Electrostatic Contributions of ATP Synthase to Cellular Energy Production

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ATP synthase is the cell's "ATP turbine" catalyzing the formation of ATP using the proton-motive force (pmf) maintained across the inner mitochondrial membrane (IMM). ATP synthase appears to contribute directly to the ΔG driving the synthesis of ATP in the mitochondrion (and not only acts as a catalyst). We propose a new term that originates from the charge distribution in ATP synthase itself. The energy per proton transferred from the intermembrane space to the mitochondrial matrix is re-written (in standard notation):

$$\Delta G/\mathrm{H}^+ = \Delta G_{\text{chem.}} + \Delta G_{\text{elec.}} \pm \underbrace{\Delta G_{\text{ATP synthase}}}_{\text{New term}} = 2.3\,RT\Delta\text{pH} + F\Delta\psi \pm \underbrace{F\Delta\psi_{\text{ATP synthase}}}_{\text{New term}}$$

We analyzed 178 ATP synthase crystal structures from bacteria, fungi, plants and mammals (including human). After cleaning, neutral-pH protonation, and AMBER charge assignment, each was subjected to Poisson–Boltzmann calculations (PDB2PQR + APBS) to generate 3D molecular electrostatic potential (MESP) maps. In-house Python pipelines quantified potential differences along the proton-translocation axis under pH 7.0, 298 K, $\varepsilon_{\text{solvent}} = 78.5$, $\varepsilon_{\text{protein}} = 6$, $\varepsilon_{\text{bilayer}} = 2\text{-}4$, and 150 mM ionic strength.

Across most non-human species, ATP synthase *reinforces* the proton-motive force ($\Delta\psi_{\text{ATP synthase}} \approx +10\text{-}45$ mV), but human ATP synthase shows an opposing field ($\Delta\psi_{\text{ATP synthase}} \approx +15$ mV), reducing the effective driving potential by ~10-15%. This "destructive" contribution lowers $\Delta G/\mathrm{H}^+$ by ~2 kJ·mol^{-1} per proton (~6-8 kJ·mol^{-1} per ATP), implying ~10% lower coupling efficiency and greater basal heat dissipation. ATP synthase thus "moonlights" as an electrostatic participant in energy transduction, and in humans this built-in inefficiency may help explain inter-individual metabolic variability and calls for a revision of standard chemiosmotic and calorimetric assumptions. (See Table 1 below).

Table 1. Electrostatic contributions of ATP synthase across selected species.

Species (PDB code)	$\Delta\psi_{\text{ATP synthase}}$ (mV)	Net Effect
Bacillus PS3 (6N2Y)	~ –18	Reinforcing
Y. lipolytica (5FL7)	~ –45	Reinforcing
Sus scrofa (6J5I)	~ –12	Reinforcing
Human (8H9T)	~ +15	Opposing/destructing

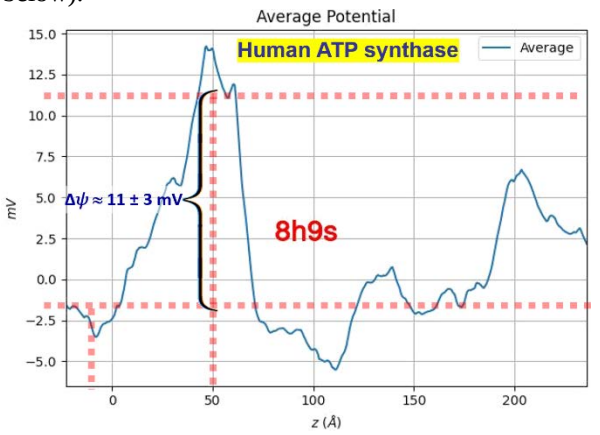

Figure 1. Average electrostatic potential of human ATP synthase along the proton-translocation (*z*-) axis showing $\Delta\psi \approx 11$ mV between entry and exit. Unlike non-human enzymes, the human enzyme exerts an opposing field (~10 % efficiency loss; ~6–8 kJ·mol^{-1} per ATP), indicating intrinsically lower coupling efficiency and greater heat dissipation.

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