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New paradigm for ATP synthesis and consumption

A central postulate of the chemiosmotic theory of ATP synthesis (Mitchell 1966) in mitochondria is the presence of a delocalized electrical potential of about 200 mV ($\Delta\varphi$) across the energy-transducing membrane between two bulk aqueous compartments. This $\Delta\varphi$ forms the major component of the driving force for ATP synthesis, according to this theory.

Experimental techniques to measure this electrical potential difference can be classified into two categories. The first method is to use ions that are permeant to the inner mitochondrial membrane or to introduce non-physiological substances that are charged and membrane-permeant. By achieving transmembrane diffusion of these ions or substances, $\Delta\varphi$ can be calculated using the assumption of equilibrium and the Nernst equation (Mitchell 1966). The second method is to employ microelectrodes to penetrate the inner mitochondrial membrane and make direct measurements of the potential across it (Tedeschi 1980). Each method has its own protagonists. The long-standing paradox in bioenergetics is that while the former method produces results favouring the chemiosmotic theory, the latter method finds results, such as a zero $\Delta\varphi$, which cannot be reconciled with the chemiosmotic theory.

A large amount of experimental and analytical research and scientific debate has taken place over several decades in an attempt to resolve the paradox. However, this has led to a polarization of scientific opinion, with each group claiming the correctness of their experimental technique. Even after such a large body of work, the paradox could not be resolved. Accordingly, all previous mechanisms, including the chemiosmotic theory, are also polarized and explain only data recorded from one set of experimental techniques. However, no one considered that both sets of experimental data could be correct and reflect some important aspect of the overall process of oxidative phosphorylation and could evolve a mechanism that could explain both poles.

In view of these facts, the emergence of Nath's torsional mechanism of energy transduction and ATP synthesis can be considered to be a milestone in the understanding of the process. The mechanism had its 10th anniversary recently (Nath 2010a, b). One key aspect of the mechanism is its ability to explain both the sets of experimental data on a rational basis. The following is a brief description of the mechanism in the membrane as per the understanding of this author.

Consider a sequence of movement of ions through the energy-transducing membrane. Assuming that there are specific access channels for the movement of anions and protons, only one type of access channel is open at a given time (or both may be closed). Now, let us assume that an anion has moved through an open access channel through the membrane. This movement closes the open anion access channel and opens an adjacent proton access channel. The local electrical potential ($\Delta\psi$) thus created is used or stored by the molecular motor. Then, the proton moves through its open access channel along its electrochemical gradient and a reciprocal process takes place. In each movement half the energy is transferred to the molecular motor. The process is akin to the principle of alternating current motors. The torque produced by the molecular motor is finally used in the synthesis of ATP. It should be noted that the time average charge in the transport cycle is zero. How can this mechanism explain the two poles of experimental data? In the first method, an external charged agent is introduced. This dissipates the $\Delta\psi$ created in the access channel during the first half-cycle and the same (that is the local potential created by the primary translocation) is measured. In the second method of measurement, the microelectrode measures an average potential after completion of a cycle, which is zero. The proposed torsional mechanism thus explains both experimental data sets without any ambiguity. Thus, the long-standing paradox of the contradictory but correct experimental results is resolved. This is an important achievement of the torsional mechanism (Nath 2010b).

Keywords. ATP synthesis; bioenergetics; chemiosmotic theory; energy transduction; mitochondria; motility; muscle contraction; oxidative phosphorylation; torsional mechanism

The chemiosmotic theory is based on equilibrium considerations and all the energy transduction occurs at equilibrium. Hence, only equilibrium thermodynamics is used in the analysis. An important advance of the torsional mechanism is that it is a non-equilibrium theory in which all sub-processes are described as occurring with their characteristic dynamical timescales that are central to the theory. The mechanism proposes the details of energy transduction which give it completeness and make it most attractive. The interested reader can consult the papers listed in the bibliography. An overview of the status of the mechanism on its fifth anniversary is also available (Jain *et al.* 2004).

ATP synthesis in mitochondria and ATP consumption in biological machines such as muscles must have unifying elements of theory. Any theory that describes the synthesis should also be able to describe the consumption. Seldom do we find that researchers attempt both aspects. One of the important achievements of the torsional mechanism (Nath and Nath 2009; Nath 2010a, b) is that both the aspects have been studied in detail. There is no contradiction in the theory between the two aspects of synthesis and consumption, and hence, the theory is more likely to be correct. In the muscle, the ATP is unlocked and the torsional energy stored is used to perform mechanical work. All the details of the energy balances, distances of movement of myosin-actin vis-à-vis the energy released per ATP, etc., have been worked out. This study leads to another important conclusion that in nature there is considerable amount of re-use of methods and principles.

In conclusion, this author believes that the work of Nath is very interesting and is perhaps the only model that is consistent with the available experimental data and explains all the aspects of energy transduction and consumption involving ATP. Further, the theory applies the engineering principles of thermodynamics and energy balances, kinetics and transport to solve a problem in biology, and is thus interdisciplinary in approach.

It is observed that most of the basic science fields progressed rather rapidly in the 18th, 19th and the first half of the 20th century, whereas the rate of growth declined considerably in the later half of the 20th century. One of the most rapidly growing fields of the 20th century was computer science, which derived its growth from inputs of almost all other scientific fields and even literary and social fields. Many other fields of science including medicine have benefited enormously from the application of computers. One of the reasons for the stagnation in scientific research may be the polarization of knowledge into groups and subgroups with less and less interaction between various disciplines. It is felt that an interdisciplinary approach to research will help solve most of the problems encountered in study of science. In particular, there are many molecular machines in biological processes that can be understood by analogy with similar manmade machines. The physical principles are the same even though the dimensional scales and sources of energy are different. In light of this, the work of Nath is a pioneering interdisciplinary contribution to the field of bioenergetics and motility.

References

Jain S, Murugavel R and Hansen LD 2004 ATP synthase and the torsional mechanism: Resolving a 50-year-old mystery. *Curr. Sci.* **87** 16–19

Mitchell P 1966 Chemiosmotic coupling in oxidative and photosynthetic phosphorylation. *Biol. Rev.* **41** 445–502

Nath S 2010a Beyond the chemiosmotic theory: Analysis of key fundamental aspects of energy coupling in oxidative phosphorylation in the light of a torsional mechanism of energy transduction and ATP synthesis – Invited review part 1. *J. Bioenerg. Biomembr.* **42** 293–300

Nath S 2010b Beyond the chemiosmotic theory: Analysis of key fundamental aspects of energy coupling in oxidative phosphorylation in the light of a torsional mechanism of energy transduction and ATP synthesis – Invited review part 2. *J. Bioenerg. Biomembr.* **42** 301–309

Nath SS and Nath S 2009 Energy transfer from adenosine triphosphate: Quantitative analysis and mechanistic insights. *J. Phys. Chem. B* **113** 1533–1537

Tedeschi H 1980 The mitochondrial membrane potential. *Biol. Rev.* **55** 171–206

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