Currents in Mitochondria and Nerve, a Slide Show

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Thanks to Tom Royston
and Jim Patton for inviting me

and for the kind support for many years
from UIC Biomedical Engineering

Abstract

Electrodynamics of current provide much of our technology, from telegraphs to the wired infrastructure powering the circuits of our electronic technology.

Current flow is analyzed by its own rules. It cannot be analyzed one charge at a time. There are too many charges.

Current flow is important in biology. Currents are carried by electrons in mitochondria. Currents are carried by ions in nerve and muscle cells.

Currents EVERYWHERE follow the rules of current flow: Kirchhoff's current law and its generalizations.

The role of electricity in generating ATP was discovered long ago. The chain of electron transport has been determined that provides protons to generate ATP in ATPsynthase. The chain of electron transport forms circuits for currents that should be analyzed by Kirchhoff's law.

Circuit analysis is easily applied to short systems like mitochondria that have just one internal electrical potential using the Hodgkin Huxley Katz HHK equation. The HHK equation combined with descriptions of chemical reactions forms a computable model of cytochrome c oxidase that is part of the electron transport chain.

Current laws are needed to analyze the flow of electrons and protons, as they generate ATP in mitochondria and chloroplasts.

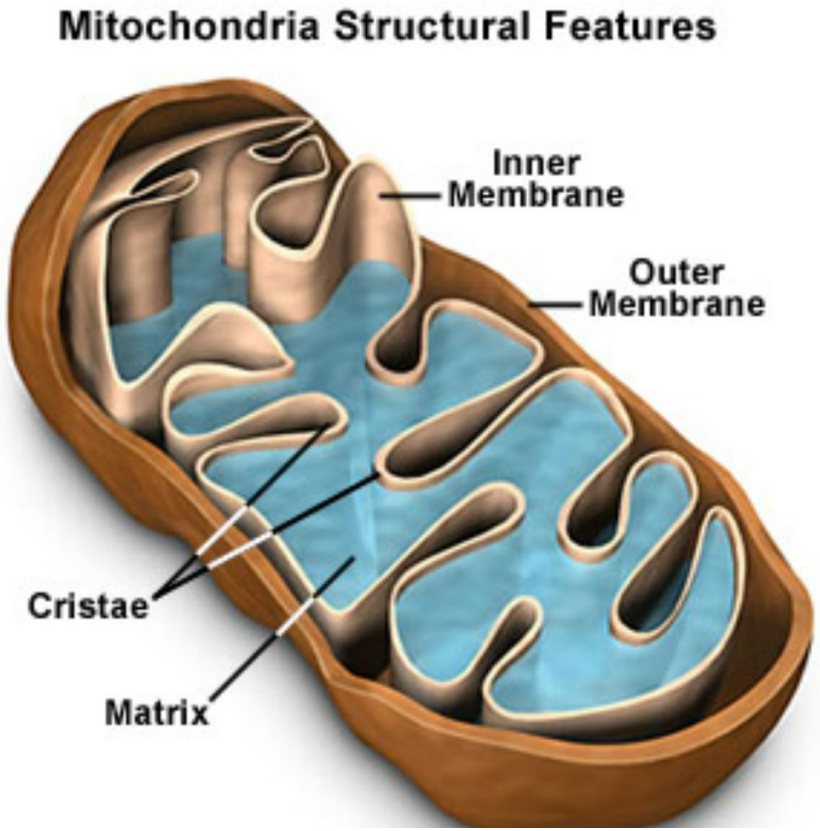
Acknowledgement

I am most grateful to the anonymous authors and artists who made the figures reproduced here. I have made zero intellectual contribution to the information in the figures.

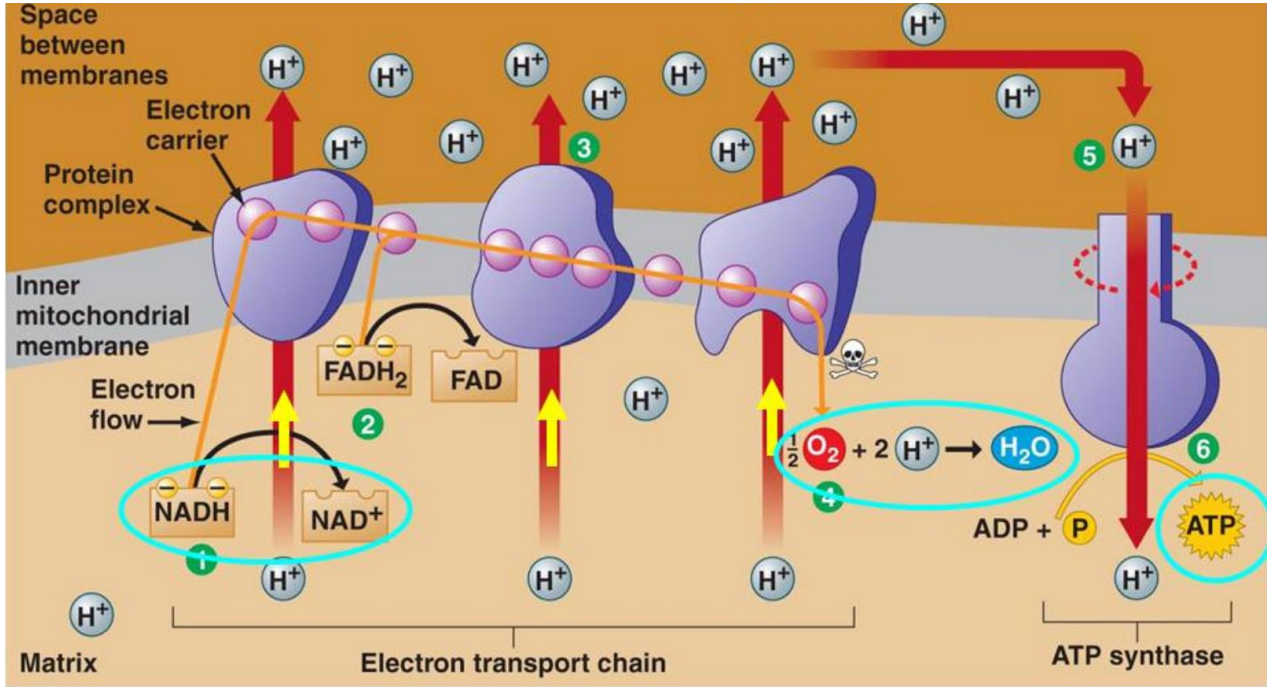
The figures convincingly document the importance of electron and proton flow as seen in the experimental literature of the respiratory chain, independent of theoretical discussion using current laws.

The figures in this paper are taken from public domain websites. It is not useful to provide individual references to these websites because they change so often. The websites all allow copying, as best I can tell. If I have inadvertently failed to give proper attribution, I will make corrections, and of course apologize.

I repeat: I have made no intellectual contribution to the figures or the work they report.



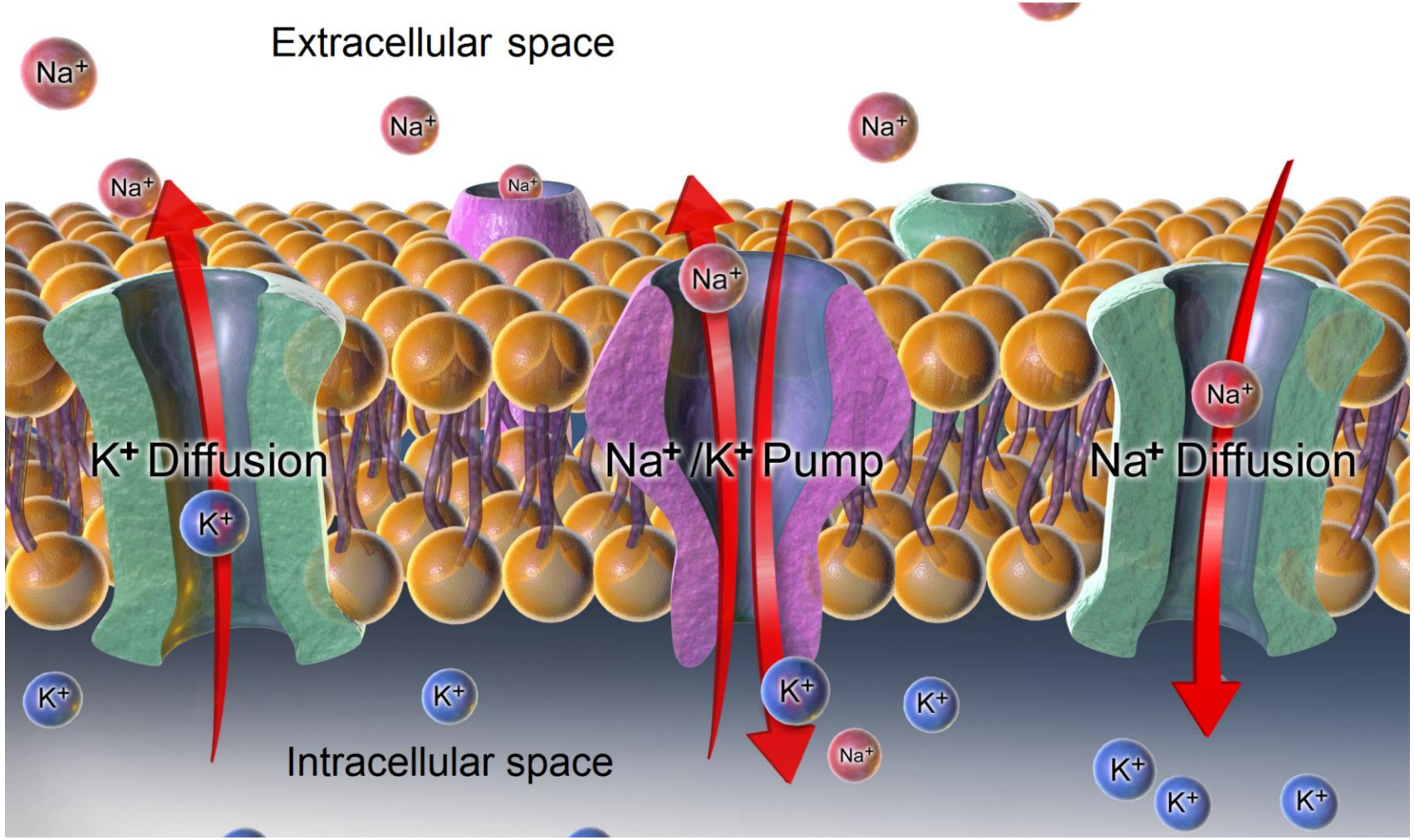
Electron Transport Chain and ATP Synthase

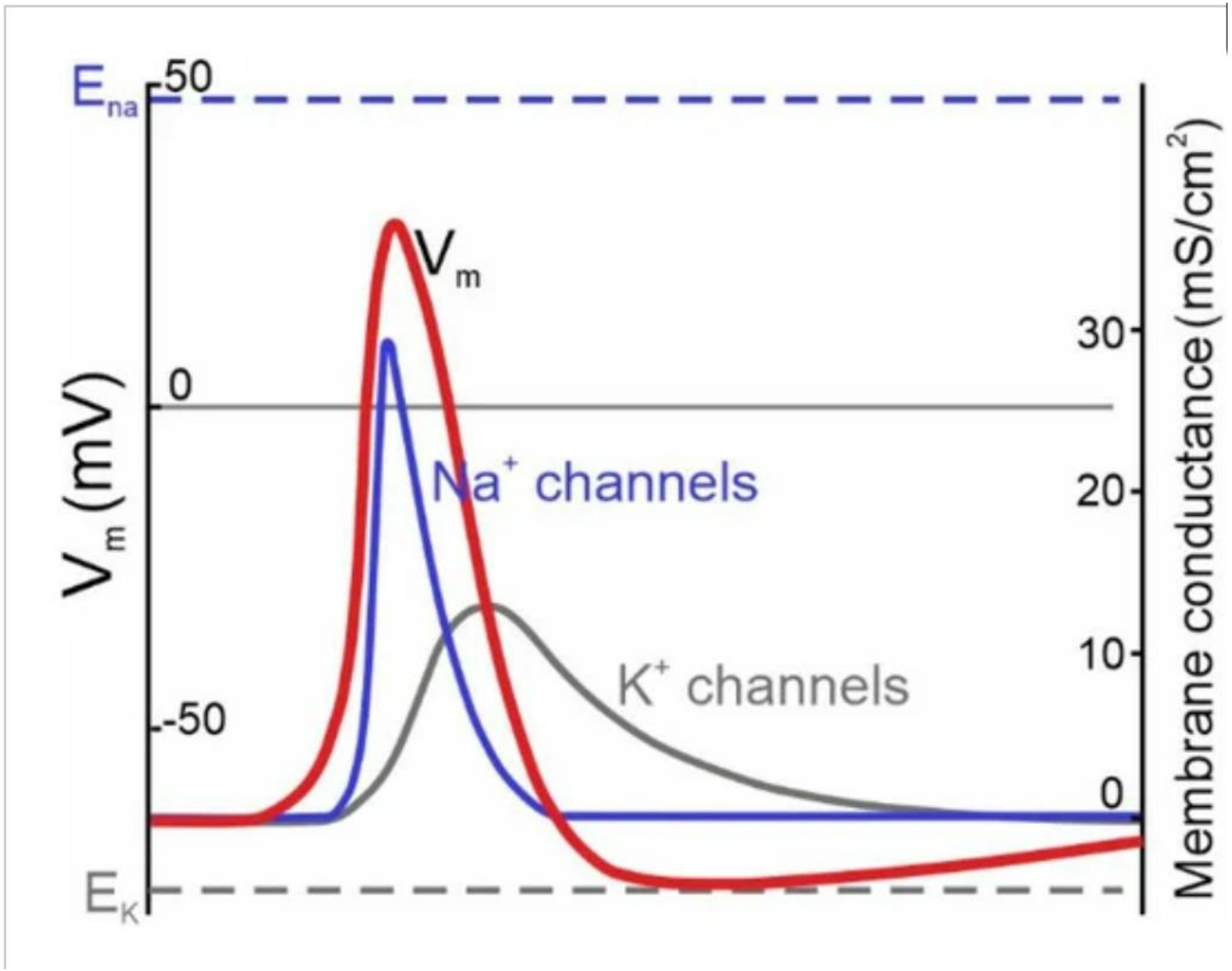


Output is ATP

What does this have to do with nerve fibers ?

Ion Channels of the Action Potential are Far Apart
They do not interact chemically



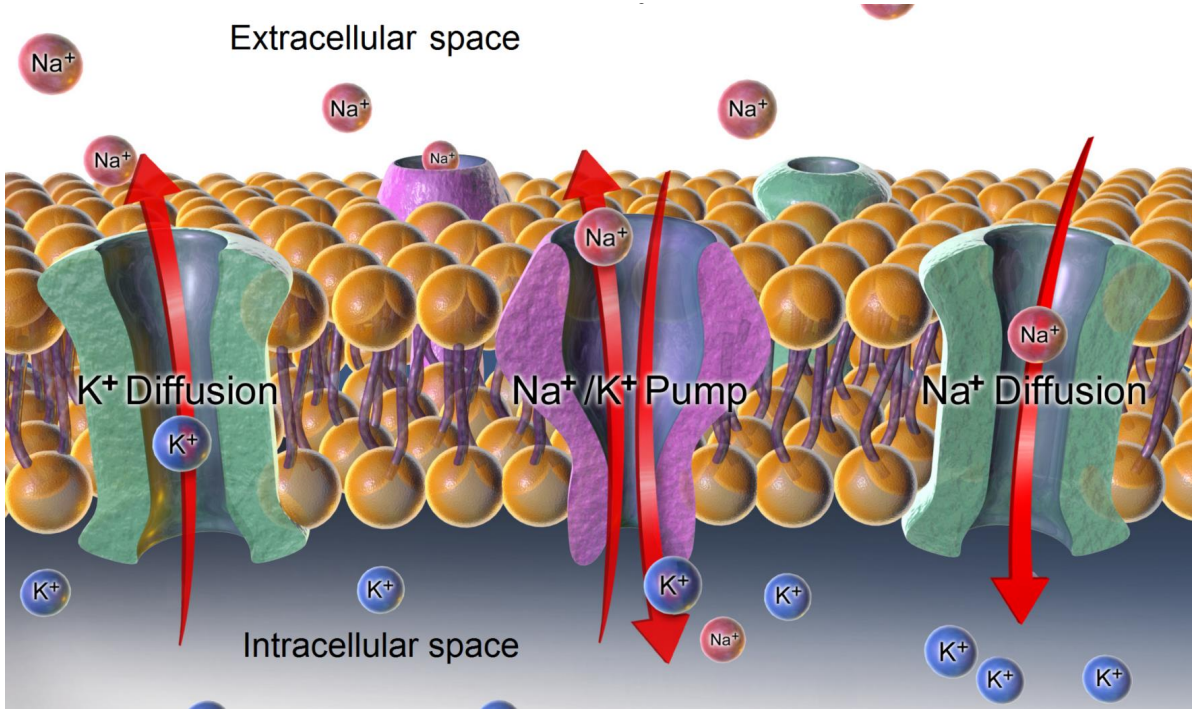


Channels Interact by Electric Field and Current Flow
NOT by biochemical interactions

Proteins Interact by Electric Field and Current Flow

Function <u>cannot</u> be explained by biochemical interactions following reaction laws

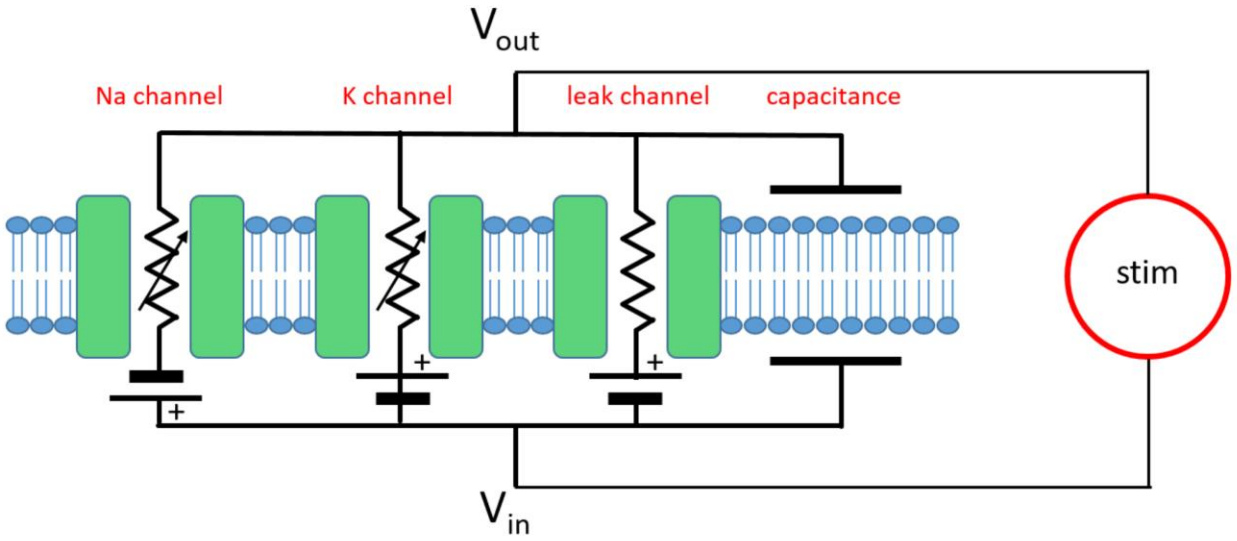
Function depends on ELECTRICAL interactions that follow laws of current flow

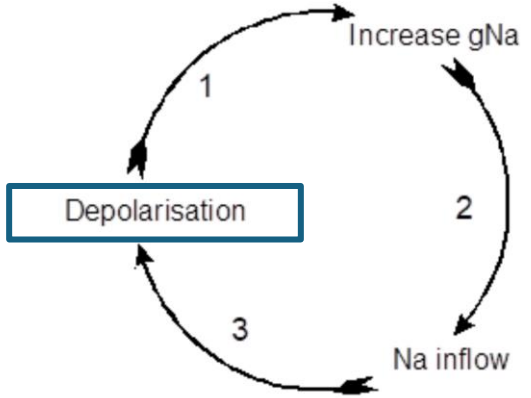


Ion Channels INTERACT to create the Action Potential

The interaction is ENTIRELY ELECTRICAL.

The channels do not interact chemically



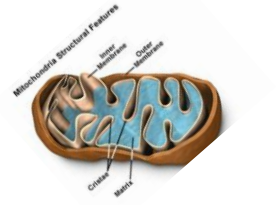


The membrane as an RC circuit. The circuit includes sodium, potassium and leakage ion channels. The batteries represent the equilibrium potential for each set of ions.

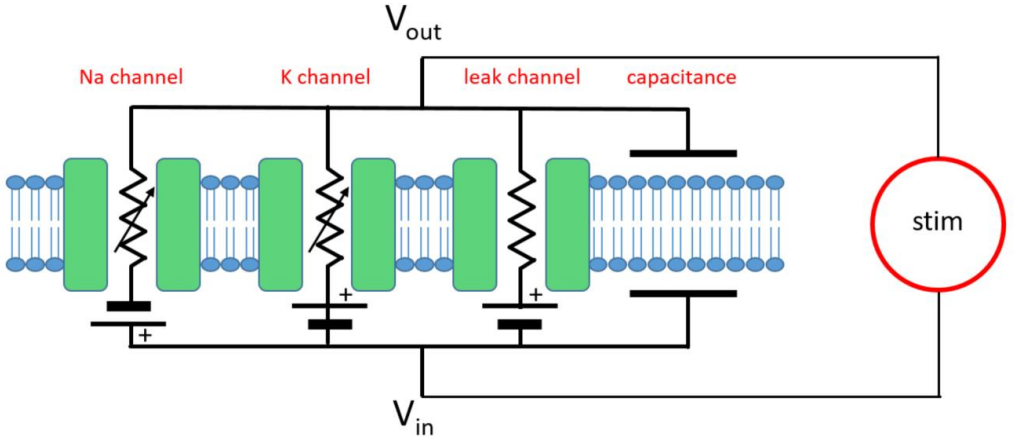
In short systems,

there is only one potential across the membrane.

Mitochondria are Short Systems



All channels and all membrane proteins have the same transmembrane potential



The membrane as an RC circuit. The circuit includes sodium, potassium and leakage ion channels. The batteries represent the equilibrium potential for each set of ions.

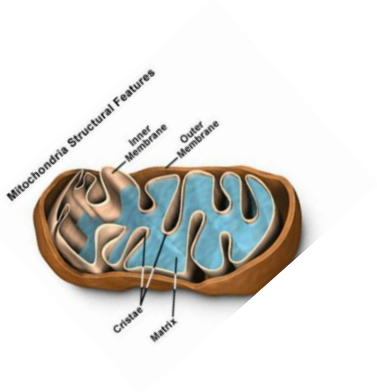
HHK equation:

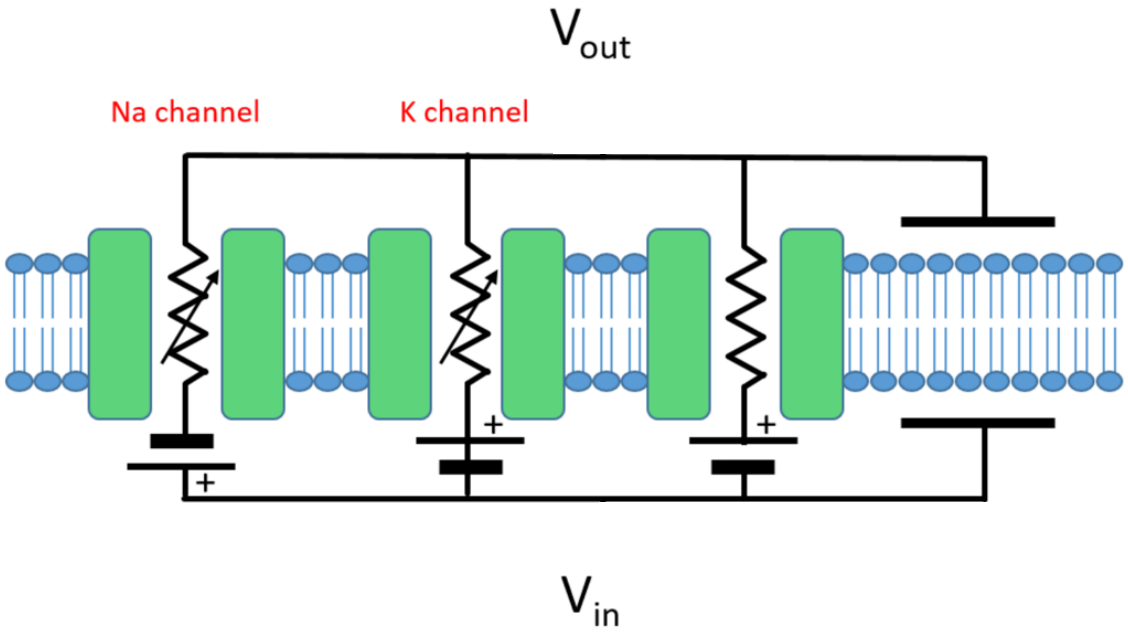
$$\text{Sum of All Currents} = \sum_j I_j + C_m \frac{\partial V}{\partial t}$$

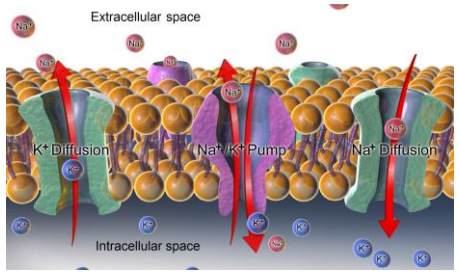
Eq. 11

Hodgkin, Huxley, Katz (1952)

'Measurement of current- voltage relations in the membrane of the giant axon of *Loligo', J. Physiol. (London), 116: 424-48.*







HHK Equation is Intuitively Obvious

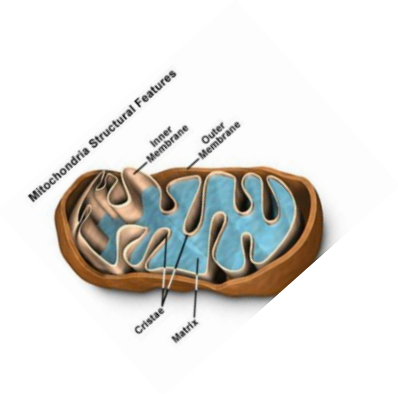
There is no place for current to go

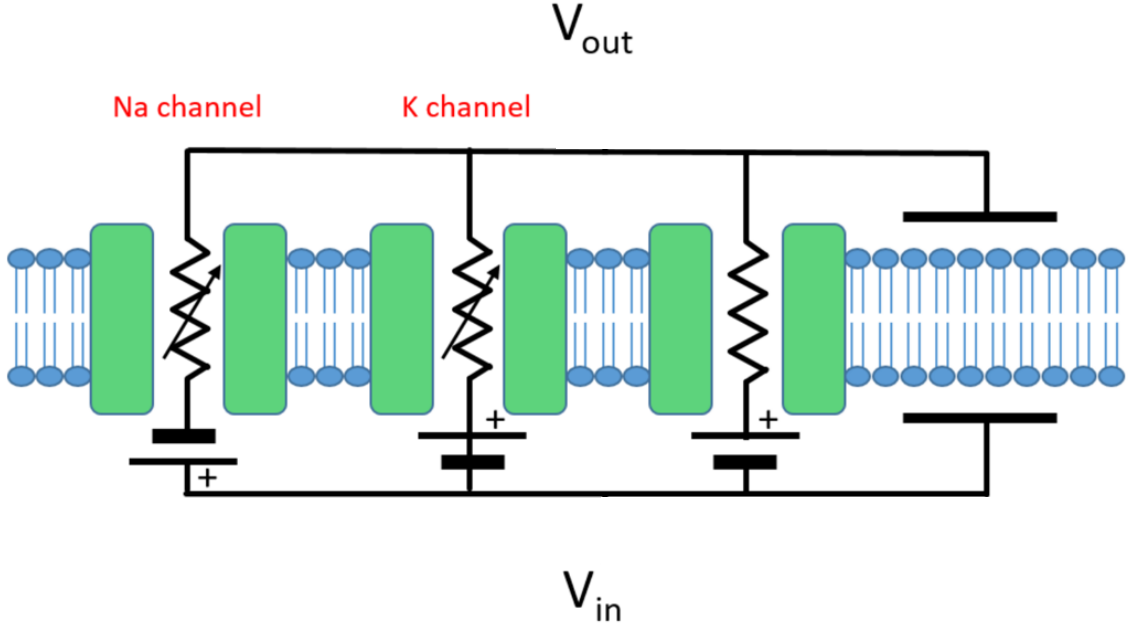
It can be derived by Kirchhoff's Current Law

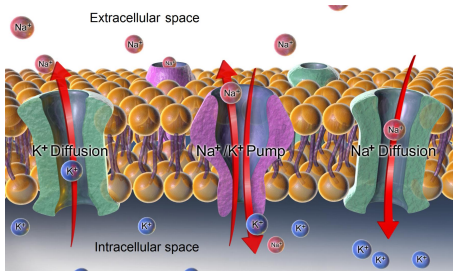
It is also a mathematical corollary of the Maxwell Equations of Electrodynamics.

It involves no assumptions.

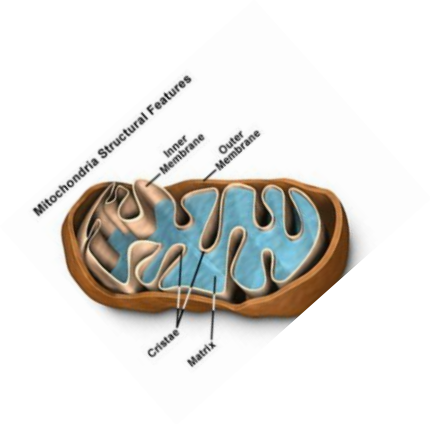
It is valid if all membrane elements have the same transmembrane potential.

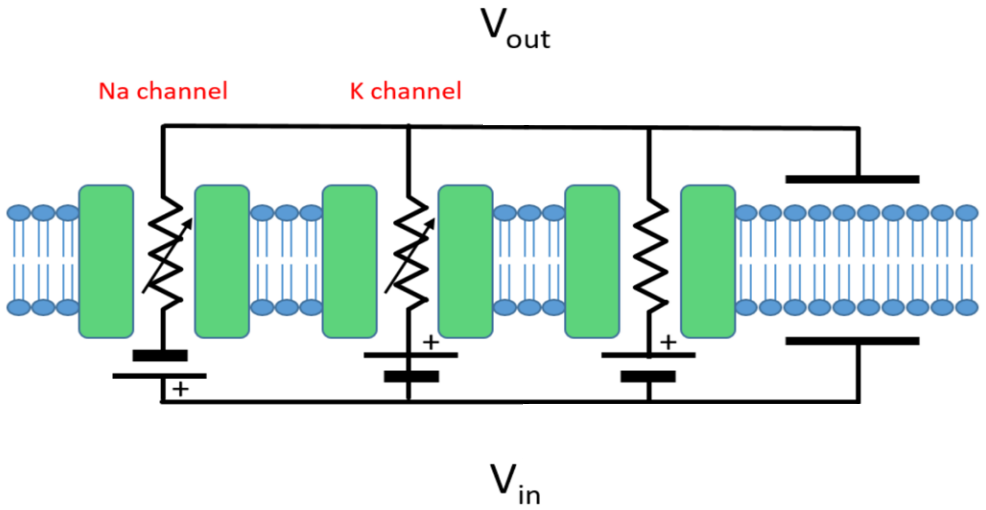


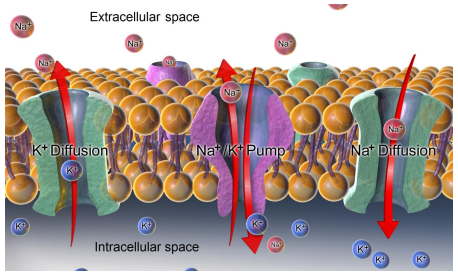




HHK Equation







One current is driven by the sum of the other currents

NO MATTER WHAT ION IS CARRYING THAT ONE CURRENT

The voltage changes so any one current equals the sum of the other currents

The currents interact

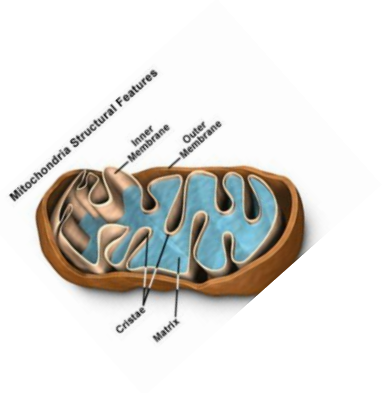
The currents are correlated

The CAUSE of one current is the sum of the OTHER CURRENTS

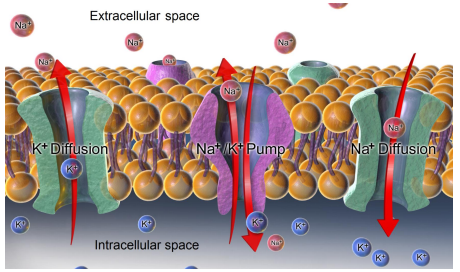
HHK Equation

One current is driven by the sum of the other currents
NO MATTER WHAT ION IS CARRYING THE CURRENT

The voltage changes so one current equals the sum of the other currents
If one current increases, the sum of the others decrease.

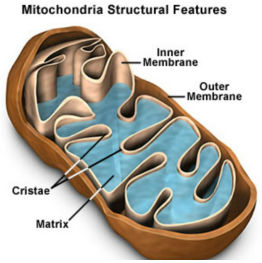


The currents interact
The currents are correlated
The cause of one current is the sum of the other currents



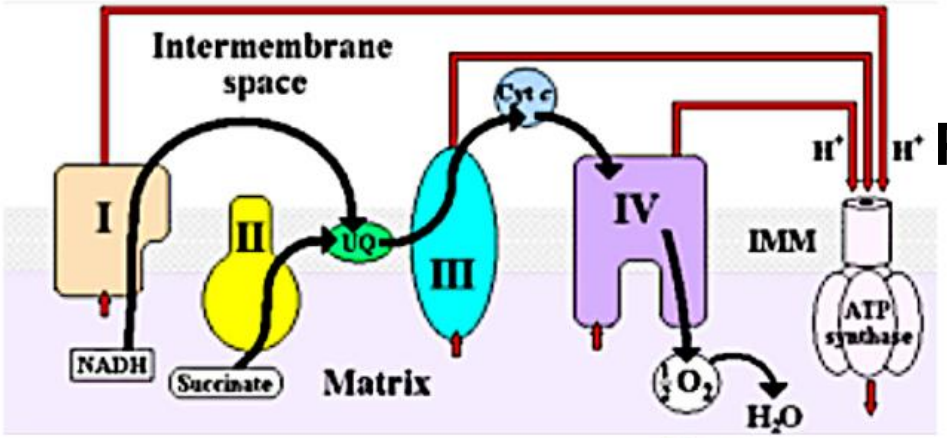
These rules apply to mitochondria.

The current through ATP Synthase is determined by the sum of all other currents.



FLOWS

Flow of Protons



Flow of Electrons

only

Input is

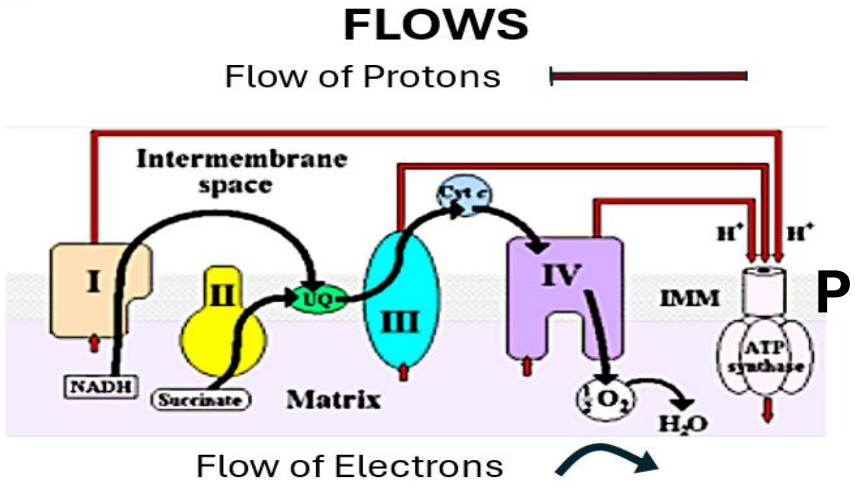
Proton Current

Output is

ATP from

ATP synthase

ATP production in mitochondria is driven by currents that obey Kirchhoff's Current Law



only

Input is

Proton Current

Output is

ATP from

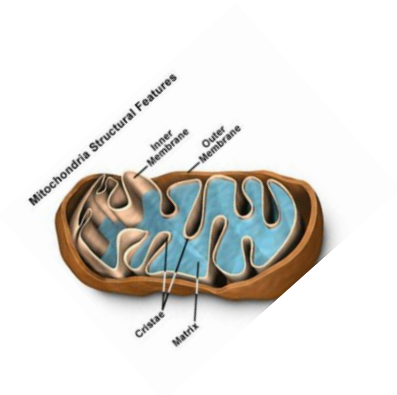
ATP synthase

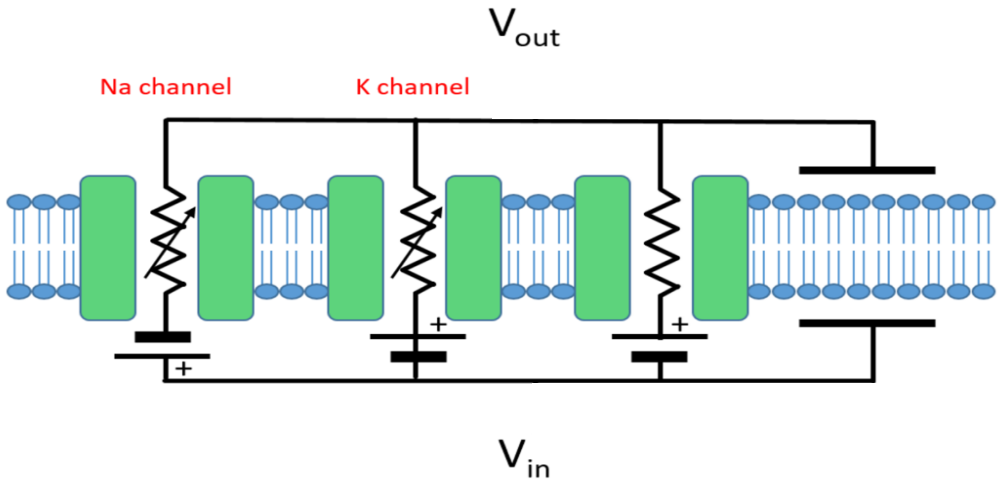
Currents in Circuits Cannot be Computed from Charges

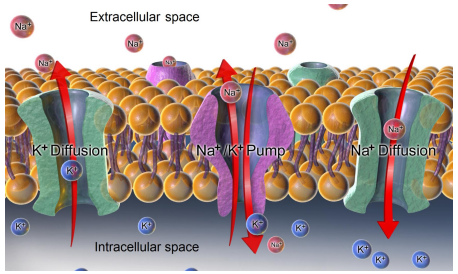
There are too many charges, something like 10^{18}

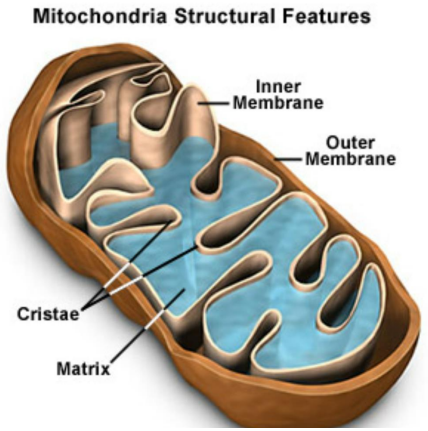
Computing charge charge interactions involves numbers like
10^{18} factorial (!)

Charge interactions, two at a time are $(10^{18})!\,(10^{18}-2)!$





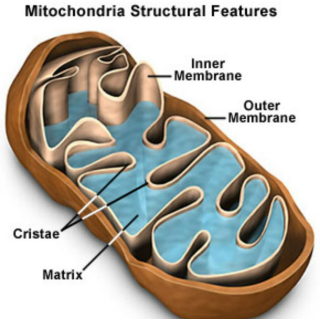




ATP production in mitochondria must be computed from Kirchhoff's Current Law

Kirchhoff's Current Law provides coarse graining of charge movement.

It is exact because it uses extra physics, the Maxwell Ampere Equation.

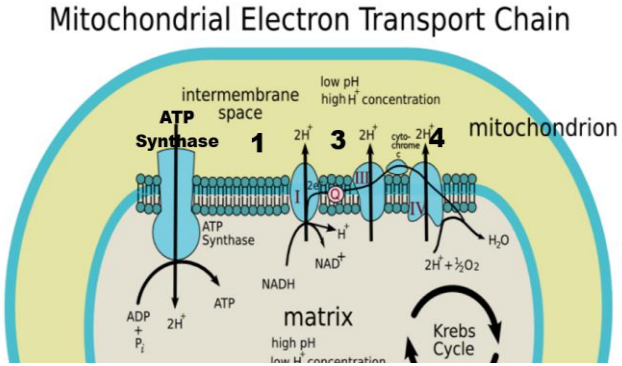


ATP production in mitochondria cannot be computed
1) from charges
2) from Coulomb's Law
3) existing Molecular Dynamics
4) from chemical reaction theory

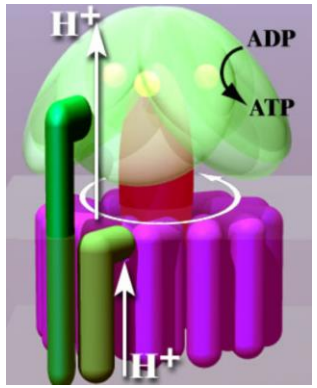
ATP production in mitochondria must be computed from Kirchhoff's Current Law

Kirchhoff's Current Law provides coarse graining of charge movement. It is exact because it uses extra physics, the Maxwell Ampere Equation.

All Components of Electron TRANSPORT chain involve Current



ATP Synthase



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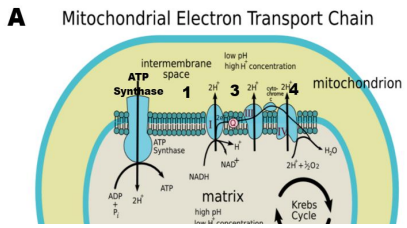
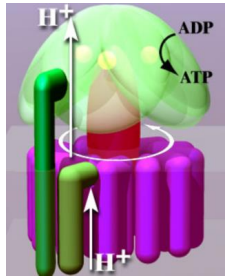
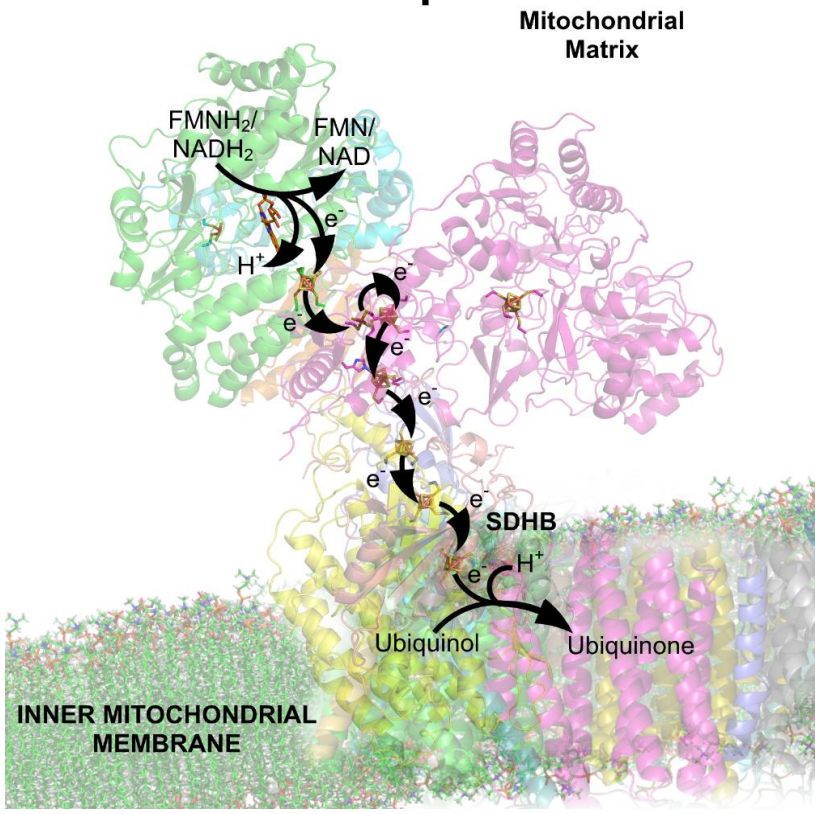


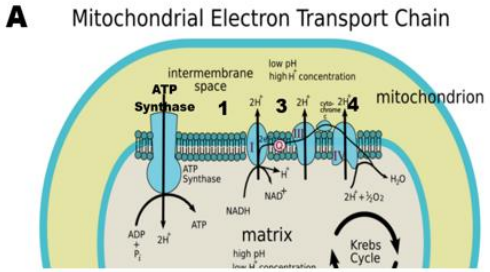
ATP Synthase



Complex 1



All Components of Electron TRANSPORT chain involve Current



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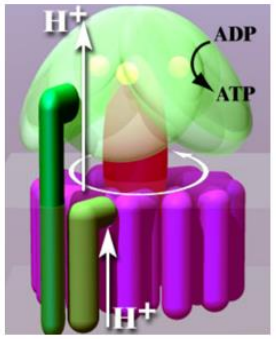
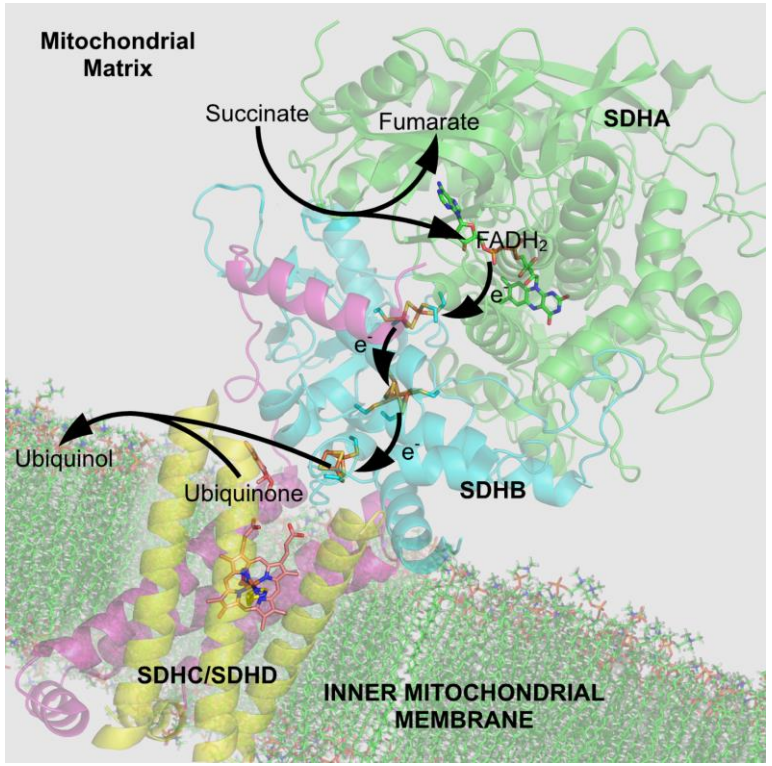
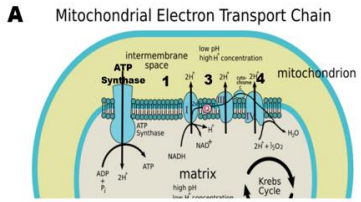


Complex 2

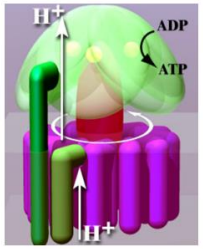
only electrons



All Components of Electron TRANSPORT chain involve Current

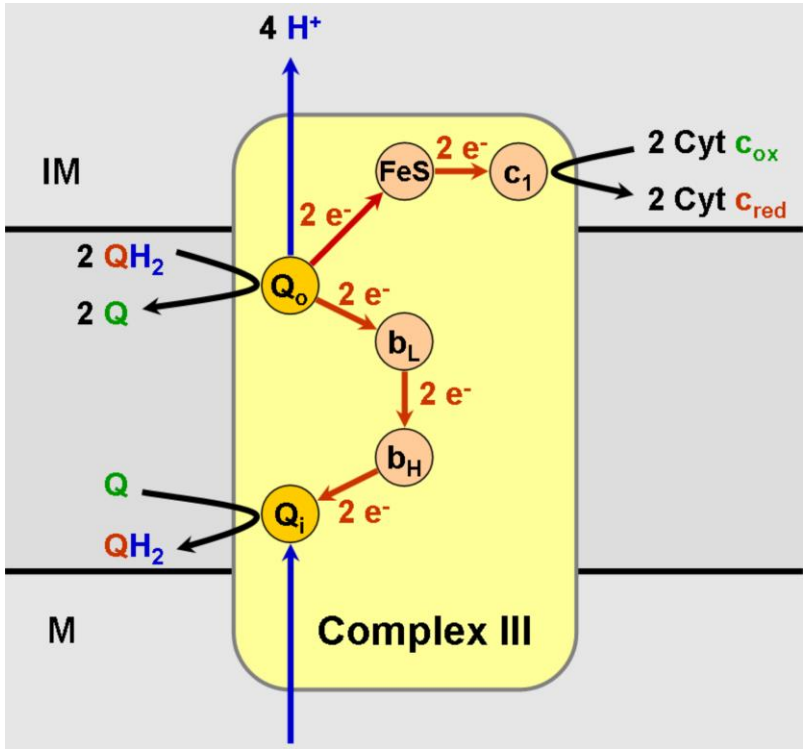


ATP Synthase

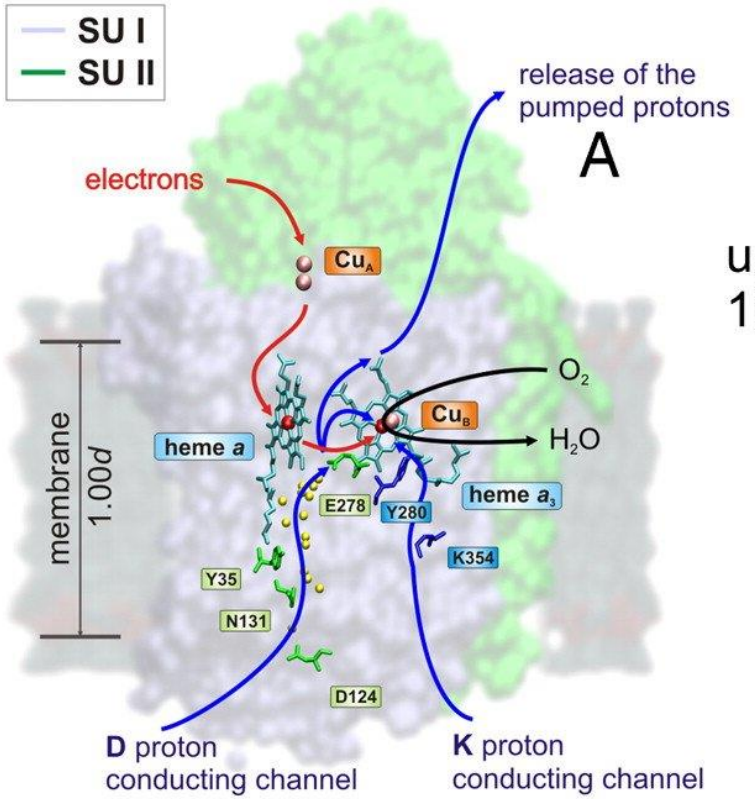


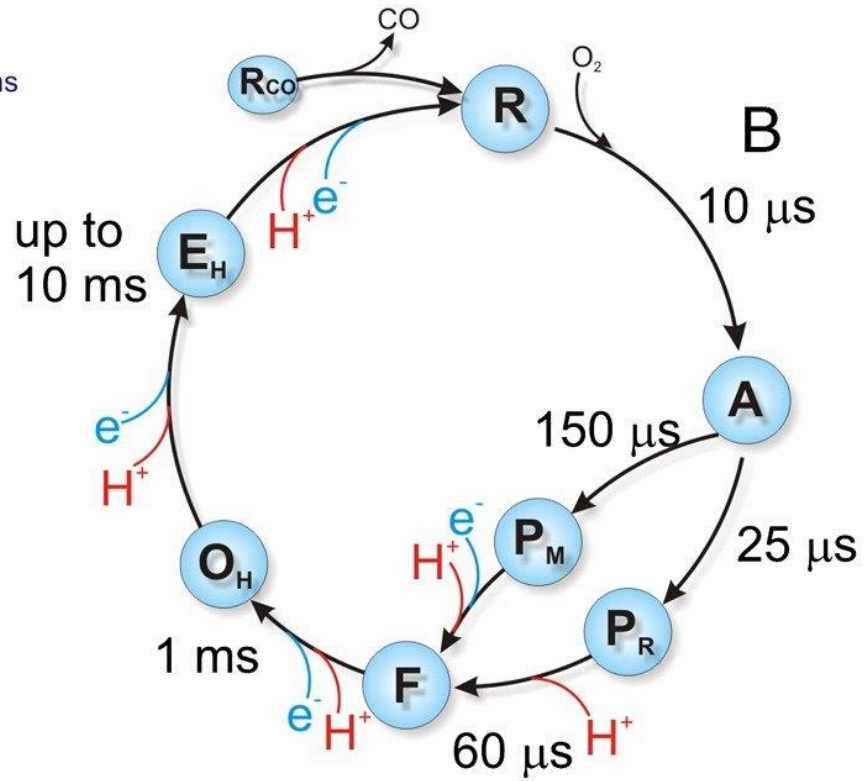
Complex 3

Coenzyme Q
Quinone pathways

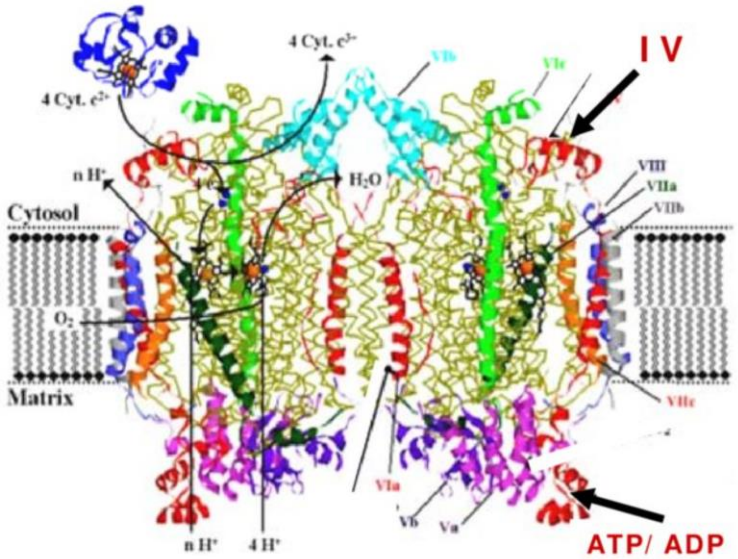


Complex 4
Cytochrome c Oxidase





Belevich et al, PNAS 2010;107:18469-74.



Circuit Model of Cytochrome Oxidase C

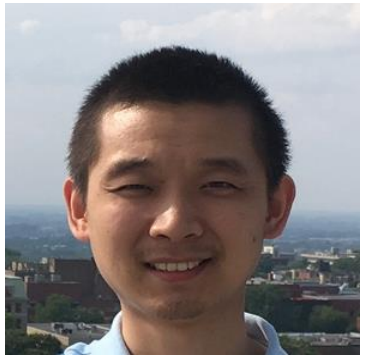
Project Leader

Shixin Xu

士鑫 徐

Huaxiong Huang

华雄 黄

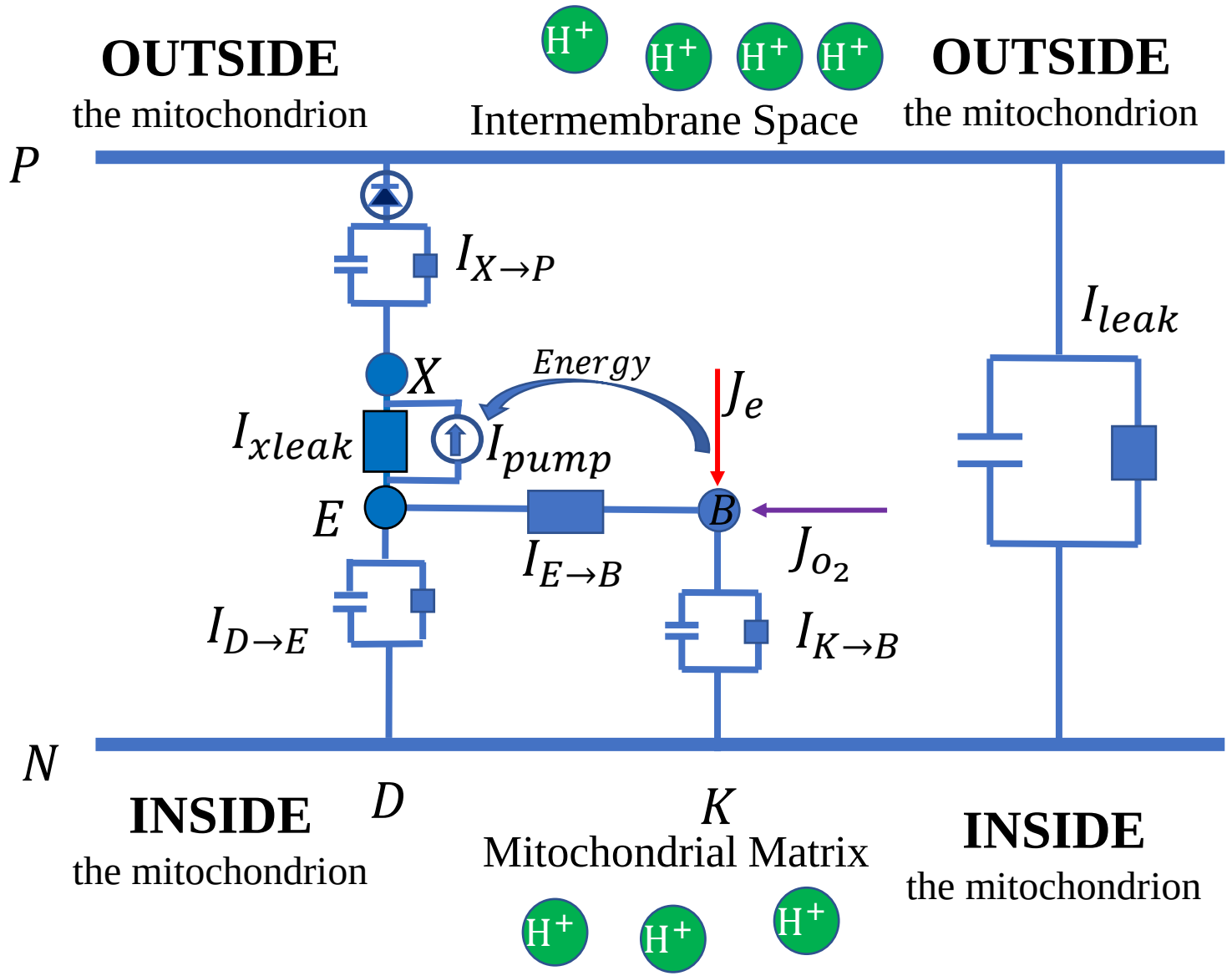


Zilong Song

宋子龙

Xu, Eisenberg, Song, and Huang. 2023. 'Mathematical Model for Chemical Reactions in Electrolytes Applied to Cytochrome c Oxidase: An Electro-Osmotic Approach', *Computation, 11: 253.*

Circuit Model of Cytochrome Oxidase C



Our Representation Without detailed reaction timings

2 Derivation of Electro-osmotic Model

We mainly focus on a mathematical model of elementary reactions

Chemical Reaction

$$\alpha_1 C_1^{z_1} + \alpha_2 C_2^{z_2} + \alpha_3 C_3^{z_3} \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \alpha_4 C_4^{z_4}, \tag{1}$$

where k_f and k_r are two constants for forward and reverse directions, $[C_i]$ is the concentration of i^{th} species, respectively. Here α_i is stoichiometric coefficient, z_i is the valence of i^{th} species and together they satisfy

$$\sum_{i=1}^{3} \alpha_i z_i = \alpha_4 z_4. \tag{2}$$

In particular, we have in mind a case where an active transporter ('pump') uses the energy supplied by a chemical reaction to pump molecules. Later, we will focus on the reaction for cytochrome c oxidase, i.e., for Complex IV of the respiratory chain

Chemical Reaction

$$2H^+ + \frac{1}{2}O_2 + 2e^- \underset{k_r}{\overset{k_f}{\rightleftharpoons}} H_2O. \tag{3}$$

According to the conservation laws, we have the following conservation of chemical elements (like sodium, potassium and chloride). Note that this conservation is in addition to the conservation of mass, because nuclear reactions that change one element in another are prohibited in our treatment, as in laboratories and most of life.

Chemical Reaction

$$\frac{d}{dt}(\alpha_4[C_1] + \alpha_1[C_4]) = 0, \tag{4a}$$

$$\frac{d}{dt}(\alpha_4[C_2] + \alpha_2[C_4]) = 0, \tag{4b}$$

$$\frac{d}{dt}(\alpha_4[C_3] + \alpha_3[C_4]) = 0. \tag{4c}$$

Field Equations
Diffusion, Convection, Migration

In order to derive a thermal dynamical consistent model, the Energy Variation Method [89] is used. Based on the laws of conservation of elements and Maxwell equations, we have the following kinematic system

$$\begin{cases} \frac{d[C_1]}{dt} = -\nabla \cdot \boldsymbol{j}_1 - \nabla \cdot \boldsymbol{j}_p - \alpha_1 \mathcal{R}, \\ \frac{d[C_2]}{dt} = -\nabla \cdot \boldsymbol{j}_2 - \alpha_2 \mathcal{R}, \\ \frac{d[C_3]}{dt} = -\nabla \cdot \boldsymbol{j}_3 - \alpha_3 \mathcal{R}, \\ \frac{d[C_4]}{dt} = -\nabla \cdot \boldsymbol{j}_4 + \alpha_4 \mathcal{R}, \\ \nabla \cdot (\boldsymbol{D}) = \sum_{i=1}^{4} z_i [C_i] F, \\ \nabla \times \boldsymbol{E} = \boldsymbol{0}, \end{cases} \tag{5}$$

where $\boldsymbol{j}_l, l = 1, 2, 3, 4$ are the passive fluxes and $\boldsymbol{j}_p$ is the pump flux, $\mathcal{R}$ is reaction rate function. All these variables are unknown and will be derived by using the Energy Variational method.

Energy Functional

The total energetic functional is defined as the summation of mix entropy, internal energy and electrical static energy.

$$\begin{aligned} E_{tot} &= E_{ent} + E_{int} + E_{ele} \\ &= \sum_{i=1}^{4} \int_\Omega RT \left\{ [C_i] \left(\ln \left(\frac{[C_i]}{c_0} \right) - 1 \right) \right\} dx + \int_\Omega \sum_{i=1}^{4} [C_i] U_i dx + \int_\Omega \frac{\boldsymbol{D} \cdot \boldsymbol{E}}{2} dx. \end{aligned} \tag{10}$$

Then the chemical potentials could be calculated according to the variation of total energy

$$\tilde{\mu}_l = \frac{\delta E_{tot}}{\delta [C_i]} = RT \ln \frac{[C_i]}{c_0} + U_i + z_l \phi e, l = 1, \cdots, 4. \tag{11}$$

It is assumed in the present work that dissipation of the system energy is due to passive diffusion, chemical reaction and the deduction that energy supplied for pump. Accordingly, the total dissipation functional Δ is defined as follows

Dissipation Functional

$$\Delta = \int_\Omega \left\{ \sum_{j=1}^{4} |\boldsymbol{j}_i|^2 + RT\mathcal{R} \ln \left(\frac{\mathcal{R}}{k_r [C_4]^{\alpha_4}} + 1 \right) \right\} dx - \int_\Omega f_p dx, \tag{12}$$

where $f_p = f_p(\mathcal{R}, \mu, x) \geq 0$ is the term induced by energy absorption in the pump.

For open systems, especially flux (current) clamp system, in which some fluxes flow in or out, entering or leaving the system altogether, we have the following generalized energy dissipation law

Dissipation Principle

$$\frac{dE_{tot}}{dt} = J_{E,\partial\Omega} - \Delta. \tag{13}$$

Here $J_{E,\partial\Omega}$ is the rate of boundary energy absorption or release that measures the energy of flows that enter or leave the system altogether through the boundary. Recall that the chemical potential of a species is the energy that can be absorbed or released due to a change of the number of particles of the given species and $J_i \cdot n$ is the total number of i^{th} particles passing through the boundary, per area per unit time. We define $J_{E,\partial\Omega}$ as follows

An Electro-osmotic Model of cytochrome c oxidase

The concentrations and potentials at E242, BNC and proton loading site (PLS) and potentials in N and P sides (see Fig.(1) (a)) are modeled using the variables ϕ_E, ϕ_B, ϕ_x, $[H]_E$, $[H]_B$, $[H]_x$, ρ_e.

Field Equations

$$\frac{d[H]_E}{dt} = \frac{S_v}{F}(I_{N\to E} - I_{E\to X} - I_{E\to B}), \tag{36a}$$

$$\frac{d[H]_B}{dt} = \frac{S_v}{F}(I_{E\to B} + I_{N\to B}) - 2\mathcal{R}, \tag{36b}$$

$$\frac{d[H]_X}{dt} = \frac{S_v}{F}(I_{E\to X} - I_{X\to P}), \tag{36c}$$

$$\frac{d\rho_e}{dt} = \frac{-S_v}{F}I_e - 2\mathcal{R}, \tag{36d}$$

$$C_E\frac{d(\phi_E - \phi_N)}{dt} = (I_{N\to E} - I_{E\to X} - I_{E\to B}), \tag{36e}$$

$$C_B\frac{d(\phi_B - \phi_N)}{dt} = I_{E\to B} + I_{N\to B} + I_e, \tag{36f}$$

$$C_X\frac{d(\phi_X - \phi_P)}{dt} = (I_{E\to X} - I_{X\to P}), \tag{36g}$$

$$C_m\frac{d(\phi_N - \phi_P)}{dt} + I_{leak} + I_{X\to p} + I_e = 0, \tag{36h}$$

with currents

Structure and Boundary Conditions

$$I_{N\to E} = max\left(g_D\left(\phi_N - \phi_E - \frac{RT}{F}\ln\frac{[H]_E}{[H]_D}\right), -SW_0\right) = max\left(\frac{g_D}{F}(\mu_N - \mu_E), -SW_0\right), \tag{37a}$$

$$I_{N\to B} = g_K(\phi_N - \phi_B - \frac{RT}{F}\ln\frac{[H]_B}{[H]_N}) = \frac{g_K}{F}(\mu_N - \mu_B), \tag{37b}$$

More Structure and Boundary Conditions

$$I_{D\to B} = g_B(\phi_E - \phi_B - \frac{RT}{F}\ln\frac{[H]_B}{[H]_E}) = \frac{g_B}{F}(\mu_D - \mu_B), \tag{37c}$$

$$I_{X\to P} = g_X(\phi_X - \phi_P - \frac{RT}{F}\ln\frac{[H]_P}{[H]_X}) = \frac{g_X}{F}(\mu_X - \mu_P), \tag{37d}$$

$$I_{E\to X} = I_{pump} + I_{xleak} = P_{pump}(R_c)(\mu_X - \mu_E) - g_E(\mu_X - \mu_E), \tag{37e}$$

$$I_e = -FJ_e, \tag{37f}$$

$$I_{leak} = g_m(\mu_N - \mu_P) = g_m(\phi_N - \phi_P - E_{other}), \tag{37g}$$

$$I_{E\to X} = I_{pump} + I_{xleak}, \tag{37h}$$

$$I_{xleak} = -g_E(\mu_X - \mu_E), \tag{37i}$$

$$I_{pump} = \begin{cases} g_{pump}max(R_c, 0)(\mu_X - \mu_E), \mu_X - \mu_E < \delta_{th}, \\ g_{pump}max(R_c, 0)\delta_{th}\exp\left(-\frac{(\mu_X - \mu_E)}{\varepsilon}\right), \mu_X - \mu_E \geq \delta_{th}, \end{cases} \tag{37j}$$

$$\mathcal{R} = k_f[H^+]^2[O_2]^{1/2}\rho_e^2 - k_r[H_2O]. \tag{37k}$$

Parameter Values

Variable	Notations	Values (with Unit)
E_{242} site effective capacitance	C_D	1E-1 $fAms/mV/(\mu m)^2$
BNC site effective capacitance	C_B	1E-1 $fAms/mV/(\mu m)^2$
PLS site effective capacitance	C_X	1E-1 $fAms/mV/(\mu m)^2$
Membrane capacitance	C_X	7.5E-2 $fAms/mV/(\mu m)^2$
D channel conductance for H^+	g_D	3.75E-3$pS/(mum)^2$
K channel conductance for H^+	g_K	1E-3 $pS/(\mu m)^2$
E2B channel conductance for H^+	g_B	5E-2 $pS/(\mu m)^2$
E2X channel conductance for H^+	g_E	1E-3 $pS/(\mu m)^2$
E2X Pump rate for H^+	g_P	369 $pSms/(\mu m)^2 \mu M$
X2P channel conductance for H^+	g_X	9.8E-4 $pS/(\mu m)^2$
Membrane conductance for leak	g_m	$1pS/(\mu m)^2$
Mito. matrix H^+ concentration	$[H]_{mat}$	0.01 μM
Mito. inner membrane space H^+ concentration	$[H]_{ims}$	0.063 μM
Nernst Potential due to other Ions	E_{Other}	$-160mV$
Reaction site $[O_2]$ concentration	$[O_2]$	0.0028 μM
Reaction site $[H_2O]$ concentration	$[H_2O]$	0 μM
Electron current	I_e	-5.24 fA
Forward reaction rate coefficient	k_f	1333
Backward reaction rate coefficient	k_r	0.005
surface volume ratio	S_v	1000
Potential Threshold	δ_{th}	210 mv
Decay rate	ε	1 $(ms)^{-1}$

Table 2: Parameters

Variable	Notations	Values (with Unit)
E_{242} site H^+ concentration	$[H]_E$	0.01196 μM
BNC site H^+ concentration	$[H]_B$	0.01682 μM
PLS site H^+ concentration	$[H]_X$	0.01441 μM
BNC site electric density	ρ_e	0.01166 μM
E_{242} site electric potential	ϕ_E	-5 mV
BNC site electric potential	ϕ_B	-14.1562 mv
PLS site electric potential	ϕ_X	200 mv
N site electric potential	ϕ_N	0 mv
P site electric potential	ϕ_P	160 mv

Table 1: Default Initial Values

Results

In models like this
either
everything can be computed
or nothing!

Everything has been Computed

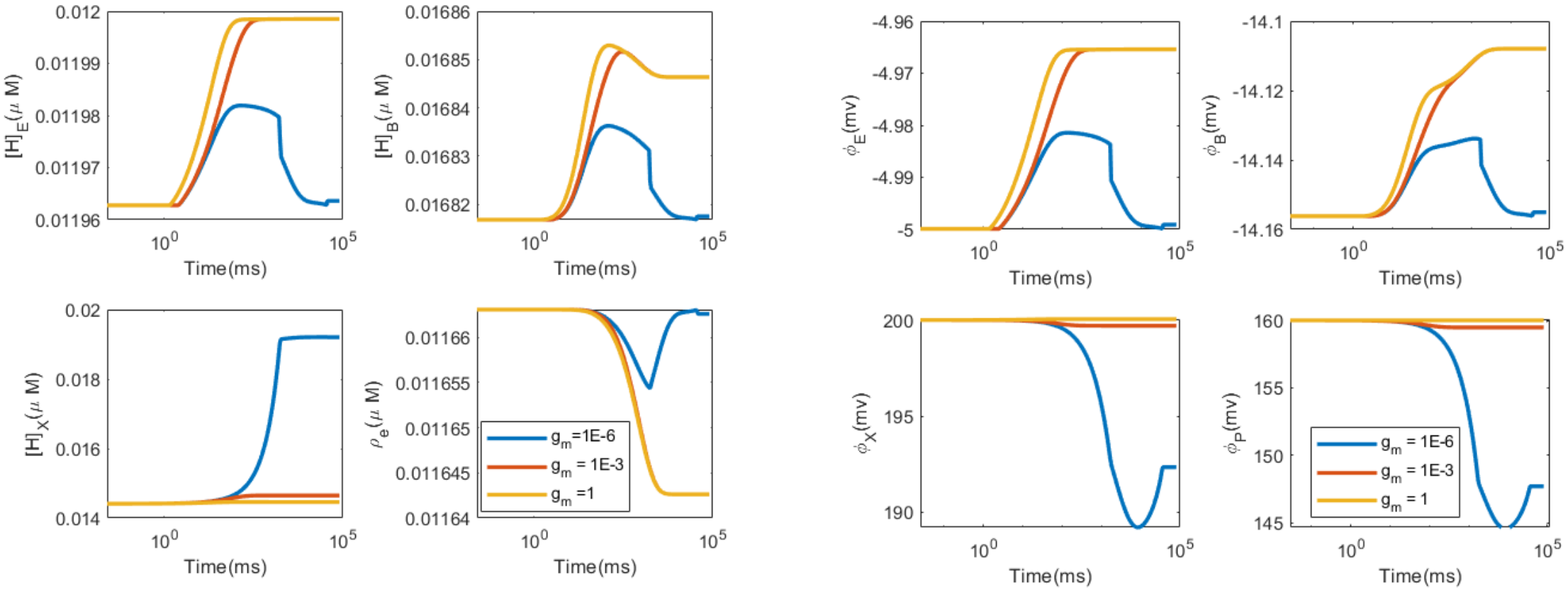
Model can be modified to deal with other information and predict experiments

Not yet digested by experimental community!

High $[H^+]_P$

BLUE is Unclamped

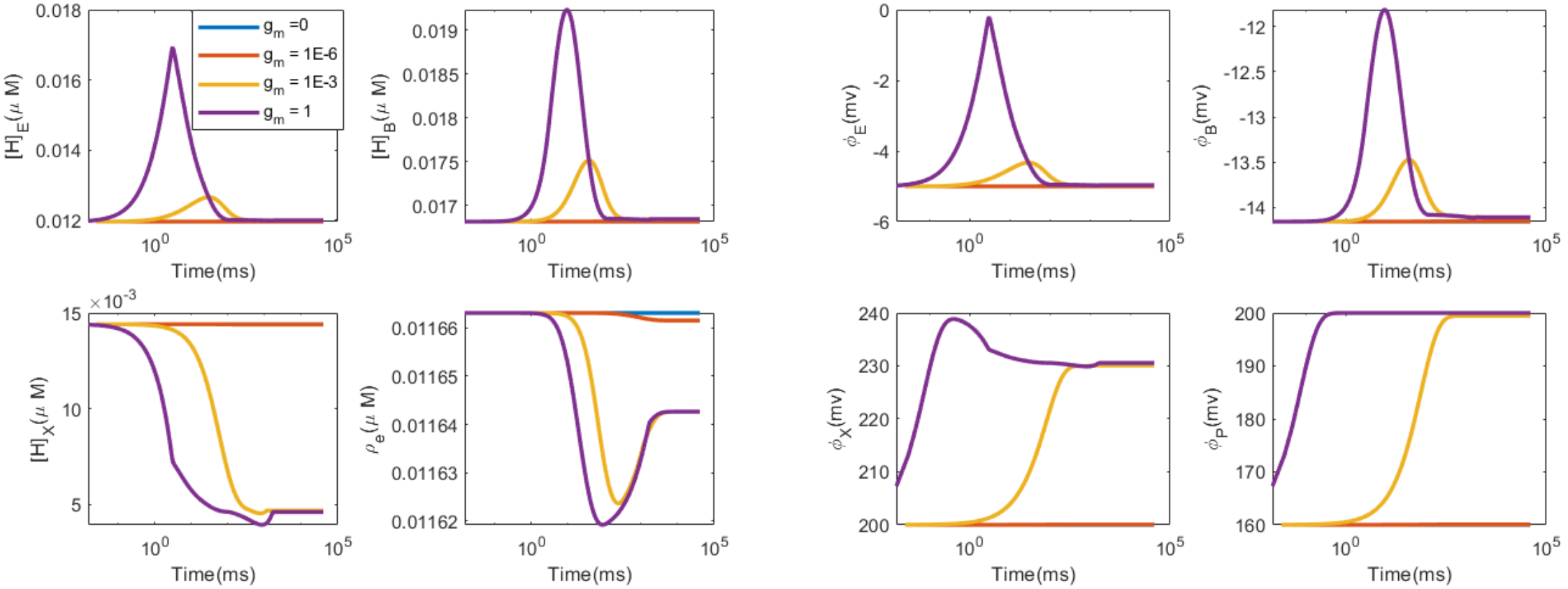
Brown is clamped by E_{other}



High E_{other}

BLUE is Unclamped

Brown is clamped by E_{other}



Any Questions?