

## Energy Transfer Mechanisms in Mitochondria

(bioenergetics/dielectric constant/phonon/polaron/conformon)

GABOR KEMENY

Department of Biophysics, Michigan State University, East Lansing, Mich. 48824

Communicated by David E. Green, July 1, 1974

**ABSTRACT** The problem of free energy transfer and transduction in mitochondria is reviewed from the point of view of conservative and dissipative mechanisms. Excited states are inherently dissipative and are not considered viable possibilities. If the free energy is already a local minimum and present in the form of potential energy, conservative transfer is possible within a properly designed medium. The design features are compatible with what is known about mitochondria.

### Conservation of free energy

The function of bioenergetic machines, as of all machines, is the transduction of free energy. The purpose of this paper is to assess some of the mechanisms suggested for energy transduction in mitochondria. One may generally classify these mechanisms as conservative or dissipative. The dissipative mechanisms are those that either do not have design features that would allow conservation of free energy or, if they do, it is unreasonable to assume that the mitochondrion should possess these features. Conservative mechanisms are those that do possess features of design capable to conserve free energy and it is reasonable to assume, on the basis of what is known about mitochondria, that these features may be operative.

The transport of free energy in a system simply means that upon arrival at some destination, some work can be performed on another system at the cost of lowering the free energy of the first system. (If we unite these two systems into a single system this process is considered to be transduction.) If the free energy cannot be lowered before arrival, because locally it already is a minimum, i.e., there is local thermodynamic equilibrium, then no loss is possible. If upon arrival the work performance is possible only if all the locally available free energy is utilized and other than that no process is possible, then the transduction preserves the free energy. So the point is that during transport and transduction the system as a whole is in local thermodynamic equilibrium and is already at a local minimum of free energy. Dissipative and conservative mechanisms are shown in Fig. 1.

### Dissipative mechanisms

The dissipative theories can be classified according to the element that supposedly carries the free energy to be conserved. The elements can be electrons, phonons, conformons, and polarons.

McClare (1) proposed a mechanism in which resonant electronic excitation energy is transferred between two sites. This mechanism was originally proposed by Kallmann and London (2) for molecules in a gas phase. It is very unlikely that the structures necessary to support resonant electronic

structures exist in mitochondria and that the excitation energy should not become thermalized within a short time (3).

Shohet and Reible (4) proposed a phonon mechanism of free energy transfer between an emitter and an absorber. The phonon is emitted, transmitted through a medium, and finally absorbed. It is difficult to see how a phonon can be focused so that it goes to the absorber with certainty. It is virtually impossible to imagine a very efficient absorber that would not let most of the energy escape.

The concept of the conformon, as introduced by Green and Ji (5-7), is a nebulous version of the phonon. It may represent the mechanical vibrations of the entire protein molecule at a low frequency. The energy of the conformon is supposed to be

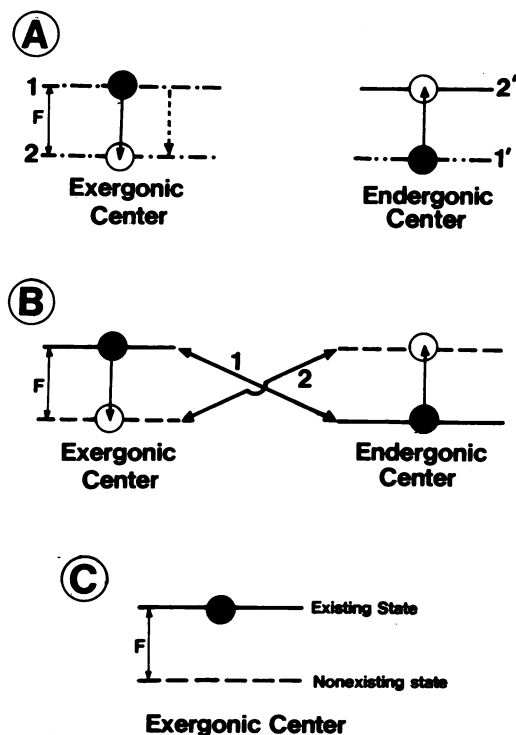


FIG. 1. (A) Dissipative mechanism. The exergonic and endergonic centers both possess two free energy states independently, for a total of four states. The transitions must be as indicated by the solid arrows to conserve the free energy  $F$ . The transition indicated by the single broken arrow is dissipative. (B) Conservative mechanism. Due to the coupling between the exergonic and endergonic centers the system possesses a total of only two free energy states, with the same free energy  $F$ . (C) Conservative mechanism. In the absence of the endergonic center the exergonic center only possesses the state with the higher free energy.

conserved throughout an oscillation. In this interpretation a conformon is simply a phonon. An alternative interpretation is that the oscillation of the protein is thermally activated. In this case the conformon is not an entity with free energy that needs to be conserved and the conformon is neither a transmitter nor a transducer of free energy. Green and Ji seem to use both possible interpretations of the conformon.

Cope and Straub (8, 9) suggested that free energy can be propagated by a polaron. According to these authors the polaron is an electron plus a phonon. The phonon part can be split off and transmitted to the site of ATP production. As far as the emitted phonon is concerned, the remarks about a phonon made above apply. The basic idea is, however, based on a misconception. A polaron is not an electron plus a phonon, but an electron plus the accompanying distortion of the substance. In the theory as developed by Holstein (10), and by Austin and Mott (11), the distortion is due to the interaction of the electron with the substance and leads to a displacement of the equilibrium positions of atomic coordinates.

The phonons near the electron, just the same as those far from it, are at thermal equilibrium and thus the phonon system is at minimum free energy. Should a phonon split off the polaron, the system of phonons near the electron would be removed from thermal equilibrium and would consequently be at a higher free energy than before. Any work done by this phonon would be against the second law of thermodynamics. Within this model the polaron can do work only if it is assumed that the phonons are not at thermal equilibrium to begin with. This disequilibrium, however, runs into other difficulties. If the polaron moves by hopping, then thermal activation is necessary. This implies that there is enough time to emit and absorb phonons; thus the initial state has enough time to equilibrate and the free energy is lost. If the polaron moves by tunnelling, a phenomenon very unlikely ever to be observed (12) due to its slow rate, again there is enough time for thermal equilibration.

The polaron referred to by Cope and Straub is the small polaron. This still leaves open the possibility that the large polaron (13) should be involved in a somewhat similar activity. The large polaron is not very different from an electron and we shall discuss it in those terms. An electron moving from residue to residue is tunnelling. This is a slow process as shown by the experiments of DeVault and Chance (14). The electron stays on one residue long enough to thermally equilibrate and any band energy it may have had is lost.

The mechanisms discussed in this section play an important historical role because they represent the various possibilities one is predisposed to think of in the context of solid state physics. Their failure had to be demonstrated to prepare one's mind for alternatives.

#### Conservative mechanisms

The mechanisms in the last section, or at least those of them that possess free energy, all have one thing in common: they are based upon excited states. Since physical systems tend to go to the ground state, these mechanisms are inherently dissipative (Fig. 1A). We have to consider the alternative possibility, namely, the storage of free energy in ground states. To be more precise, we should say a thermal mixture of states that includes the ground state (Fig. 1C).

Since there is charge separation in the electron transfer chain we must attribute free energy to the charged pair

( $A^+$ ,  $B^-$ ). Since the pair is imbedded in a medium, the free energy has to be attributed to the charges and to the protein. We shall not attribute free energy to excitations, e.g., phonons, because that is dissipative. Therefore, all free energy has to be attributed to interactions. There are three of these for a charged pair: interaction of the two charges with each other, the interaction of each of the charges with the medium, and the self-interaction of the medium. If we generalize the concept of the polaron to include any kind of charges, then we have here two polarons. The interaction of the two charges with each other is simply the Coulomb interaction. The interaction with the medium is a more complex matter.

Let us consider an electron first in a totally rigid medium. Removing the electron from a molecule requires an amount of free energy called the ionization potential. Placing it on another molecule returns some of this free energy which is called the electron affinity. The response of the medium can be split into two parts: the response of sites within the range of the electronic wavefunction and of those sites beyond this range. The second part of the response can be handled by introducing the polarizability of these sites or the dielectric constant. With the first part we have two alternatives. We may modify the values of the ionization potential and the electron affinity to account for this short-range response, or we may formally introduce a polarizability and so a dielectric constant too and handle the long and short-range responses together (10). Charges other than electrons can be handled analogously.

It is known from the study of organic and biological semiconductors (15) that the interaction of a charge with a dielectric can be very substantial, of the order of tens of kilocalories/mole. It is also known that positive charges can enter the mitochondrial inner membrane only when imbedded in ionophores (16) that are highly polarizable. It is therefore reasonable to propose that the dielectric constant plays an important role with regard to the free energy. It is clear that the dielectric constant alone cannot characterize the situation completely, in view of the ionization potential and electron affinity mentioned above, and in view of the analogous quantities applying to other charges. But it is also clear that the dielectric constant plays a major role. The following discussion will be in terms of the dielectric constant, to use simple language, but we shall keep in mind these other quantities.

The mitochondrial inner membrane is an inhomogeneous and anisotropic medium. The dielectric constant is large near the surfaces of the membrane where the polar groups are, and small inside. The dielectric constant varies not only in space but also in time due to conformational changes. Cytochrome *c* undergoes a conformational change when it is oxidized and high dielectric substance moves near the heme (17). As a charge moves in such a medium or as the medium moves compared to the charge, the free energy will change. A charge in a high dielectric region has a lower free energy than in a low dielectric region. It is possible for a pair of charges to exchange free energy utilizing the inhomogeneity and anisotropy of the medium.

Let us consider a charged pair,  $A^+$  and  $B^-$ . Due to the inhomogeneity and anisotropy of the medium their free energy is minimum if they move in their respective "channels" and, according to the pairing principle, they keep a more or less fixed distance from each other. As they move through regions of different dielectric constant, the free energy of each charge

changes. If matters are carefully arranged the free energy of the pair as a whole can remain constant. We assume that one of the charges starts at a high dielectric region of the medium, the other in a low dielectric region. If in moving parallel to each other their final position with respect to the dielectric constant distribution is reversed, they have exchanged their free energy. A similar mechanism was proposed earlier (18). We have indicated above that the free energy of a charged pair consists of three parts: the Coulomb interaction of the two charges, the interaction of the two charges with the medium, and the self-interaction of the medium. The change is mostly in the second contribution. It is evident that the concept of free energy attributed to one charge is meaningful only if its change refers to this second contribution. It may turn out later that the free energy of more than a pair of charges has to be considered simultaneously.

The free energy transfer mechanism suggested here is analogous to a pulley with two weights. The charges are the weights, the interaction of charges with the medium corresponds to the effect of the earth's gravitational pull on the weights and the motion of charges at a fixed distance corresponds to the motion of the weights on the pulley with a rope of fixed length. One weight moving down moves the other weight up and thus they exchange potential energy. The weight which is now up can be transferred to a neighboring pulley, move down and pull up another weight. This corresponds to a cation in the coupling system, transferring free energy from the electron to phosphate in antiport coupling (19, 20).

The author is indebted to Professors David E. Green and Barnett Rosenberg for valuable discussions and to the U.S. Atomic Energy Commission for support.

1. McClare, C. W. F. (1974) *Ann. N.Y. Acad. Sci.* **227**, 74-97.
2. Kallmann, H. & London, F. (1929) *Z. Physik. Chem.* **B2**, 207-243.
3. Discussion of Dr. McClare's paper (1974) *Ann. N.Y. Acad. Sci.* **227**, 108-115.
4. Shohet, J. L. & Reible, S. A. (1974) *Ann. N.Y. Acad. Sci.* **227**, 641-650.
5. Green, D. E. & Ji, S. (1973) *Proc. Nat. Acad. Sci. USA* **70**, 904-908.
6. Green, D. E. (1974) *Ann. N.Y. Acad. Sci.* **227**, 6-45.
7. Ji, S. (1974) *Ann. N.Y. Acad. Sci.* **227**, 419-437.
8. Cope, F. W. & Straub, K. D. (1969) *Bull. Math. Biophys.* **31**, 761-774.
9. Cope, F. W. (1974) *Ann. N.Y. Acad. Sci.* **227**, 636-640.
10. Holstein, T. (1959) *Ann. Phys. (New York)* **8**, 325-389.
11. Austin, I. G. & Mott, N. F. (1969) *Advan. Phys.* **18**, 41-102.
12. Bosman, A. J. & VanDaal, H. J. (1970) *Advan. Phys.* **19**, 1-117.
13. Kittel, C. (1963) in *Quantum Theory of Solids* (Wiley, New York), pp. 130-149.
14. DeVault, D. & Chance, B. (1966) *Biophys. J.* **6**, 825-847.
15. Rosenberg, B., Bhowmik, B., Harder, H. C. & Postow, E. (1968) *J. Chem. Phys.* **49**, 4108-4114.
16. Green, D. E. (1974) *Biochim. Biophys. Acta* **346**, 27-78.
17. Dickerson, R. E. (1974) *Ann. N.Y. Acad. Sci.* **227**, 599-612.
18. Kemeny, G. (1974) *J. Theor. Biol.* **46**, in press.
19. Kemeny, G. (1974) *Proc. Nat. Acad. Sci. USA* **71**, 2655-2657.
20. Kemeny, G. (1974) *Proc. Nat. Acad. Sci. USA* **71**, 3064-3067.