Redox Modification of the Arrhythmic Substrate in Heart Failure

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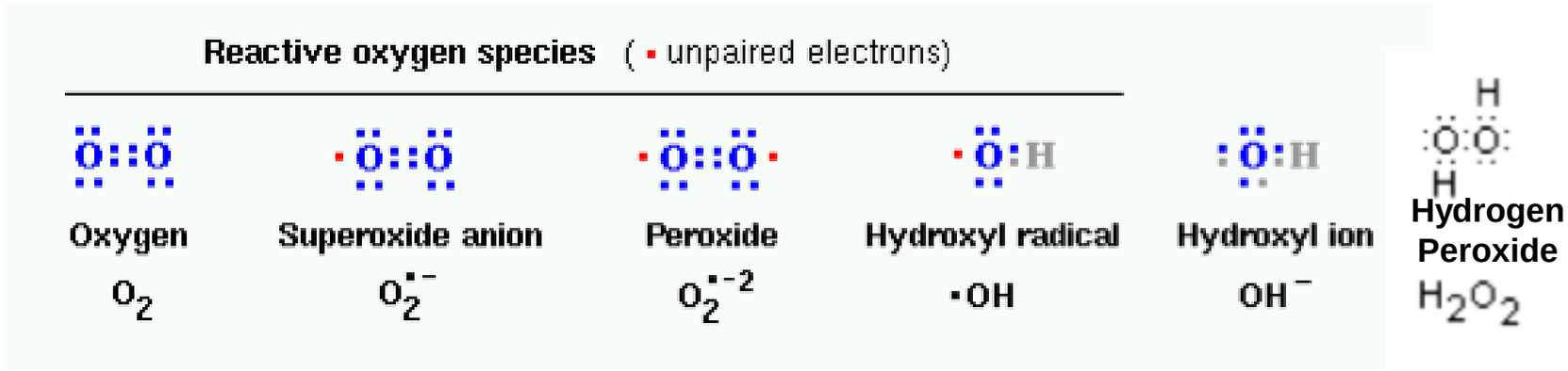
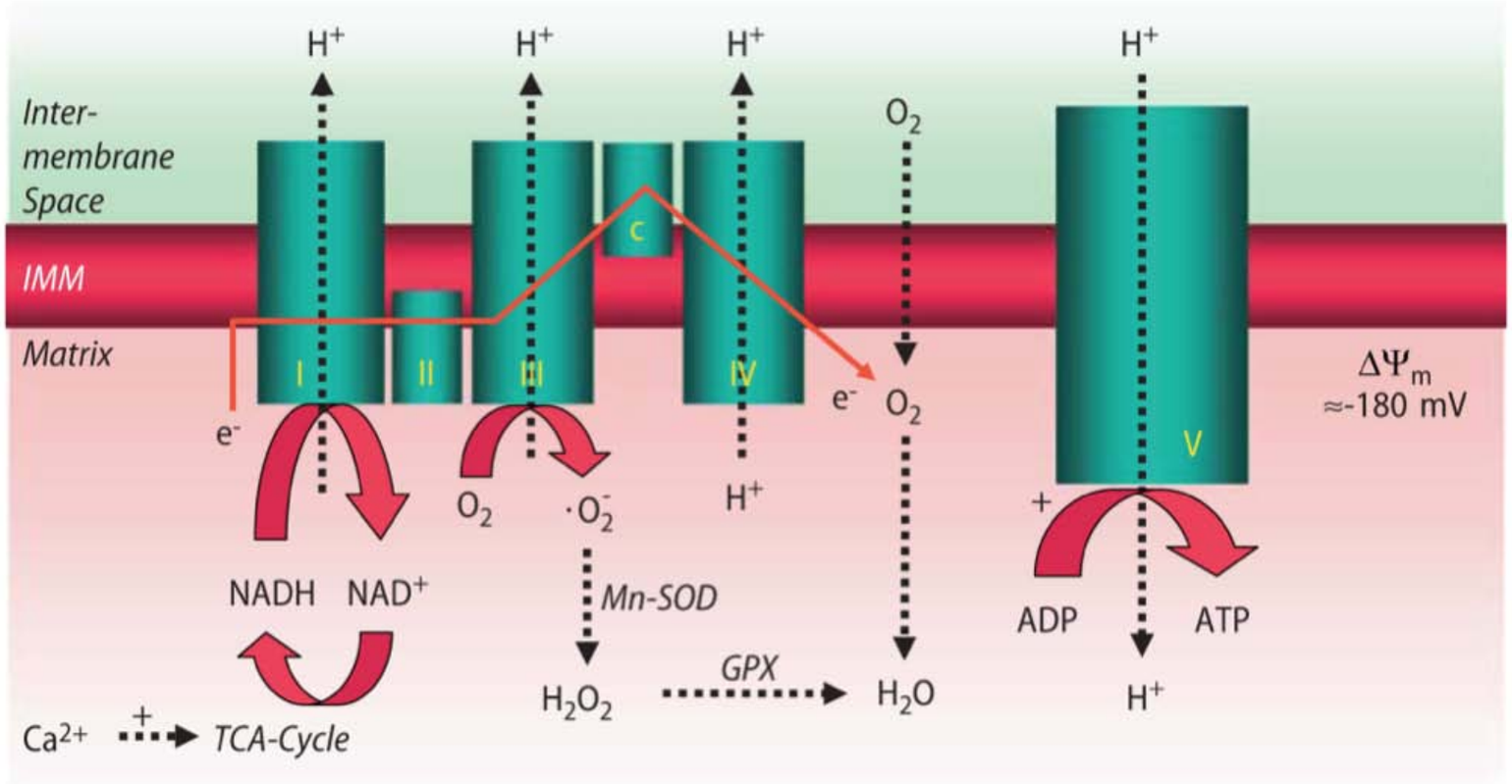
Redox Modifications

Reactive Oxygen Species (ROS)





- Produced directly or indirectly by the ETC
- Complex regulation by anti-oxidant systems
- Elevated in HF and ischemia-reperfusion
- Target ion several channels, transporters, signaling molecules

Simpler to More Complex Models[1]

What Has Driven Our Progression?

- Models are sometimes “simple” only in hindsight
  - Hodgkin-Huxley theory of the action potential
  - Probably not viewed as being simple at the time
  - Was viewed as being mechanistic

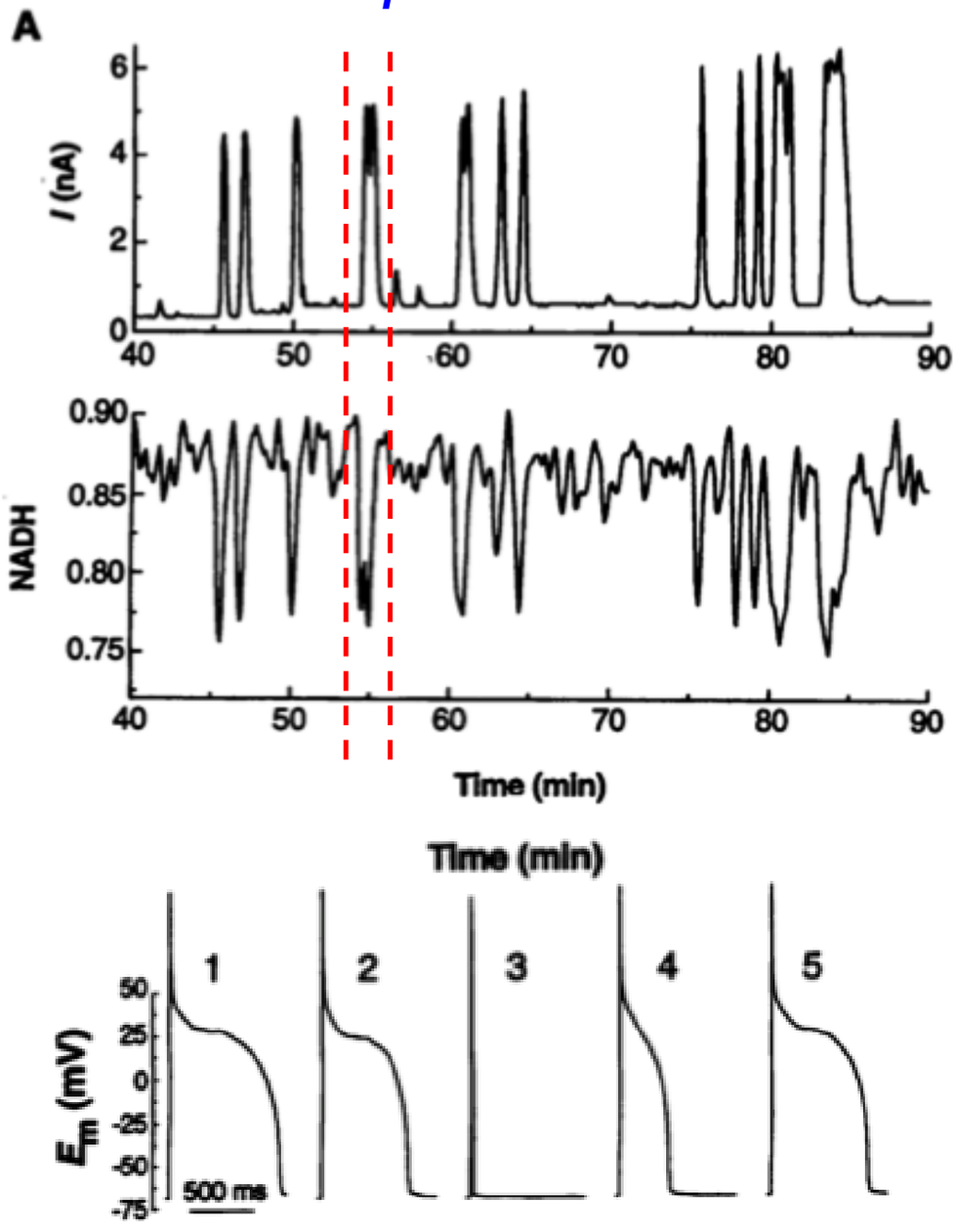
- As were H & H, we need to be faithful to the biology and go for mechanism

- Mechanistic models can be both complex (i.e., high-dimensional, many parameters) *and* constrained

How Did This Work Begin?

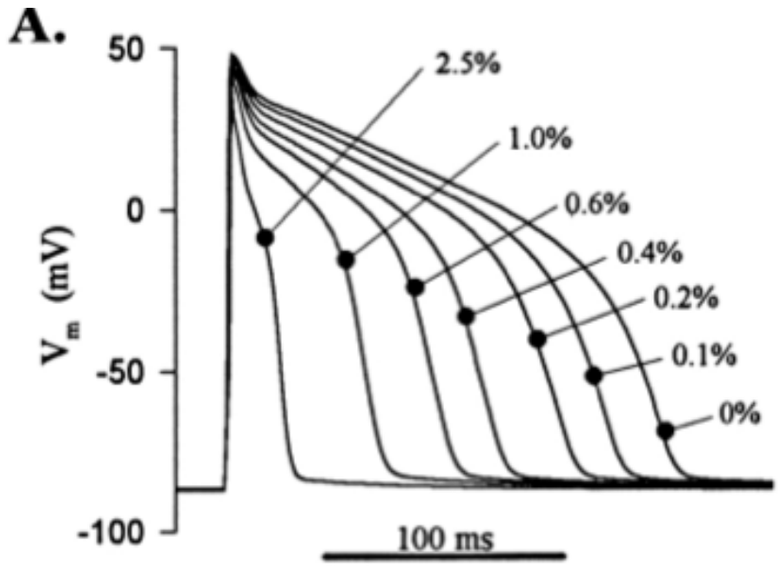
With Apparent Simplicity - Metabolic Oscillations

Experiments



O'Rourke et al (1994) *Science* 265: 962

Model



$I_{K,ATP}$ Model ATP-dependent K^+ channel
Open probability increases with increasing ADP:ATP ratio

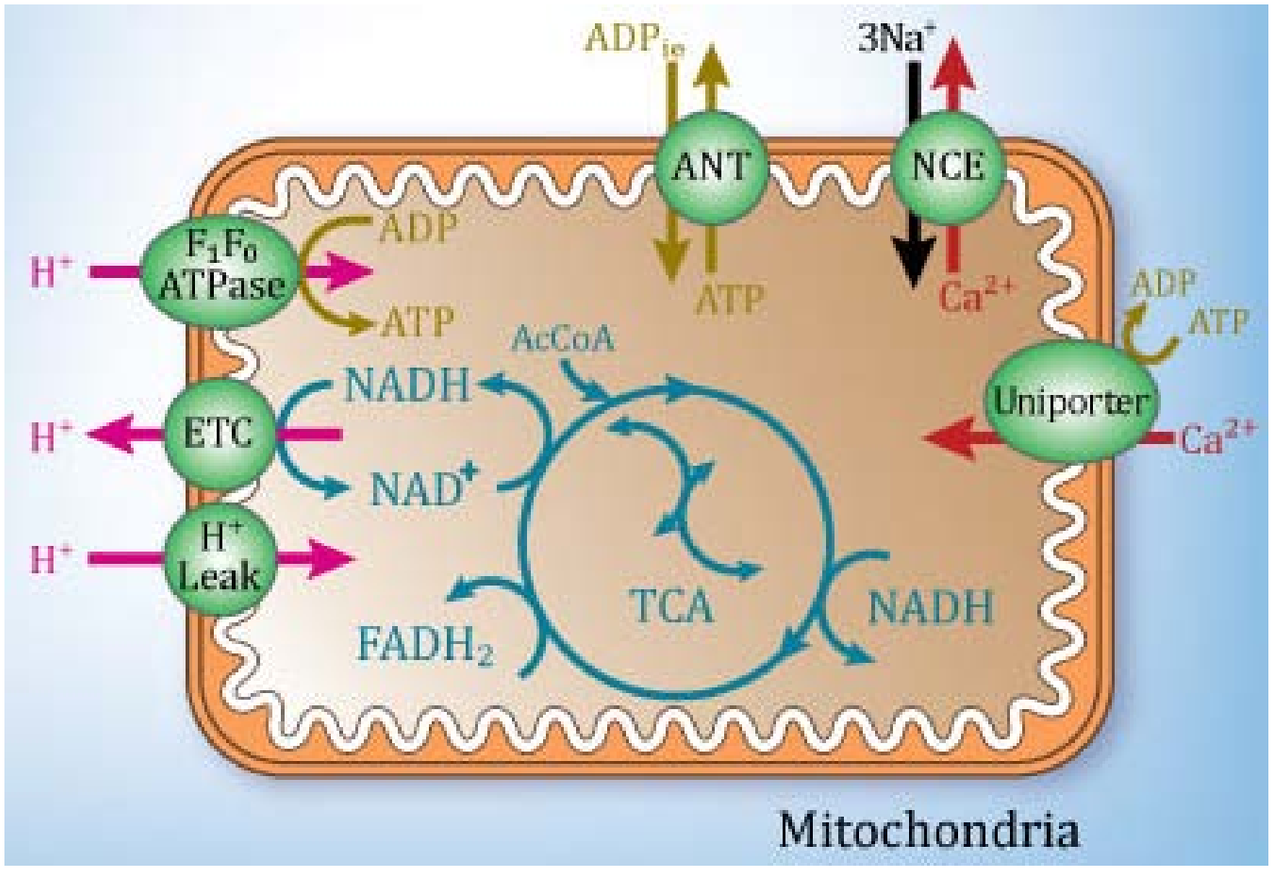
Simple ionic models predict AP shortening

Insight into function - AP shortening, the "metabolic sink hypothesis", arrhythmia

Ferrero et al (1996) *Circ. Res.* 79: 208

How Do Oscillations Arise?

Not So Simple – Need a Mitochondrial Model

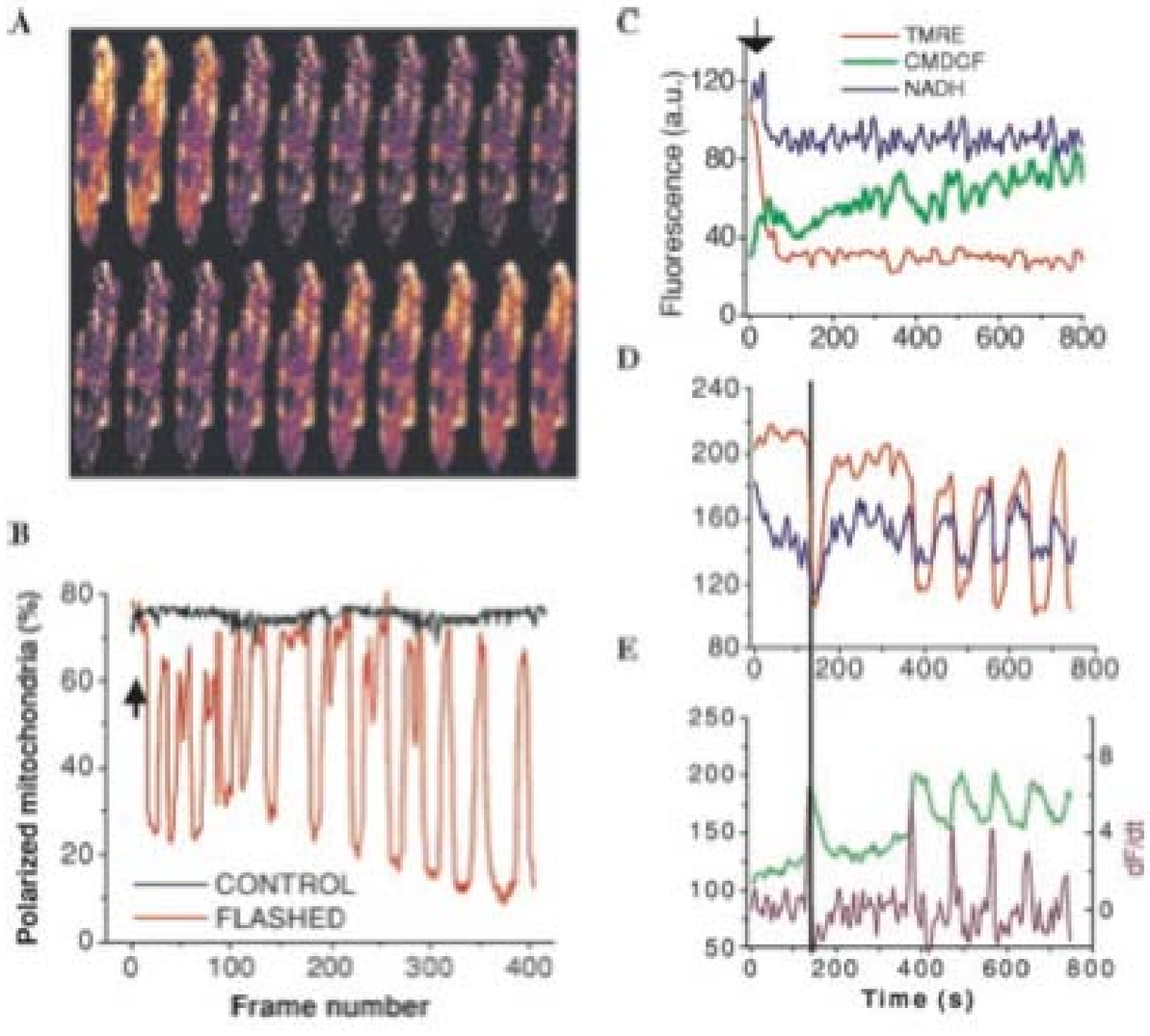


- A framework to address mechanism
- Must model NADH, ATP production
  - TCA Cycle 8 dynamic variables
  - ETC, F_1F_0 ATPase, ANT, CaU, mNCE
  - $[Ca_m]$, [NADH], $\Delta\Psi_m$, $[ADP_m]$
- 12 ODEs
- Necessary, but not sufficient
- Needed more data on mechanism of oscillations

Cortassa et al (2003). *Biophys. J.* 87(4): 273

How Do Oscillations Arise?

Key Mechanism (ROS; $O_2^{\bullet-}$) Starts With Simplicity



$\Delta\Psi_m$ ROS (superoxide anion) NADH

<u>ROS-Induced ROS-Release Hypothesis</u>

- ROS_m buildup increases ROS release through IMAC
- ROS_i buildup causes regenerative IMAC opening
- Opening of IMAC collapses $\Delta\Psi_m$
- SOD scavenging removes ROS, IMAC closes

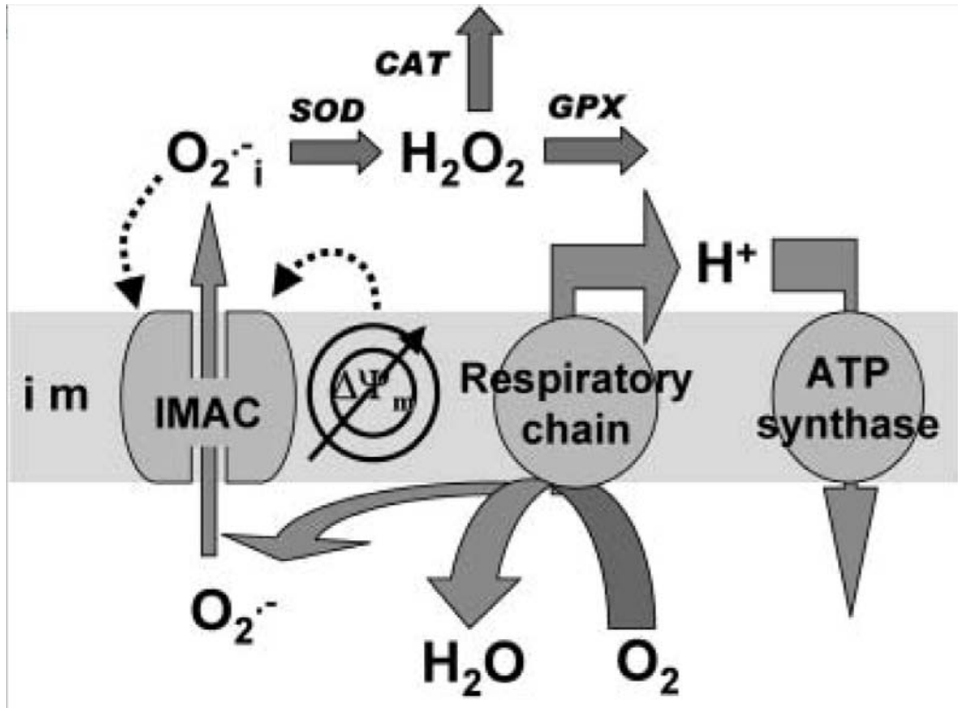
<u>Support</u>

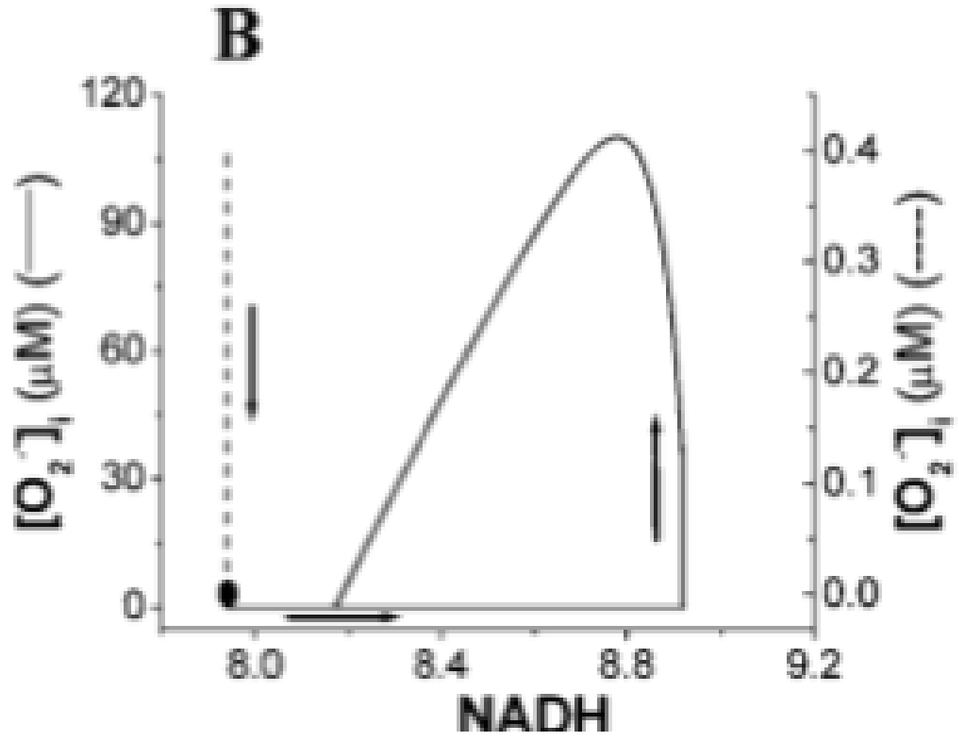
- Oscillations ablated by increased ROS_i scavenging, block of IMAC

Cortassa et al (2004) *Biophys. J.* 87(3): 2060

How Do Oscillations Arise?

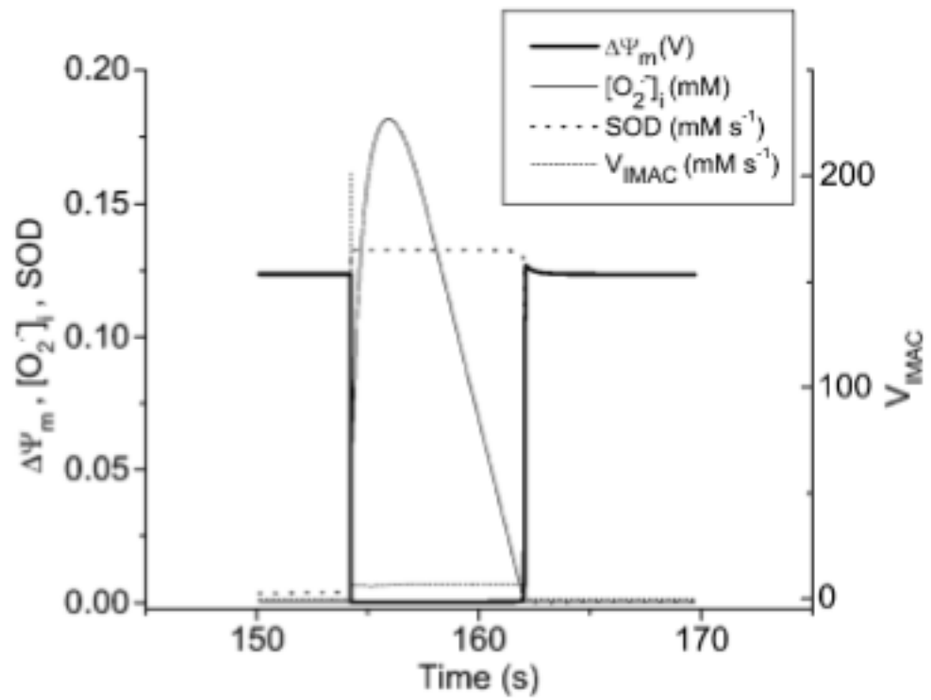
"Minimal" Model of ROS Oscillation





Model

- 4 new dynamic variables $[O_2^{\cdot-}]_i$, $[O_2^{\cdot-}]_m$, $[H_2O_2]$, [GSH]
- Phenomenological model of $[O_2^{\cdot-}]_m$ production by electron shunt through Complex III
- "Robust" oscillations, period (Sec to hours) depends on [SOD]

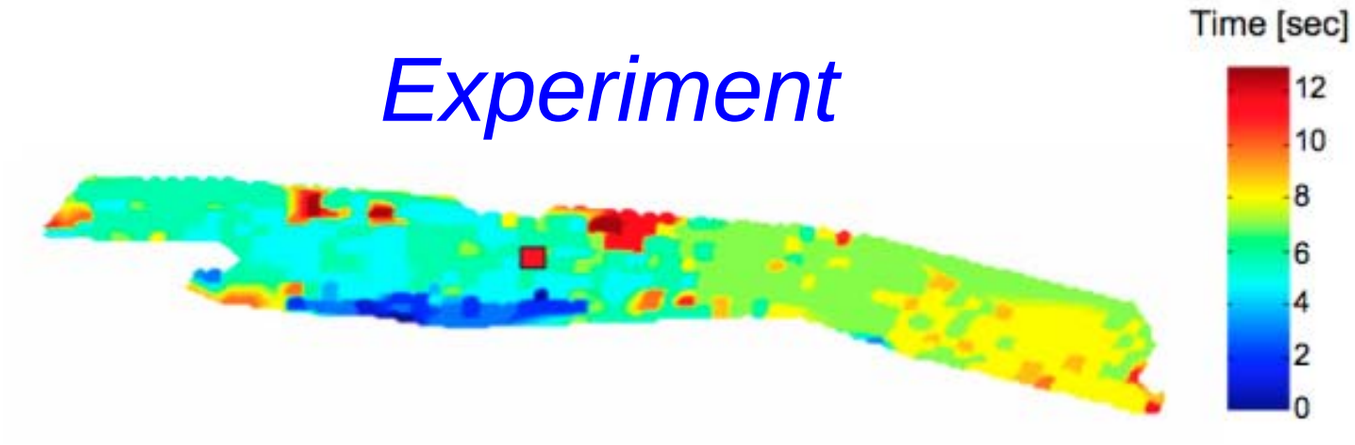


Cortassaet al (2003) *J. Biol. Chem.* 278(45): 44735

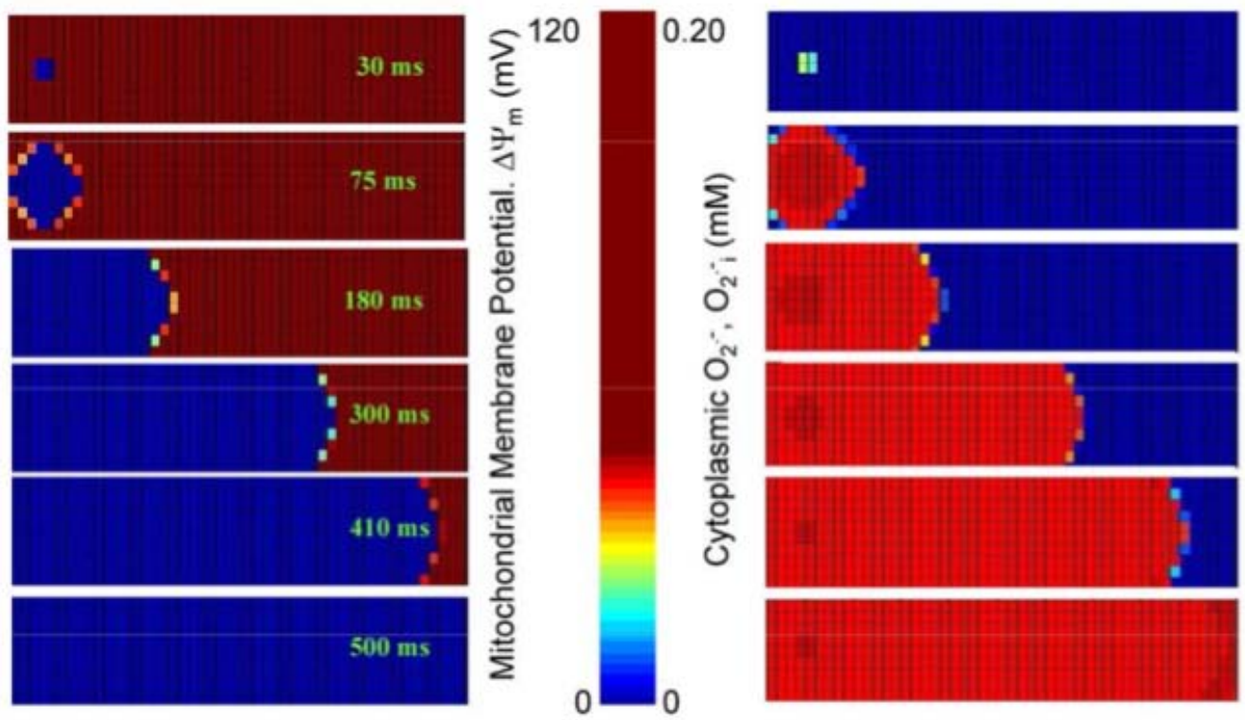
Propagating ROS Waves

Model Reconstruction

Experiment



2D Reaction-Diffusion Model

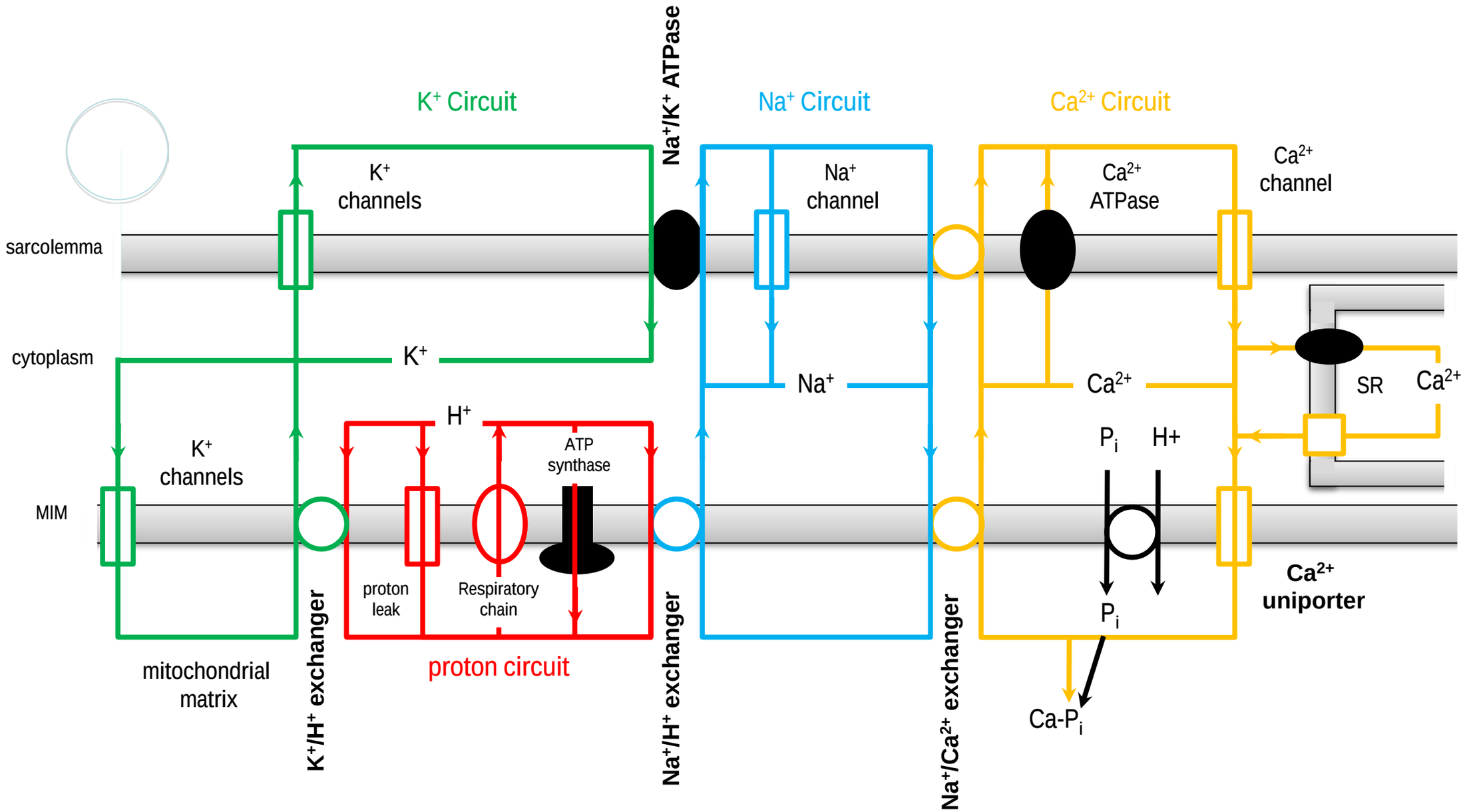


Zhou et al et al (2010) *Plos Comp Biol* 6(1): e100065

Need for More Complex Models

Does It Have To Be This Complicated?

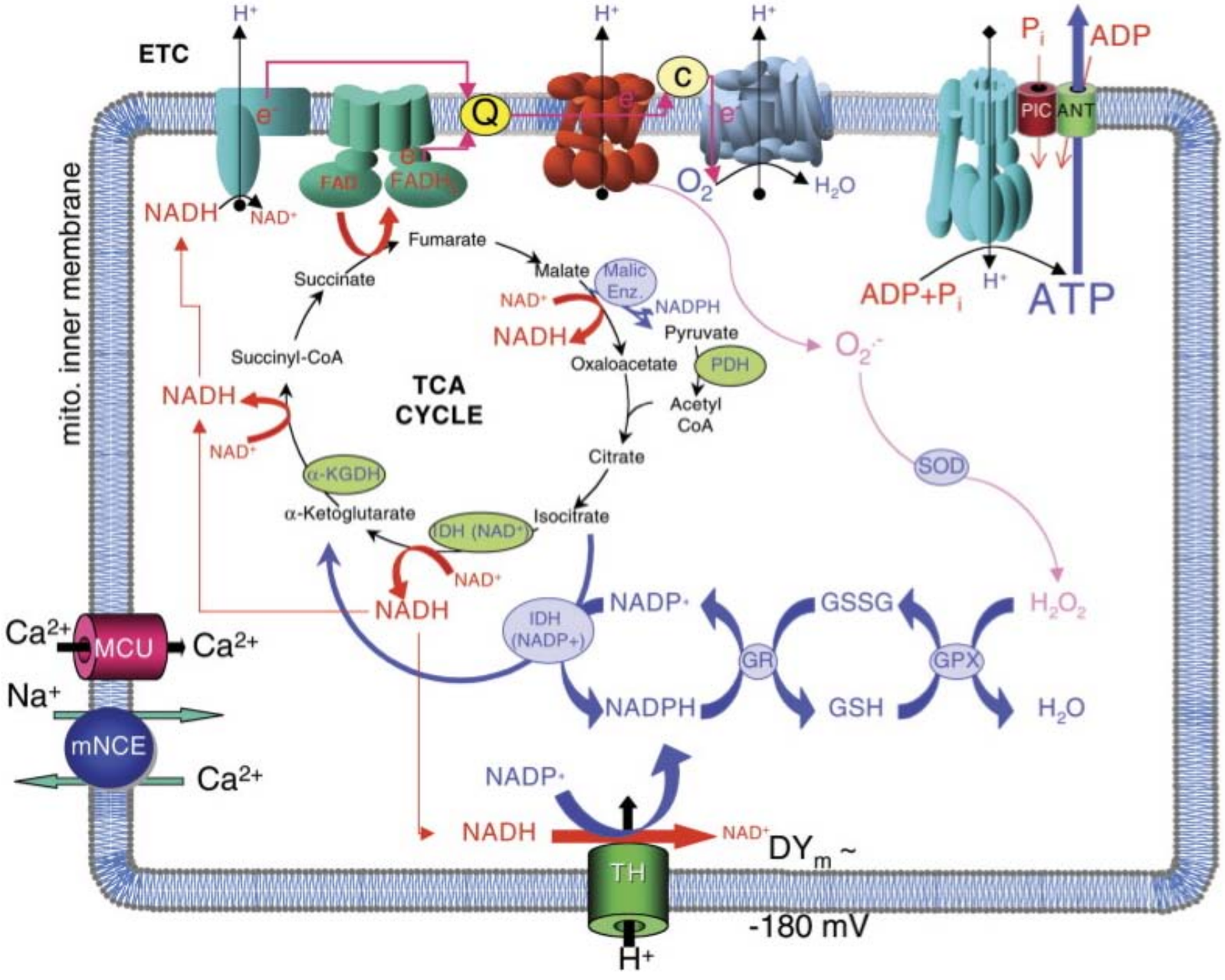
Ion Circuits Couple Mitochondria, Cytosol, Sarcolemma



Cortassa et al (2003). *Biophys. J.* 87(4): 273

Need for More Complex Models

Ion Circuits, Redox Regulation in Heart Failure

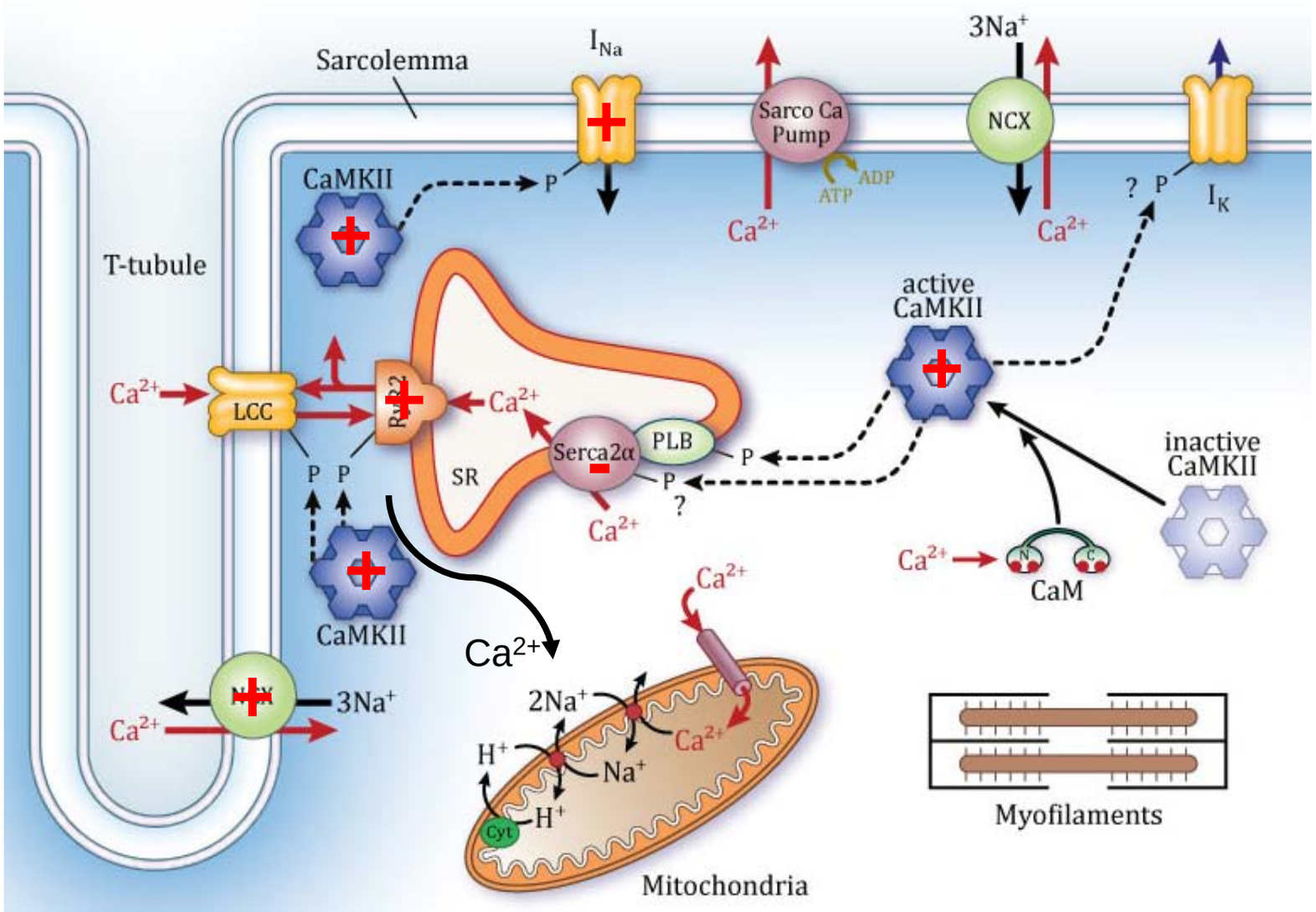


- [Nai] ⇑ in HF (~ 15 mM)
- mNCE extrudes Ca^{2+}
- NADH, NADPH ⇓
- V_{GR}, V_{GPX} ⇓
- H_2O_2 ⇑

O'Rourke and Maack al (2008). *Drug Discov Today Dis Models* 4(4): 207

Need for More Complex Models

ROS Targets



- [Nai]⇑ in HF (~ 15 mM)
- mNCX extrudes Ca^{2+}
- NADH, NADPH⇓
- GPX activity⇓
- H_2O_2 ⇑ (~ 20x)

Red shows H_2O_2 action

O'Rourke and Maack al (2008). *Drug Discov Today Dis Models* 4(4): 207

Simpler versus Complex Models?

- Develop models tailored to the questions being asked, using available information on mechanisms
- Sometimes complexity is unavoidable – e.g., highly coupled biological processes