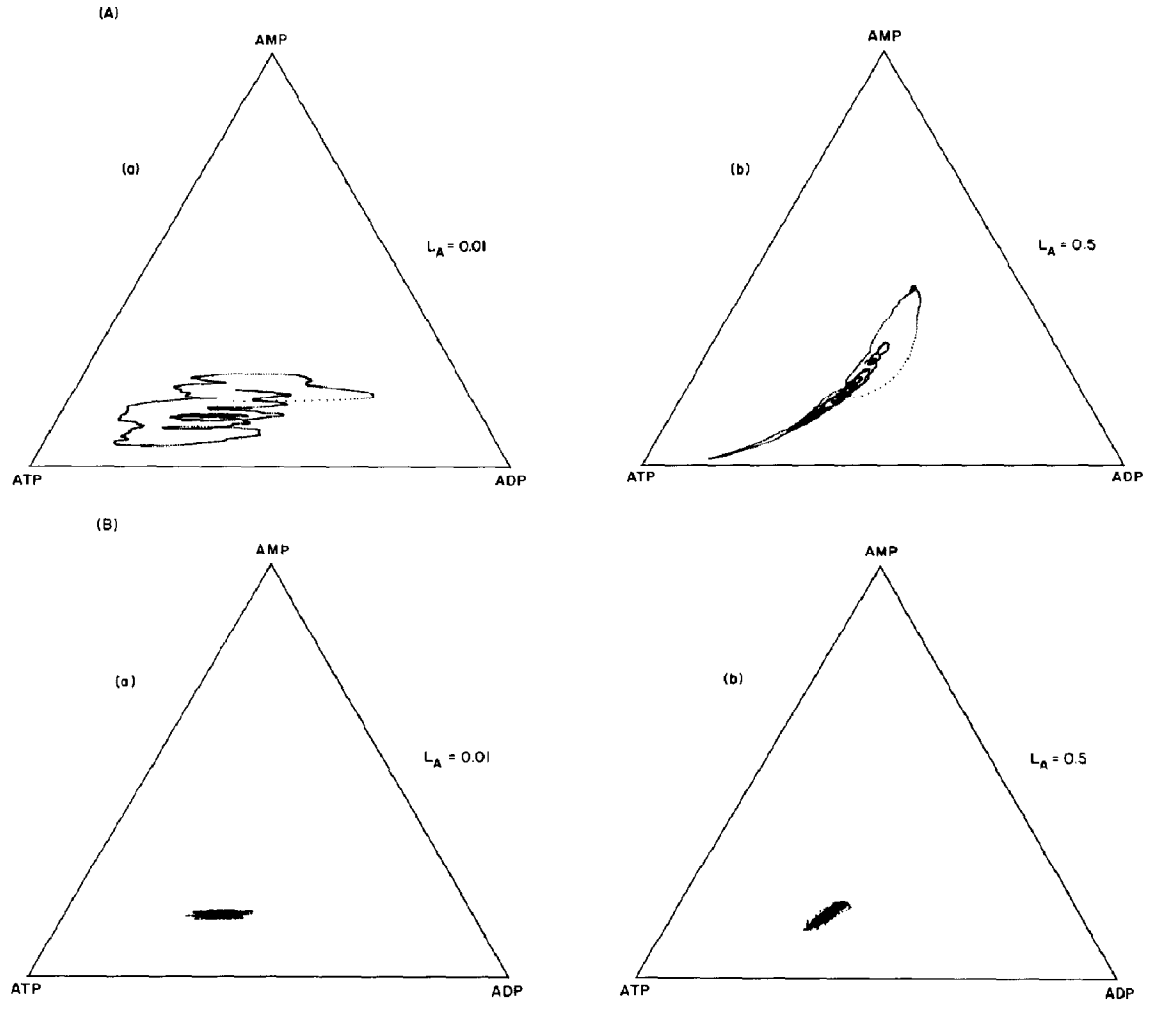

Fig. 3. Trajectories of the transients in the adenylate kinase reaction simplex. The system was perturbed by fluctuating load conductances as shown in fig. 2a with $\gamma = 100$ (A) and in fig. 2c with $\gamma = 10000$ (B), the other parameters being $L_1 = 0.0571$ and $\rho_\tau^\circ = N(0,0.0001)$. Panels a and b depict the effect of different values of L_a on the trajectories. The values of the fixed parameters were taken as [6]: $L_o = 0.027$, $L_p = 0.243$, $L_{po} = 0.0787$, $X_o = 45$ kcal, $\Delta G_p = 8.5$ kcal and $\Delta G_a = 0.15$ kcal. The initial steady-state adenine nucleotide concentrations were: [ATP] = 1.039 mM, [ADP] = 0.647 mM and [AMP] = 0.316 mM. The changes of adenine nucleotide concentrations as a function of time were calculated by numerical integration of eqs. 5–7. These data were sampled at intervals of 0.0001 arbitrary time units and plotted in the reaction simplex.

about the state of optimal efficiency is significantly reduced when the adenylate kinase is operative in this system. In particular, these simulations showed that the calculated variances of the force ratio and of the efficiency were reduced by about 35% through the adenylate kinase reaction. This effect is, however, much less pronounced when considering the same probability density estimates of a system with a load conductance perturbed with colored noise characterized by a longer correlation time ($\gamma = 100$, not shown). Here the adenylate kinase reduced the variances by only about 15%. This observation indicates that the frequency composition of the load conductance

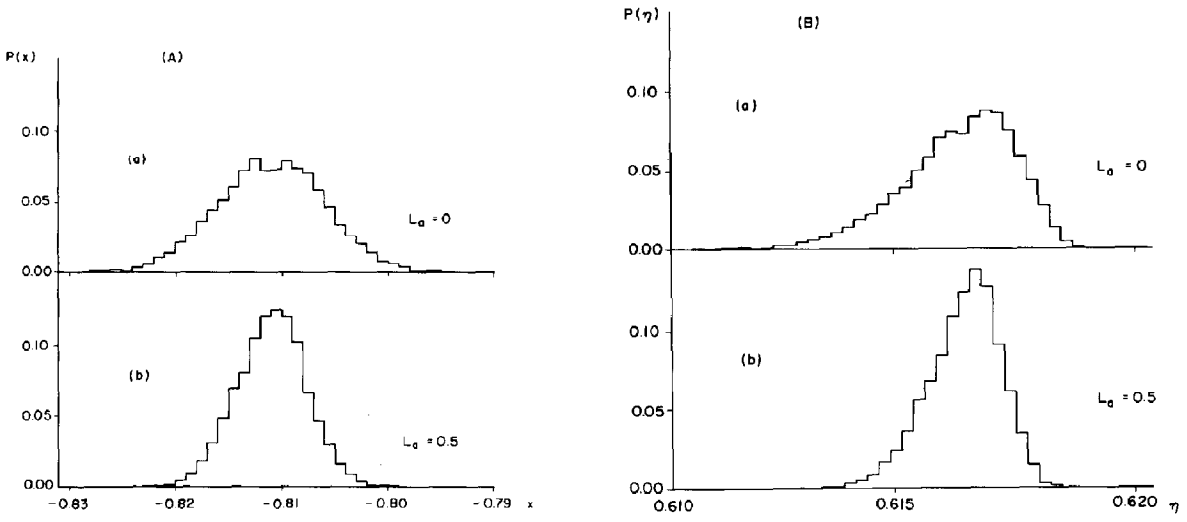

Fig. 4. Probability density estimates of the force ratio (A) and the efficiency (B). The system was perturbed by a fluctuating load conductance generated with $\gamma = 10000$. In panels a the system was working without adenylate kinase and in panels b with adenylate kinase. The probability density was estimated from 10000 integrated points, calculated as described in fig. 3.

strongly influences the buffering effect of the adenylate kinase reaction.

In fact, the analyses of several computer simulations revealed that the buffering effect of the adenylate kinase reaction is optimal only within a specific frequency domain of the load perturbations. This suggests that the adenylate kinase reaction acts as a frequency filter with respect to the fluctuations of the load conductance. In order to test this hypothesis we calculated the power spectral density estimates of the force ratio and of the efficiency [13]. Fig. 5 shows a representative example of the power spectrum of the efficiency. The power spectrum of the force ratio exhibited very much the same pattern as that of the efficiency (not shown). In this simulation a noise with $\gamma = 10000$ was chosen, allowing representation of a large frequency domain.

Comparing the power spectrum of the input, i.e., the fluctuating load conductance (fig. 2B, panel c), with that of the output, i.e., the fluctuating efficiency (fig. 5), reveals that oxidative phosphorylation indeed acts as a frequency filter which considerably damps the influence of the high-frequency contributions of L_1 to the fluctuations of the efficiency. Hence, oxidative phosphorylation alone, or more specifically, the adenine nucleotide pool itself, acts as a low-pass frequency filter for the parametric noise imposed on the system via L_1. This feature was already suggested

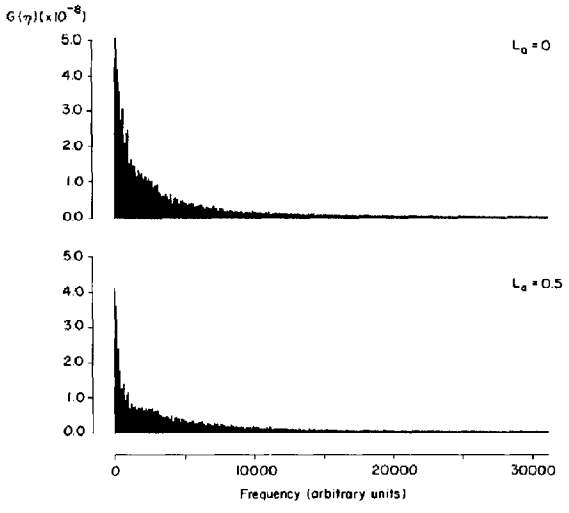

Fig. 5. Power spectral density estimates of efficiency (stochastic perturbation of L_1). From the data calculated as described in fig. 3, the power spectral density was estimated via a fast Fourier transform method as described in ref. 13. All other conditions were as specified in fig. 4.

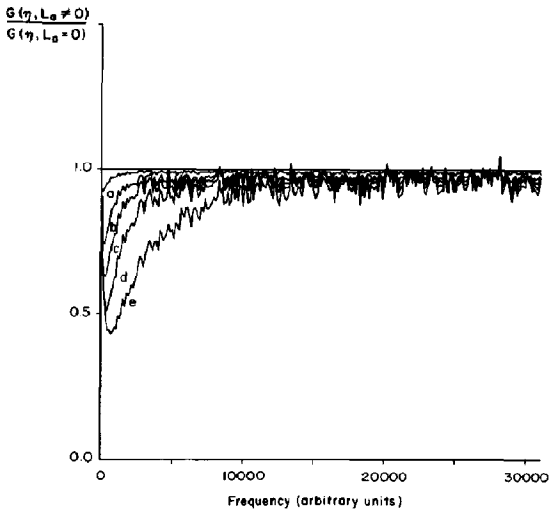

Fig. 6. Ratio of the efficiency power spectra for $L_a \neq 0$ and $L_a = 0$. Power spectral densities were estimated as described in fig. 5. The ratios of the spectra with $L_a \neq 0$ and with $L_a = 0$ were then plotted in this figure. The L_a values for the curves with $L_a \neq 0$ are: 0.01 (a), 0.05 (b), 0.1 (c), 0.2 (d) and 0.5 (e).

by fig. 3B. On the other hand, the adenylate kinase reaction extends the damping of the system's response towards lower frequencies.

The domain of the specific contribution of the adenylate kinase to the filtering effect becomes more evident when plotting the ratio of the power spectra corresponding to $L_a \neq 0$ and $L_a = 0$ as depicted in fig. 6. From this plot it can be deduced that the frequency filtering effect of the adenylate kinase is enhanced upon increasing L_a. Moreover, for each value of L_a there exists a specific frequency where the filtering effect is maximal. As L_a increases this frequency is shifted towards higher values.

From several additional simulations (not shown) it could furthermore be seen that the filtering ability of the adenylate kinase was less effective upon lowering γ. However, under these circumstances the interpretation of this effect is hampered by the fact that the intensity of each frequency is changed by the variation of the correlation time. Hence, in order to arrive at a general statement we have chosen to study the influence of this effect with a better defined variation of the load conductance than colored noise, i.e., a purely sinusoidal perturbation.

4. Response of the system to sinusoidal perturbations of the load conductance

In order to investigate the filter properties of the adenylate kinase reaction towards fluctuations of the load conductance at specific frequencies, we replaced the stochastic process in eq. 9 by a simple sinusoidal function

$$L_1 = L_1^m + A \sin(\omega t) \qquad (13)$$

This purely artificial perturbation offers the possibility of testing the response of the system at a single frequency of the load conductance with a well defined intensity. With this procedure it then becomes possible to compare the filtering effects of the adenylate kinase at several frequencies for different values of L_a.

Fig. 7 shows the power spectra of the efficiency of oxidative phosphorylation after a purely sinusoidal perturbation of the load conductance for different values of L_a. These power spectra consist of a main peak at the frequency of the load conductance plus several higher harmonics which are due to the nonlinearities of the system. Here the filtering effect of the adenylate kinase is clearly manifest: the intensity of the frequency response diminishes significantly upon increasing L_a. In order to obtain more concise information about this effect we calculated the integral of the power spectra which equals the mean square value of the efficiency [13]. In fig. 8 the ratio of these integrals for $L_a \neq 0$ and $L_a = 0$ was plotted as a function of the frequency of the perturbation of the load conductance. Again, as in the case of colored noise, both the filtering effect and the value of the frequency where this effect is maximal increase with increasing L_a. At low conductances of the adenylate kinase the filtering effect tends to disappear. Rather paradoxically, the system may even be driven to a situation where the efficiency of oxidative phosphorylation is smaller in the presence than in the absence of the buffer enzyme provided that the frequency of the perturbation of the load conductance is small and the activity of

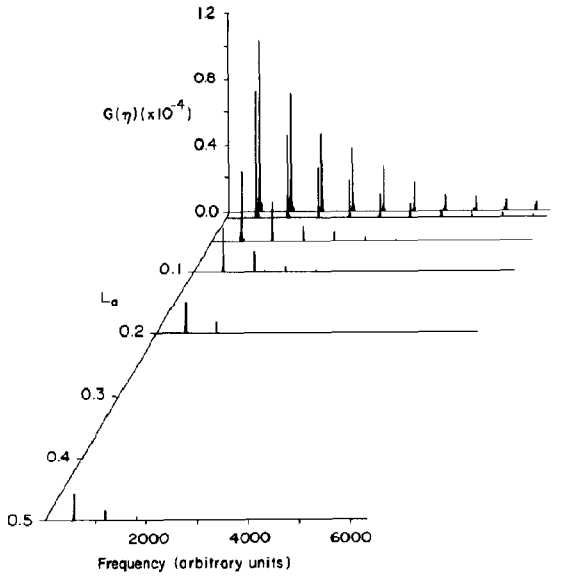

Fig. 7. Power spectral density estimates of the efficiency (sinusoidal perturbation of L_1). The amplitude of the sinusoidal load conductance about L_1 was $A = 0.05$ and the frequency was chosen as $\omega = 600$. The efficiency was calculated for 2000 integrated points. The integration conditions were as in fig. 3, except that the time interval of sampling was set to 0.0005 units. Power spectral densities were estimated from these data with the fast Fourier transform method as described in fig. 5.

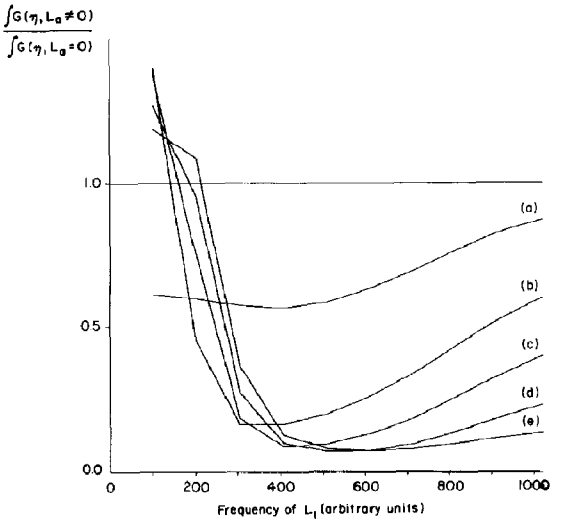

Fig. 8. Ratio of integrated power spectra of $L_a \neq 0$ and $L_a = 0$ plotted as a function of the frequency of the load conductance. The amplitude of the sinusoidal perturbation of the load conductance about L_1 was $A = 0.05$ at the frequencies of the perturbations of the load conductance as shown in the figure. The values of L_a were chosen as follows: 0.01 (a), 0.05 (b), 0.1 (c), 0.2 (d) and 0.5 (e). The power spectra were calculated for each frequency ω of the load perturbation as described in fig. 7 and were then integrated.

the adenylate kinase is high. This adverse effect is diminished when the amplitude of the perturbation of the load conductance decreases (not shown). Nevertheless, the buffering effect of the adenylate kinase reaction remains small at low frequencies of L_1, except for small values of L_a.

These results may be explained by the fact that, at high activities of the adenylate kinase and low frequencies of the load perturbation, the dynamics of the system becomes quite independent of the adenylate kinase reaction since the system is always driven along states which are close to the equilibrium of this reaction. Since these states mostly do not correspond to optimal efficiency, a low or even inversed buffering due to adenylate kinase results. In this context it must be stressed that thermodynamic buffering through adenylate kinase is a transient phenomenon which is only operative as long as there is either a net accumulation or utilization of AMP, i.e., provided $J_a \neq 0$ [6]. Lowering of L_a thus prevents the adenylate kinase from reaching its equilibrium at low-frequency perturbations and thus prolongs thermodynamic buffering. On the other hand, lowering the amplitude of the perturbation of the load conductance results in trajectories which are close to optimal efficiency. Thus, the curves in fig. 8 are a result of the interactions of different relaxation times, i.e., those of the perturbations of the load conductance and those of the adenylate kinase reaction which interdepend on each other in a complicated manner.

By and large, these simulations confirm the findings described in section 4 where it was also observed that lowering of γ, emphasizing the low-frequency contributions of the load conductance, resulted in a decrease of the buffering effect. Again we note that there exists a defined frequency of the load perturbation for every value of L_a where the filtering effect is maximal.

5. Concluding remarks

The concentrations of adenine nucleotides and consequently the phosphate potential can assumed to be fairly constant in the cytosol. For the case of isolated mitochondria it was shown that, at least to a certain extent, adenylate kinase can regulate the phosphate potential to stay close to the value permitting optimal efficiency of oxidative phosphorylation through thermodynamic buffering [6]. In addition, this enzyme deeply influences the transient kinetics of oxidative phosphorylation [7]. In liver in vivo it was shown that the adenylate kinase operates close to its thermodynamic equilibrium except when there are drastic changes of the metabolic conditions imposed from the outside [5]. In these experiments, however, the time scale of the observations was too coarse in order to give clues about the operation of thermodynamic buffering on a very short time scale.

Such features can, at present, only be investigated by computer simulations of a realistic model of the major reactions which determine the intracellular concentrations of the adenine nucleotides. In particular, these simulations allowed us to investigate the response of the system to random fluctuations of the load conductance over a large range of frequencies.

This study has revealed two main results:

(1) Fluctuations of the adenine nucleotide concentrations due to high-frequency perturbations of the load conductance are mainly damped by the adenine nucleotide pool itself due to the blindness of oxidative phosphorylation towards perturbations of very high frequencies.

(2) The adenylate kinase reaction can extend this damping effect towards lower frequencies whereby for each particular frequency there exists a particular activity of the adenylate kinase which allows maximal damping.

In studies concerned with the influence of parametric noise on system dynamics conventionally the case of white noise is considered [10]. This noise has the advantage that, by virtue of its flat power spectrum, each frequency has the same finite intensity. The disadvantage of white noise is, however, that its total intensity is infinite. In addition, perturbations extending to infinite frequencies with the same intensities are not very likely to occur in natural systems. For these reasons we have chosen a colored noise to investigate the response of the system's dynamics to perturbations of the load conductance which is certainly a much better approximation to reality than white noise. In addition, the Ornstein-Uhlenbeck process offers the possibility of tailoring the power spectrum of the fluctuation over the whole range of frequencies from zero to infinity through variation of the correlation time. The disadvantage of this manipulation is, however, that the intensities of the individual frequency components also depend on that parameter in a complicated manner. This renders a quantitative comparison of the system's response to noises with different correlation times rather impractical.

In order to overcome this problem we have therefore chosen a perturbation consisting of only one frequency, i.e., a purely sinusoidal perturbation of the load conductance. This kind of simulation seems to be purely artificial. However, it is quite possible that for oscillating metabolic reactions with low amplitudes this kind of perturbation may be a valid approximation. It is also important to note that the results obtained with sinusoidal perturbations are in perfect agreement with those obtained with colored noise.

All these simulations clearly demonstrate the adaptability of the buffer effect of the adenylate kinase reaction to specific metabolic situations. Indeed, a simple change of the activity of this enzyme is sufficient to change the domain of the main frequency components of the perturbations of L_1 where thermodynamic buffering is most effective. Nevertheless, this adaptability is rather limited. As L_a increases, the optimal damping is shifted to higher frequencies of the load perturbation. At very high frequencies, however, the damping due to the adenine nucleotide pool may dominate such that the contribution from the adenylate kinase becomes negligible. Lowering of L_a shifts the optimal damping to lower frequencies of the load perturbation. However, in this case the buffering effect of the adenylate kinase reaction tends to zero and only low-frequency perturbations with low amplitudes can be effectively damped under these circumstances. Hence,

low-frequency perturbations with a high amplitude cannot be damped and may even be amplified. In such cases an additional thermodynamic buffer enzyme, for example, the creatine kinase, could minimize the fluctuations of the adenine nucleotides and hence deviations from optimal efficiency of oxidative phosphorylation. Preliminary simulations indicate, however, that this is rather improbable. The more likely response of the system to very slow changes of the load conductance consists of regulating the degree of coupling of oxidative phosphorylation such that conductance matching is again restored. For the case of liver in vivo this has indeed been shown to be the case [5].

Acknowledgements

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References

1 A. Katchalsky and P.F. Curran, Nonequilibrium thermodynamics in biophysics (Harvard University Press, Cambridge, MA, 1965).
2 J.W. Stucki, Eur. J. Biochem. 109 (1980) 269.
3 T.L. Hill, Free energy transduction in biology (Academic Press, New York, 1977).
4 O. Kedem and S.R. Caplan, Trans. Faraday. Soc. 21 (1965) 1897.
5 S. Soboll and J.W. Stucki, Biochim. Biophys. Acta 807 (1985) 245.
6 J.W. Stucki, Eur. J. Biochem. 109 (1980) 257.
7 J.W. Stucki, L.H. Lehmann and P. Mani, Biophys. Chem. 19 (1984) 131.
8 L. Arnold, Stochastische differentialgleichungen (Oldenburg, Munich, 1973).
9 M.C. Wang and G.E. Uhlenbeck, Rev. Mod. Phys. 17 (1945) 323.
10 W. Horsthemke and R. Lefever, Noise-induced transitions (Springer-Verlag, Berlin, 1984).
11 R. Kubo, M. Toda and N. Hashitsume, Statistical physics II (Springer-Verlag, Berlin, 1985).
12 H. Risken, The Fokker-Planck equation (Springer-Verlag, Berlin, 1984).
13 J.S. Bendat and A.G. Piersol, Random data: Analysis and measurement procedures (John Wiley, New York, 1971).