Energy Transfer Dynamics

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Herbert Fröhlich on His Eightieth Birthday

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22. Non-Thermally Excited Modes and Free Energy Transduction in Proteins and Biological Membranes

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ABSTRACT

The thermodynamic properties of aqueous globular proteins are considered, both when at equilibrium in a heat bath and during enzymatic catalysis. It is recognized that they exhibit thermally driven conformational fluctuations of great complexity and on time scales that may be much faster than the enzyme turnover time. Yet conformational states of proteins can store free energy under macroscopically isothermal conditions. This requires that they possess special, collective, non-thermally excited modes both during enzymatic catalysis and, in particular, during free energy conservation. Electron transport phosphorylation and related membrane processes provide well-defined examples of this latter behavior.

INTRODUCTION

It is indeed a singular honor and pleasure to be able to contribute to this Festschrift celebrating, on the occasion of his 80th birthday, the many achievements of Professor H. Fröhlich in physics and biophysics. For a young biochemist such as myself to have had the opportunity to enjoy intellectual contact with a physicist of genuine stature is inevitably an educative, revealing, and rewarding experience; that it has also been an outstandingly pleasurable highlight of my scientific career is due to the warm welcome and courteous, generous, and patient help I have always received from Professor Fröhlich during my studies of the salient features of his general theory of collective behavior in biological systems.

A fresh approach to a field of scientific enquiry by a brilliant outsider can often produce results of a special character, qualitatively different from those of Kuhn's (1970) "normal science". With such thoughts in mind, the Académie Francaise convened in 1967 a meeting, in the elegant surroundings of the palace of Versailles, at which they invited several of the outstanding theoretical physicists of the time to consider, from a physical perspective, the nature and problems of living systems and cellular organization. Whilst Schrödinger's (1944) classic essay in this direction had indicated that the apparent violation of the Second Law by living systems was accounted for by the realization that they are thermodynamically open systems, and the Brussels school (e.g. Nicolis and Prigogine, 1977) developed the idea of dissipative structures within the framework of a general treatment of the thermodynamics of irreversible processes, these treatments were essentially macroscopic in character. By contrast, Fröhlich's (1968, 1969) assessment at this meeting was of a more molecular or quantum mechanical character, and sprang from his

knowledge of the unusual dielectric behavior of biological membranes and his earlier experience with nonlinear systems in general and (I assume) with superconductivity in particular.

The general idea, then as now, is that certain kinds of relatively well-defined physical systems can, by the *collective, nonlinear* behavior of ensembles of the particles of which they are constituted, display or develop a macroscopic order that would not result from, nor be predicted by, the linear superposition of their individual coordinates, velocities, and interatomic potentials. What Fröhlich (1968, 1969) suggested in particular, by extending certain general equations of microscopic physics, was that nonlinear interactions between the electric and acoustic modes of certain biological macromolecules could lead to the generation and stabilization of long-lived, polar modes, via a mechanism analogous to the Einstein condensation of a gas of bosons. Because my background is in bioenergetics, I shall concentrate upon what this means for *proteins*, especially those capable of free energy conservation or transduction. However, since proteins are highly sophisticated and complex arrays of atoms, we must inquire first whether they can or do exhibit such nonlinear behavior and stable, out-of-equilibrium states, and second, if they do, as to the types of mechanism by which this occurs. More explicitly, we must consider that the modes stabilized within biological systems by these nonlinear phase transitions must be highly resistant to the impact of the disordering tendencies of their internal thermal vibrations and those elicited by collisions with solvent and other molecules, allowing the system to store energy for times which are long compared to the normal cycle times of free-energy-transducing enzymes.

What I wish to do in the following, rather personal overview, therefore, is to summarize, within the framework of the above ideas, some of the key problems in bioenergetics as seen from a more biological or biochemical standpoint, and to indicate why I think that the generalized theory of Fröhlich concerning collective or coherent excitations in biological systems does provide a new, exciting, and persuasive formalism for the evolution of this subject. It is not my intention to review in detail either the theory and its mathematical foundation (Fröhlich, 1980) or some of the pertinent experimental evidence (Webb, 1980; Pohl, 1981; Fröhlich and Kremer, 1983; Del Giudice et al., 1984). Rather this paper is to illustrate, in very summary and elementary terms, some modern ideas concerning the structure, dynamics, and organization of isolated proteins, to extend this to situations in which proteins are catalyzing *favorable* chemical reactions, and finally to distinguish and discuss in a mechanistic fashion the very special biophysical features of some proteinaceous devices that are considered to take part in the storage and conservation of free energy in biology.

THE STRUCTURE OF ISOLATED GLOBULAR PROTEINS

The average three-dimensional ("tertiary") structure of a native, isolated, globular protein, both in solution and in the crystalline state, is determined purely by the primary sequence of amino acids which it contains. But a protein of molecular weight 20 kD can in principle possess or explore some 10^{80} conformational states (e.g., Jaenicke, 1984). However, since the Universe is "only" some 10^{17} s old (Barrow and Silk, 1983), even if we allowed our protein to assume these states at a rate of 10^{15} per second, it could not conceivably explore all of those available in passing from the unfolded to the folded state. Thus, given experimental realities, in the strictest terms, even an isolated protein in thermal equilibrium in a heat bath of solvent molecules cannot truly be considered as an ergodic system.

To allow progress, therefore, we consider macroscopic, "average" conformational states and substates, whose free energy difference $\leqslant kT$, a procedure that allows us to speak of "a" structure or conformation. Indeed, one may read in any biochemistry textbook that the energetically favorable transition from a "random coil" (unfolded state) to globular protein (folded state) may be accounted for by the formation of covalent, hydrophobic, dipolar, electrostatic, and van der Waals bonds between the amino acid units of the protein, and the changes in the angles and lengths of such bonds caused by amounts of energy equal to kT are both relatively small and are observable in the electron density map obtained by X-ray diffraction measurements (e.g., Ringe and Petsko, 1985). This in itself allows us to distinguish (with a "noise" amounting to kT) the conformation and free energy of a protein under a given set of conditions (of pH, temperature, ionic strength, etc) from those of the other molecules (solvents, ligands, etc) present, and of course, in this sense, the ("static") structures of many proteins are known to atomic resolution. What happens when we ask our protein to do something, for instance to catalyze a thermodynamically favorable reaction such as $A \rightarrow B$? To answer this, we must enquire not only into the "structure" but the *dynamics* of such proteins.

DYNAMIC BEHAVIOR OF AQUEOUS, GLOBULAR ENZYMES

One may discern two general types of approach that have allowed us to make progress in devising a mechanistic basis for the astonishing rate enhancements and specificity of which enzymes are capable. The more (physico-)*chemical* treatment (Jencks, 1980; Fersht, 1985) has shown how enzymes can, by virtue of their conformational flexibility, exploit the favorable free energy of substrate binding so as to stabilize the transition state, and has concentrated, as a result, on the interaction between the substrate and the protein side-chains to which it is bound at the "active site". A perhaps more genuinely dynamical and more purely (bio-)*physical* approach (reviews: Lumry and Biltonen, 1969; Careri et al., 1979; Lumry, 1980; Welch et al., 1982; Somogyi et al., 1984; and Welch, 1986) has stressed the view that the time-dependent, thermally induced conformational mobility *of the entire protein molecule* contributes significantly to the rate enhancements of chemical reactions catalyzed by enzymes, a view at least consistent with the fact that attempts quantitatively to imitate enzymatic activity with synthetic ligands of low molecular weight that mimic the active site alone have so far failed (Sinnott, 1979; Kell, 1982; Mutter, 1985). Obviously both treatments are important, but for the present purposes of developing a set of arguments, I shall lay stress mainly on the latter.

If we take this approach it might appear, from an equilibrium thermodynamic standpoint, that the following paradox arises: our enzyme is acting *isothermally* in a heat bath, yet we seem to be saying that it can not only exchange energy with the solvent but can in some way "use" this energy during its enzymatic cycle, violating

the Second Law. The solution to this paradox (see e.g. Kemeny, 1974; Lumry, 1980; Cooper, 1984; Somogyi et al., 1984) is that such thermodynamic reasoning requires only that the *overall* ΔG for the enzyme-solvent interaction = 0 under these conditions, whilst the enthalpy and entropy may fluctuate considerably (owing to the molecular size of the protein molecule), *provided that such fluctuations ae compensatory.* As phrased by Kemeny (1974), therefore: "this does not mean that heat energy is turned into free energy but rather that the transduction of internal energy and heat exchange with the reservoir are part of the same mechanism." In other words, the enzyme may "borrow" heat energy from its surroundings but must "return" it after use, a phenomenon which abundant experimental evidence has shown is manifest in a huge variety of fluctuational modes about its "equilibrium" conformation (e.g., Gurd and Rothgeb, 1979; Englander and Kallenbach, 1984; McCammon, 1984). Indeed, it is worth mentioning that these fluctuations are probably crucial to the antigenicity of proteins and small polypeptide, protein-mimetic vaccines (Berzofsky, 1985; Williams and Moore, 1985), a topic of much current interest.

In devising treatments and mechanisms for this type of behavior, then, we must consider the *time scale* of protein fluctuations, for it is the time scale that tells us *how long* the protein will take to equalize any "excess" thermal energy between a number of degrees of freedom sufficient for it to be indistinguishable from kT. What we find especially (Careri et al., 1979; Welch et al., 1982) is that the exchange of energy at protein surfaces occurs (by collisions with solvent and buffer molecules, and in particular by proton-exchange equilibration) with characteristic frequencies of some 10^8 Hz. In contrast, the turnover time for a typical enzyme is say 10^{-3} s. Thus the view has evolved that whilst an enzyme is indeed a highly stochastically fluctuating molecule and, for a given free energy, possesses a *wealth* of conformational substates (at ambient temperatures), it is an "equilibrium chemodynamical machine" which, at every metastable, intermediate stage in its enzymatic cycle is, for practical purposes, in thermodynamic equilibrium with its surroundings. (This is not to say that it does not exhibit internal collective modes during transitions *between* macrostates in its reaction cycle (Ansari et al., 1985)). This is, at least to a first approximation, a reasonably satisfying picture for enzymes catalyzing the approach to equilibrium of a thermodynamically favorable chemical reaction. Our satisfaction is less than complete, however, when we come to consider enzymes that catalyze *free energy transduction.*

HOW CAN A PROTEIN MOLECULE STORE FREE ENERGY OVER LONG PERIODS UNDER ISOTHERMAL CONDITIONS?

We have seen that a typical enzyme, buffeted by its solvent environment, can only remain slightly out of equilibrium with its surroundings for a time scale that is short relative to its turnover time. In contrast, some enzymes can store free energy of a magnitude that is large relative to kT for a period that may be very long not only on these time scales but even relative to its "normal" turnover time. If we consider the synthesis of ATP from ADP and inorganic phosphate ($\Delta G^\circ = +31$ kJ/mol) "catalyzed" by an ATP synthase (normal turnover time ca. 10

ms), we find that biological systems containing an ATP synthase can store free energy (for instance, in photosynthesis, following absorption of a photon) as a "primary macroerg" (Blumenfeld, 1983) for periods of *seconds* before using it to make ATP. If such free energies are stored in protein conformational states (or in other states in equilibrium therewith), one must perforce seek a description of how this is achieved in the face of the same thermalizing environment that we have already admitted above would cause relaxation of the protein conformation to other conformations with a free energy equal to that in its (appropriately liganded) "ground" state $\pm kT$. This, in fundamental terms, is the key problem of principle in molecular bioenergetics (Somogyi et al., 1984; Welch and Kell, 1986). Obviously some mechanisms must be operative to restrict, in a kinetic sense, the decay of these conformational states to equilibrium, or, in Fröhlich's (1969) phrase, very strongly to excite a few modes of motion.

One way of restricting the number of kinetically available states is by putting the protein in an electrically (protonically) insulating membrane and maintaining an electrical potential or pH gradient across that membrane, a principle that forms the basis of Mitchell's chemiosmotic theory (Mitchell, 1966; Nicholls, 1982). Whilst there are nowadays many reasons to doubt that ATP synthesis in vivo occurs strictly according to this principle (Kell and Hitchens, 1983; Westerhoff et al., 1984; Ferguson, 1985; Kell and Westerhoff, 1985), Mitchell's ideas, and the experiments that they have stimulated, leave little room for doubt that electrogenic proton translocation reactions lie at the heart of ATP synthesis "catalyzed" by a membrane-located ATP synthase whose free energy is generally supplied by the exergonic reactions of electron transport. Bioenergeticists therefore now routinely refer to such devices as *proton pumps.* We are thus led to consider the possibility of long-lived, metastable, *out-of-equilibrium* states that may be attained when protons interact with proteins in general, and with the membranous systems of electron transport phosphorylation in particular.

FREE ENERGY STORAGE AND TRANSDUCTION IN PROTEINS AND BIOMEMBRANES BY SOLITONS AND OTHER OUT-OF-EQUILIBRIUM STATES

What we have learned from the above, and has in particular been brought home to me by my contact with Fröhlich and his writings, is that certain collective motions of ensembles of atoms can lead to the formation of a degree of macroscopic order under conditions in which normal frictional forces would have damped out any such ordering. Thus, in contrast to the impression one might gain simply by a general study of the more mainstream bioenergetic literature, it is at least plausible, and in my view the available evidence dictates, that proton pumps embedded in biological membranes also indulge in such collective motions as an (if not *the*) essential part of their biological activity. If this is so, one must be able to devise experiments which, from a bioenergetic standpoint, are both entirely novel and may be expected greatly to improve our understanding of electron transport phosphorylation.

For a variety of reasons, most authors who have considered the general problem of "high energy" states of proteins have suggested that solitary excitations (soli-

tons) might possess the type of property required to account for the behavior of free-energy-conserving proteins. A soliton is a special kind of wave packet (phonon) which, because of the type of wave equation that it obeys (there are several different types), can carry energy over "long" distances in an essentially *dispersionless* fashion, without losing its energy by thermal exchange. It thus maintains its energy at a level greater than that expected on the basis of a Boltzmann distribution of vibrational energies at the ambient temperature. Solitons are thus characteristic of the non-thermally excited modes referred to in the title of this article, and are one of the internal modes of proteins generally for which Somogyi et al. have coined the general term *zymons*. It is not for me here to seek to distinguish the various proposals in detail (see e.g. Bilz et al., 1981; Blumenfeld, 1983; Davydov, 1983; Jardetzky and King, 1983; Ribeiro et al., 1983; Scott, 1983; Yomosa, 1983; Chou, 1984; Lomdahl, 1984; Careri and Wyman, 1984; Carter, 1984; Del Guidice et al., 1984; Lomdahl, et al., 1984; Somogyi et al., 1984 for an entrée to the literature), but what does come out of this work is that the existence of collective excitations in proteins is firmly established, both in well-defined theories and by experimental observation (mainly spectroscopic). What is not known with any degree of certainty at all is *exactly* which of the available models (if any) is actually used in vivo. Nor have I seen a treatment to date that is aimed specifically at considering the properties of solitons in membranes and proteins within the framework of Fröhlich's more general theory of coherent excitations. And neither has the exact role of the proton been established in this context. Most so-called localized coupling theories propose that protons move in concert with specialized modes of proteins (and perhaps lipids), and it is obvious that the *obligatory* vectorial movement of a proton as part of a solitary excitation will greatly affect the "normal" behavior of both the proton *and* the soliton (Kell and Westerhoff, 1985). In this context, it is extremely interesting that a recent dielectric study by Careri and colleagues (1985) has shown a highly cooperative channeling of protons (with a 7th-order dependence on the number of bound protons) from all over the surface of lysozyme towards the enzyme's active site. Such measurements show directly that there are indeed highly nonlinear interactions between the electric and acoustic modes of biological materials, as predicted by Fröhlich.

We ourselves have initiated a study of the dielectric properties of microbial membranes in the frequency range from ca 10 Hz-10 MHz. In the absence of protonmotive activity, the chief novel finding to date is that one may learn more about the movement of lipids and proteins than of protons (Kell, 1983; Harris and Kell, 1985; Kell and Harris, 1985). When ~~is considered~~, the effect of membrane energization (i.e., proton pumping activity) on the dielectric behavior is considered, the search for possible resonant modes is bedevilled by the small number of *net* charges that are actually pumped (Kell and Hitchens, 1982; Hitchens and Kell, 1984) relative to the background conductivity in aqueous suspensions (Harris et al., 1984). Experiments at lower levels of hydration might ameliorate matters.

Since in the space available it is impossible adequately even to summarize the present status of the controversial subject of membranous proton-coupled free-energy-transducing systems, which has anyway been done elsewhere at some length (Kell and Hitchens, 1983; Westerhoff et al., 1984; Ferguson, 1985; Kell and Westerhoff, 1985), I wish finally to state the following point of view. This is that

the enormous wealth of detailed (if often paradoxical) knowledge concerning protonmotive systems does indicate very strongly, when taken as a whole, that if collective excitations *sensu* Fröhlich are the norm in living systems, it is to electron transport phosphorylation that one might fruitfully first turn to describe them in a well-defined and clearly free-energy-conserving system. Whether such behavior is actually to be expected for *fundamental* reasons, as suggested in particular by McClare (1971), is at least plausible (Welch and Kell, 1986).

CONCLUDING REMARKS

There is now a growing realization that functional order in noncrystalline systems does not require a strict spatial order; more subtle types of behavior are possible, not only in inorganic systems such as lasers, superconductors, and superfluids but also in proteins and biological membranes. Whilst progress in such an interdisciplinary area is not without its difficulties, the acceptance that many types of nonlinear system obey fundamentally similar equations (Haken, 1977) can only hasten the day when biologists and physicists themselves indulge more fully and more regularly in collective behavior. That many are doing so already is due in no small degree to the ideas and efforts of Herbert Fröhlich.

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23. Herbert Fröhlich, and the New Biophysics of Cooperativity

Herbert A. Pohl*

If one word is to be used for a description of the research created by Professor H. Fröhlich, that word is *cooperativity*. The phenomena of cooperative and collective phenomena have been much advanced by his insights, and recently, especially in biology. In commemoration of his 80th birthday on December 9, 1985 it is appropriate for us to honor this most productive scientist and friend.

In 1968, Herbert Fröhlich, already famous for his theoretical insights into solid state physics in such fields as superconductivity, semiconductor transport properties and instabilities, dielectric breakdown, and a host of others; turned his attention to cooperative phenomena in biology. In series of papers he opened up a new approach to biophysics. It has created a wealth of insights into how cells behave, especially in response to electromagnetic fields.

Said briefly, Professor Fröhlich pointed out that many of the various oscillators which comprise the living state will obey Bose-Einstein rules of cooperativity. This results in there being possible the existence of "boson-like condensations" leading to cooperativities appearing as the energy throughput reaches critical levels. The situation is rather like that of the operation of a laser. At a certain minimum power input, the laser begins to lase. Analogously, at a certain minimum energy throughput, as Professor Fröhlich showed, the cellular vibrators can "condense" to a cooperative state of interactions. The result is the appearance of long range ordering and sensitive interactions, observed, but unexpected by conventional classical approaches.

Some of these theoretical predictions have already borne fruit, and more is likely. For example, the astoundingly long range (up to 4 microns) interactions between live erythrocytes observed by Rowlands et al. can presently only be understood in terms of Froehlich interactions. Moreover the cooperative electromagneitc phenomena predicted by Fröhlich to occur in the experimentally difficult realm of about 100 GHz have been seen by Russian, German and American scientists, although this evidence is still developing. Terms such as "limit cycles," oscillating chemical reactions, cooperative degeneracies, Davydov solitons, "polar mode softening" and the like are beginning to invade the world of the biologists and biophysicists.

In broad brush strokes, he has pointed the way. A whole new science of vital oscillatory phenomena is evolving, due in large part to the stimulus and insights of Herbert Fröhlich.

*Deceased June 23, 1986.