ATP-Synthase: More than an Enzyme

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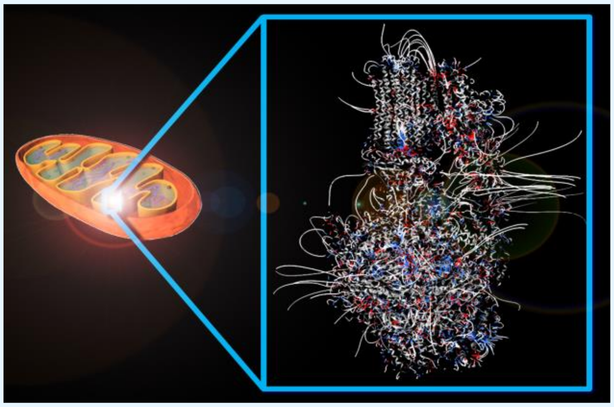
GRAPHICAL ABSTRACT

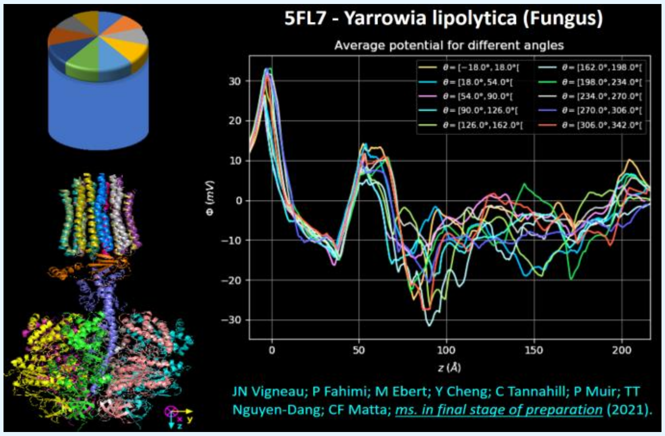


ABSTRACT

This talk underscores the biological role of electric fields and potentials of enzymes beyond their roles as catalysts. Recent crystallographic structures of ATP synthase from 5 species have been used to calculate and compare their approximate electrostatic potentials and fields. Striking patterns in these scalar and vector fields are discovered across ATP synthases obtained from 5 species. The crucial biophysical role of this field and its associated potential in the function of ATP synthase is briefly outlined below in the context of Mitchell's chemiosmotic theory (Nobel Prize 1978). The textbook equation that captures chemiosmotic theory is:

$$\begin{aligned} \Delta G &= \Delta G_{\text{chem.}} + \Delta G_{\text{elec.}} \\ &= 2.3nRT\left(\log[\mathrm{H}^+]_{\mathrm{P}}^{\text{out}} - \log[\mathrm{H}^+]_{\mathrm{N}}^{\text{in}}\right) + \mathscr{F} Z\Delta\psi \\ &= 2.3RT\Delta\mathrm{pH} + \mathscr{F} Z\Delta\psi \;. \qquad (1) \end{aligned}$$

Our calculations suggest that, due to the intrinsic field of ATP synthase itself **(Fig. 1 and 2)**, Eq. (1) must be augmented by including a term that accounts for the contribution to ΔG of the difference in ATP synthase's electrostatic potential, $\Delta\psi_{\text{ATPase}}$, between the points of entry and exit of the protons in the mitochondrion.



5FL7 - Yarrowia lipolytica (Fungus)

JN Vigneau; P Fahimi; M Ebert; Y Cheng; C Tannahill; P Muir; TT Nguyen-Dang; CF Matta; *ms. in final stage of preparation* (2021).

Fig. 1 Electrostatic potential as a function of radial angle (averaged over 36^{o} segments) in different planes as a function of the z-coordinate (the long molecular axis). (See Fig. 2 as well).

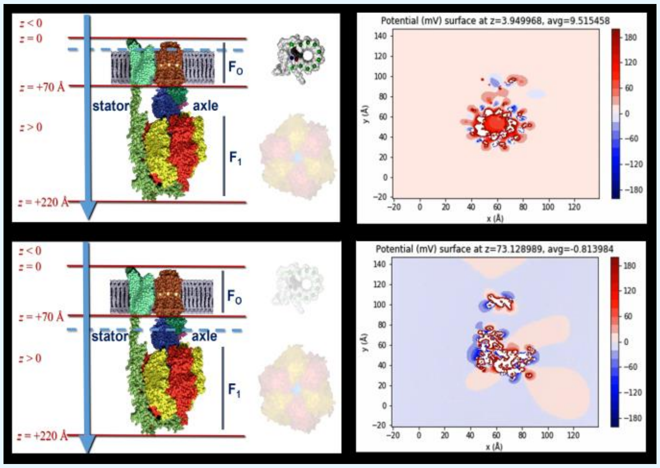


Fig. 2 Cross sections at 2 heights (z-coordinate) showing the topography of the electrostatic potential. Near the entry, the proton encounters a ***positive potential (red)*** that represents a barrier (see Fig. 1), while at the point of exit it finds a ***negative potential (blue)***. The positions of the planes along the z-coordinate (the long molecular axis) is indicated by the dashed horizontal blue line on the diagram representing ATP synthase on the left panel.

With the new energy term, we propose an "augmented" chemisomotic theory equation:

$$\Delta G = \Delta G_{\text{chem.}} + \Delta G_{\text{elec.}} + \Delta G_{\text{ATPase}} \tag{2}$$

which, written explicitly is:

$$\begin{aligned}\Delta G &= 2.3nRT\Delta\text{pH} + n\mathscr{F}Z\Delta\psi + n\mathscr{F}Z\underbrace{\Delta\psi_{\text{ATPase}}}_{\text{NEW TERM}} \\ &= 2.3nRT\Delta\text{pH} + n\mathscr{F}Z\left(\Delta\psi + \Delta\psi_{\text{ATPase}}\right)\end{aligned} \tag{3}$$

Summing-up → we can assign _3 separate but complementary roles_ to ATP synthase :

(1) Its _putative role_, and that is the ***catalysis*** (_i.e._ lowering the $\Delta G^{\ddagger}$) of the reaction:

$$\text{ADP} + \text{P}_\text{i} \rightleftarrows \text{ATP} + \text{H}_2\text{O} \tag{4}$$

(2) _A novel role_, that is, of ***altering the ΔG of the reaction of translocation of protons*** from the inter-membrane gap in the mitochondrion to the mitochondrial matrix, _i.e._, the reactions:

$$\text{H}^+_{\text{inter-membrane space}} \rightleftarrows \text{H}^+_{\text{matrix}} \tag{5}$$

$$\Delta G = \Delta G_{\text{chem.}} + \Delta G_{\text{proton grad.}} \boxed{+\underbrace{\Delta\psi_{\text{ATPase dipolar field}}}_{\text{NEW TERM}}} \tag{6}$$

(3) ATP synthase appears to _create a potential energy barrier that regulates the rate of proton translocation itself_ (the power, i.e., the rate of release of energy by the chemiosmotic process)

Said differently, due to the enzyme's *very structure* and due to the *chemiosmotic origin of the free energy it harnesses*, ATP synthase functions over and above its role as an enzyme and is more than strictly a biological catalyst.

Since this is a part of a larger programme of research in our group, time permitting, we will also touch on topics such as the "Mitochondrion Paradox".

Keywords: ATP synthase; chemiosmotic theory; mitochondrial biophysics; electric field; electrostatic potential

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