



## Review

# Analysis of molecular mechanisms of ATP synthesis from the standpoint of the principle of electrical neutrality



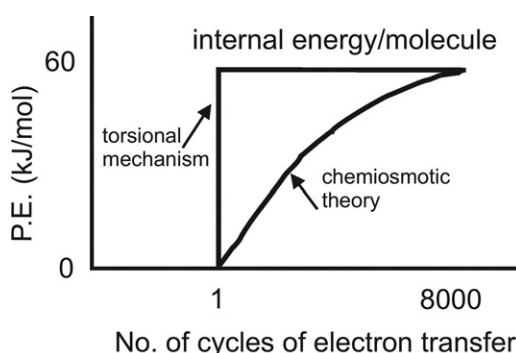
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## HIGHLIGHTS

- Theories of biological energy coupling and mechanisms of ATP synthesis are reviewed.
- Current ATP theories are evaluated based on the principle of electrical neutrality.
- Mitchell's chemiosmotic theory is shown to violate the electroneutrality principle.
- A dynamically electrogenic but overall electroneutral mode of ion transport is proposed.
- Nath's torsional mechanism satisfies electroneutrality and is a more complete theory.

## GRAPHICAL ABSTRACT



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F<sub>1</sub>F<sub>0</sub>

Ion transport

## ABSTRACT

Theories of biological energy coupling in oxidative phosphorylation (OX PHOS) and photophosphorylation (PHOTO PHOS) are reviewed and applied to ATP synthesis by an experimental system containing purified ATP synthase reconstituted into liposomes. The theories are critically evaluated from the standpoint of the principle of electrical neutrality. It is shown that the obligatory requirement to maintain overall electroneutrality of bulk aqueous phases imposes strong constraints on possible theories of energy coupling and molecular mechanisms of ATP synthesis. Mitchell's chemiosmotic theory is found to violate the electroneutrality of bulk aqueous phases and is shown to be untenable on these grounds. Purely electroneutral mechanisms or mechanisms where the anion/counteranion gradient is dissipated or simply flows through the lipid bilayer are also shown to be inadequate. A dynamically electrogenic but overall electroneutral mode of ion transport postulated by Nath's torsional mechanism of energy transduction and ATP synthesis is shown to be consistent both with the experimental findings and the principle of electrical neutrality. It is concluded that the ATP synthase functions as a proton-dicarboxylic acid anion cotransporter in OX PHOS or PHOTO PHOS. A logical chemical explanation for the selection of dicarboxylic acids as intermediates in OX PHOS and PHOTO PHOS is suggested based on the pioneering classical thermodynamic work of Christensen, Izatt, and Hansen. The nonequilibrium thermodynamic consequences for theories in which the protons originate from water vis-a-vis weak organic acids are compared and contrasted, and several new mechanistic and thermodynamic insights into biological energy transduction by ATP synthase are offered. These considerations make the new theory of energy coupling more complete, and lead to a deeper understanding of the molecular mechanism of ATP synthesis.

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## 1. Introduction

The synthesis of adenosine-5'-triphosphate (ATP), the universal biological energy currency, catalyzed by the enzyme  $F_1F_0$ -ATP synthase is the fundamental means of cellular energy production in animals, plants and microorganisms. It is among the most important and frequently occurring enzyme reactions in biology. ATP synthesis is achieved by coupling of the reactions of oxidation and phosphorylation in the process of oxidative phosphorylation (OX PHOS) or light reactions and phosphorylation (PHOTO PHOS) in photosynthesis. The prevailing theory of energy coupling serves as a guiding compass for several sectors of biochemical and biophysical research. Hence, the mechanism underlying the coupling of chemical reactions on the redox/photo and ATP sides is among the most important questions of physical and biophysical chemistry. In this invited article, the major theories of biological energy coupling are briefly delineated (Sections 2 and 3). In Section 4, these theories of energy coupling and molecular mechanisms of ATP synthesis are critically examined from the standpoint of the principle of electrical neutrality. It is shown that the principle imposes strong constraints on possible mechanisms of energy transduction, coupling, and ATP synthesis.

## 2. Classical theories of energy coupling in OX PHOS

The first theory of energy coupling in OX PHOS proposed by Slater [1] envisaged a chemical high-energy intermediate as the link between oxidation and phosphorylation. The theory was abandoned after a massive and lengthy search (lasting ~20 years) for the elusive chemical intermediate proved futile, and was eventually replaced by Mitchell's chemiosmotic theory of energy coupling [2,3]. The chemiosmotic theory postulated that energy coupling was achieved in OX PHOS by a “protonmotive force”  $\Delta p$  [Eq. (1), where  $\Delta p$  is in units of mV] obtained by addition of the bulk-to-bulk  $\Delta pH$  and a delocalized electrical potential,  $\Delta\phi$  between bulk aqueous phases created by translocation of uncompensated protons across the membrane by the redox complexes in the respiratory chain.

$$\Delta p = \Delta\phi - 60\Delta pH \quad (1)$$

In the theory of chemiosmosis, the electrogenic  $\Delta p$  created across bulk aqueous phases is considered as the obligatory energy intermediate

coupling oxidation and phosphorylation [3,4]. According to the theory, the membrane itself plays no active role in the energy transduction, serving only as “insulation material” for separating two bulk phases, and Mitchell repeatedly emphasized this point and the key role of such “energized bulk aqueous media” [4]. The chemiosmotic theory is an equilibrium theory lying in the realm of classical equilibrium thermodynamics, and the  $\Delta p$  is considered by the theory to equilibrate both with the respiratory chain and the high-energy squiggle (the  $\sim$ ) in ATP [2–4].

### 2.1. The ongoing debate on OX PHOS since the 1960s

The chemiosmotic theory itself had a contentious history, with part of the accumulated body of experimental evidence supporting the theory, and part of it in conflict with it [summarized in refs. 5–7]. The theory was severely criticized by many stalwarts of 20th century biochemistry, including E. C. Slater [8], R. J. P. Williams [9], Albert Lehninger [10], Gregorio Weber [11], and David Green [12] on the grounds of it either being “physically unsound,” involving “unrealistic assumptions,” or being “unsupported by experiments” and having “no basis in fact” [8–12], and specifically of violating “the necessity to observe charge neutrality in chemical reactions” [12]. However, despite long and heated debates, among the most acrimonious in modern science, and commonly known as “the OX PHOS wars” [13], the controversies were never resolved [5–7]. Even the scientific ingenuity of the above stalwarts of biochemistry and biophysics and the efforts of a large number of researchers in the field of bioenergetics in the 20th century could not formulate a theory of energy coupling that might be put in place of chemiosmosis. Moreover, the design of experiments and the interpretation of data failed to offer any guidance either in devising a rational substitute. The chemiosmotic theory was incorporated into the textbooks more by erosion of the opposition than by any decisive experimentation or theoretical analysis.

## 3. New conceptual framework for energy coupling in OX PHOS and PHOTO PHOS

Following a fresh *molecular systems biology/engineering* approach to the problem, an alternative theory of energy coupling and molecular

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