

# A new systems biology model of mitochondrial bioenergetics: application to mitochondrial pathologies

Ivan Chang<sup>1,2\*</sup>, Claire Pertuiset<sup>3</sup>, Margit Heiske<sup>3</sup>, Thierry Letellier<sup>3</sup>,  
Douglas Wallace<sup>4,5</sup>, Pierre Baldi<sup>2,6</sup>

1. Department of Biomedical Engineering, UC Irvine, Irvine, USA
2. Institute of Genomic Biology, UC Irvine, Irvine, USA
3. INSERM U688 “Physiopathologie mitochondriale”; Université Victor Segalen-Bordeaux 2, Bordeaux, France
4. Department of Ecology & Evolutionary Biology, UC Irvine, Irvine, USA
5. Center for Molecular & Mitochondrial Medicine and Genetics, UC Irvine, Irvine, USA
6. School of Information and Computer Sciences, UC Irvine, Irvine, USA

\*E-mail: [iychang@uci.edu](mailto:iychang@uci.edu)

## Extended Abstract

Mitochondrial oxidative phosphorylation (OXPHOS) is the principle source of energy production in cells, and reactive oxygen species (ROS). Dysfunctions of this system have been associated with more than 120 human syndromes. We have constructed an integrative OXPHOS model to provide quantitative analysis of the dynamics between the rate of electron transfer, proton translocation, work done by the proton circuit, as well as the production of ROS, while focusing on the adaptability of the model to different tissues or pathological state. This model contains detailed kinetics and thermodynamics constraints on the same basic components of OXPHOS as previous models (transporters, respiratory chain, ATP synthase, etc. [1,2]); however, we present a new view on the energy transduction complexes with the introduction of a novel flux equation that can be adapted to the characteristics of each individual respiratory chain complex, through experimental determination of the equation parameters.

Each complex in the electron transport chain (ETC) is viewed as a chemiosmotic black-box that couples the release of the free energy from the electron transfer between a higher and a lower potential carrier, to the translocation of proton across the membrane. It contains three electron transfer processes: donor to complex, internal, and complex to acceptor (Figure-1). We derived the corresponding steady-state flux equation via non-equilibrium thermodynamic (NET) force-flux relation [3], and assumption of rapid equilibrium at the boundaries; the result is a reversible flux equation with kinetic and NET constraints on the flux through the complex. An electron slippage, such as the loss of electron to ROS, can be viewed as a reduction in the force-flux efficiency, and is included as a parameter,  $\gamma$ , in the NET constraint.

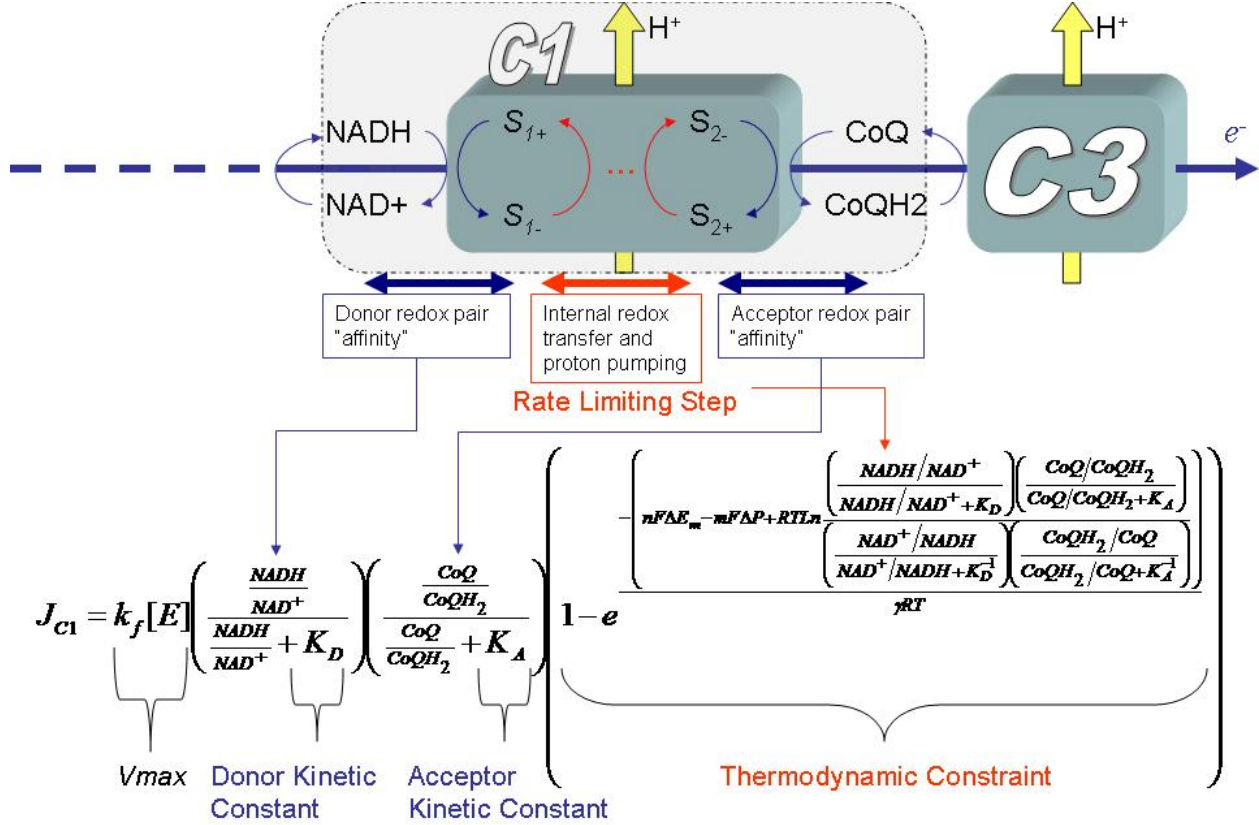
Parameters from the equation are grouped into three: kinetic parameters describing affinity constants of the donor or the acceptor redox pair ( $K_D$ ,  $K_A$ ), thermodynamic constants describing the changes in total chemical potential across the black box ( $\Delta E$ - $\Delta P$ ), and free parameters of each complex ( $V_{max}$ ,  $\gamma$ ). To experimentally determine the kinetic parameters, we reduced the complexity of the equation by saturating one of the substrate concentrations to ensure that the thermodynamic constraint and the kinetic factor of the saturating electron carrier are maintained

at values close to unity, leaving the flux as a function of the only remaining kinetic factor. We then used spectrophotometry to find the  $K_D$  or the  $K_A$  as the correlation between the changes in flux and the oxidized/reduced ratio of the electron carrier.

Preliminary results have shown that with these three groups of parameters, we were able to fit and predict the functioning of each individual complex, and also able to mimic pathology by fitting the experimental behavior of OXPHOS (threshold). We addressed those fittings with a variant of Genetic Algorithm that included the concept of degeneration, where unnecessary parameters are lost through the survival of the solution despite accumulated damages [4]. This simplifies the adaptation of the general model to specific tissue or pathogenic training data, and allows for automated testing of new hypothetical parameters.

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3. Hill, TL (1977) *Free energy transduction in biology: The steady-state kinetic and thermodynamic formalism*. New York: Academic Press.
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Figure 1



Representation of the chemiosmotic black-box for respiratory chain complexes: The derivation of the flux equation for Complex I is shown as example.