Biological Engineering Education and Computational Methods

EFFECT OF THE GEOMETRICAL STRUCTURE OF MITOCHONDRIA ON THE SYNTHESIS AND DIFFUSION OF OXIDATIVE METABOLITES

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Introduction

- Abundant new information on the structure and dynamics of living cells are currently available
  - Aided by advances in Microscopy & Molecular biology.
- Computational approaches are needed to link all these new data
- Issues in computational approach: Cell systems are complex
  - Interdependent chemical reactions and structural components regulates cell processes

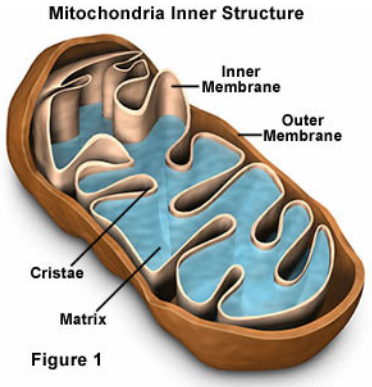
Introduction

- Spatiotemporal computational approaches - one way to answer the complexity
- Partial differential equations - defines concentration changes in space and time.
  - ODEs can define reactions, membrane transport and electrical potential
  - Diffusion of molecules within complex geometry defined by using PDEs

Research background – Mitochondria cristae structure

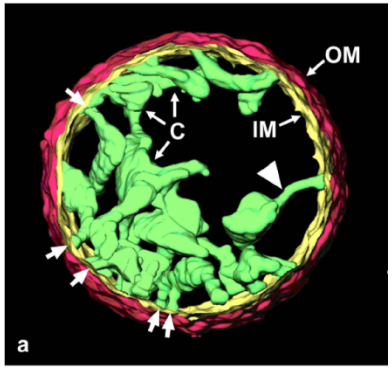
Early Mitochondria structure

- Cristae was considered as a simple in-folding



Latest Studies indicate pleomorphic and flexible cristae.

- Cristae are connected to inner membrane by tubular connections called cristae junctions.
- Junction dimensions: 30-40nm Diameter, 150-200nm in length.



Research Questions

Are tubular junctions posing a barrier to diffusion between the intracristal compartments and the intermembrane space?

Is it possible for the membrane potential to be different due to curvature and concentration differences?

Previous Work

Previous Model

- Virtual Cell program was used to study changes in ADP concentration
- Only ATP synthase and ATP/ADP antiporter reactions were considered
- Depletion of ADP caused reduction in ATP production

A model considering all the events of oxidative phosphorylation will yield better results on the influence of cristae morphology

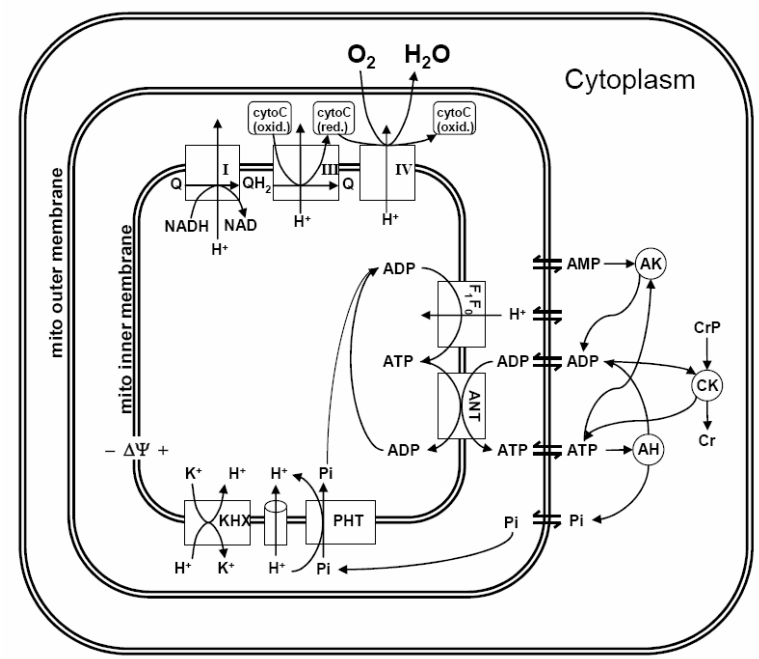
- All reactions at the inner membrane should be considered
- Proton gradient and reactions in the matrix should also be included

Model Development

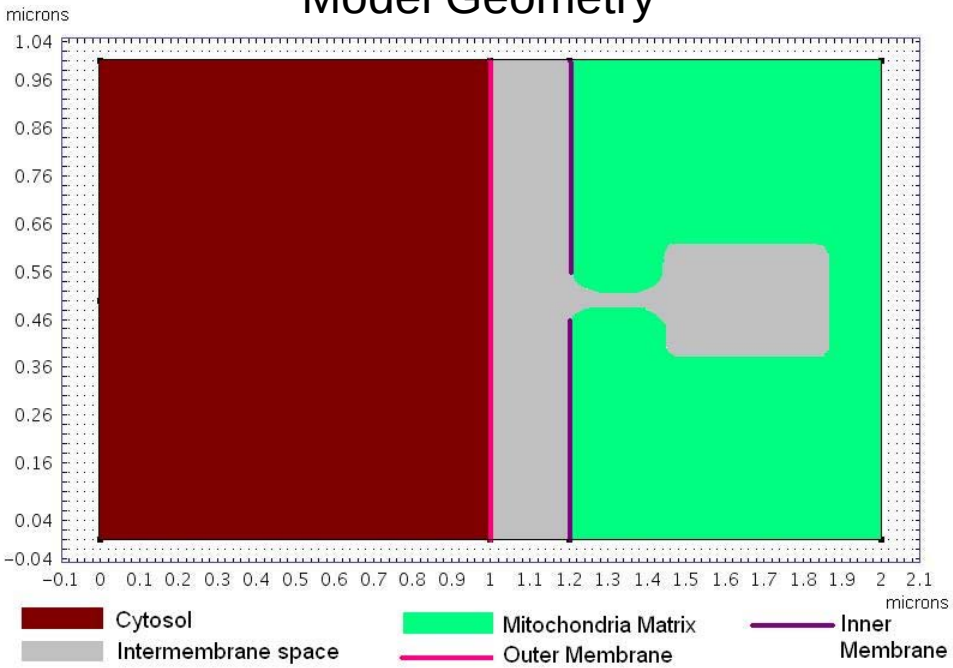
The model by Wu et al(2006) on oxidative phosphorylation in skeletal muscles was used as the reference model.

- All reactions in oxidative phosphorylation are taken into account. (Complex-I,III,IV,V, ANT flux, proton leak etc.)
- Membrane potential is treated as a state variable.
- Equations are based on mechanics and thermodynamic laws: more accurate representation
- ATP utilization reactions in cytosol are included.

Model Development



Model Geometry



Governing Equation

$$\frac{\partial c_i}{\partial t} + \nabla \cdot (-D_i \nabla c_i) = R_i$$

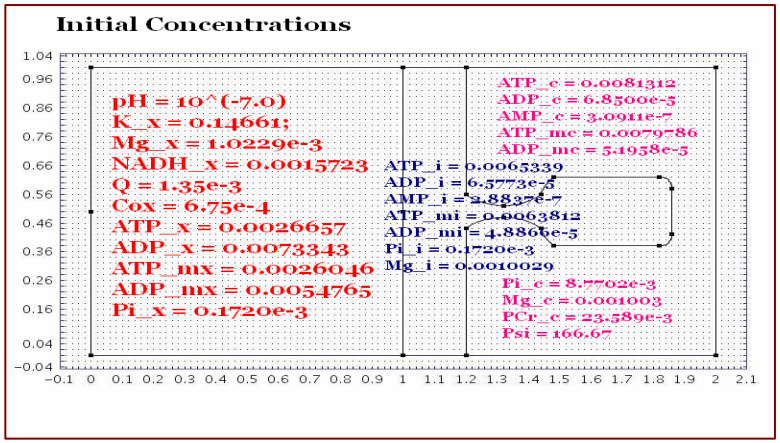
Diffusion Coefficients from literature were used for most metabolites (D_{ATP}, D_{ADP}=1.45x10^2 µm^2/s).

Finite Element Method was used to solve the PDEs.

Model Development

Initial Concentrations

- The initial concentrations are taken from experimental results on skeletal muscles (All concentrations are expressed in mM, Potential: mV)

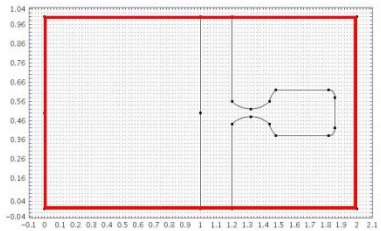


Reactions and fluxes at boundaries are defined as diffusive fluxes

$$-\mathbf{n}\cdot(-D\nabla c) = N_0 + k_c(c_b - c)$$

Boundary conditions

- Outside boundaries are defined as insulation or symmetrical boundaries



$$\mathbf{n}\cdot(-D\nabla c) = 0$$

Model Development

Reaction Rates

- For any reaction $A \Leftrightarrow B$ the rate of reaction is calculated as $J = K[B] - [A]$ and K is defined based on free energy: $K = A \exp\{\Delta G_0 + \Delta E + RT \ln([B]/[A])) / RT)$

Example: For complex I the reaction rate is defined as $j_{C1} = x_{C1}\left\{\exp\left(-\frac{\left(\Delta G_{0,C1} + 4\Delta G_H - RT\ln\left(\frac{[H^+]_x}{10^{-7}}\right) - RT\ln\left(\frac{[Q]}{[QH_2]}\right)\right)}{RT}\right)[NADH]_x - [NAD]_x\right\}$

The TCA cycle in the matrix is reduced to only the dehydrogenase reaction

- $$j_{DH} = x_{DH}\left(\frac{1+[Pi]_x / k_{pi,1}}{1+[Pi]_x / k_{pi,2}}\right)(r[NAD]_x - [NADH]_x)$$

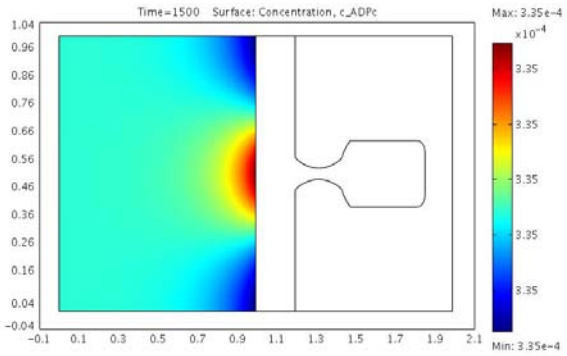
Variable name

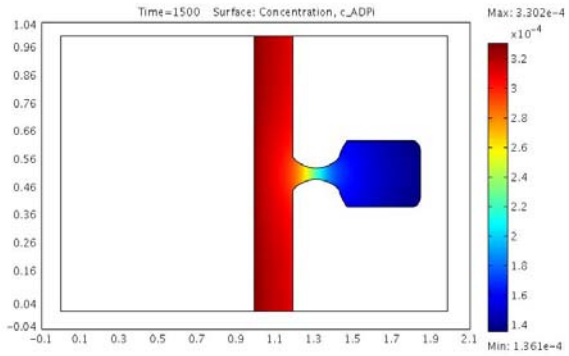
- Same species in separate domains have different variable name– (ADPc, ADPi, ADPm)

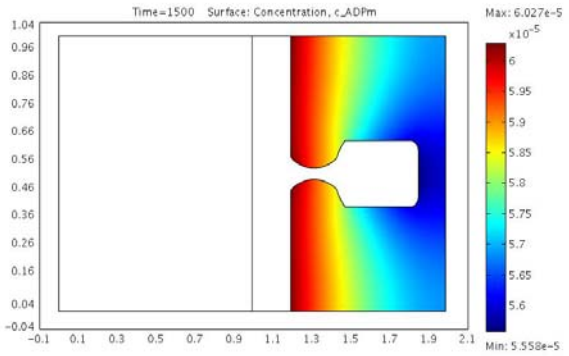
Assumptions

- Fluxes arising from the inner membrane are evenly distributed
- Diffusion coefficient of each species is assumed constant everywhere

Results – Effect of the tubular junction on ADP concentration

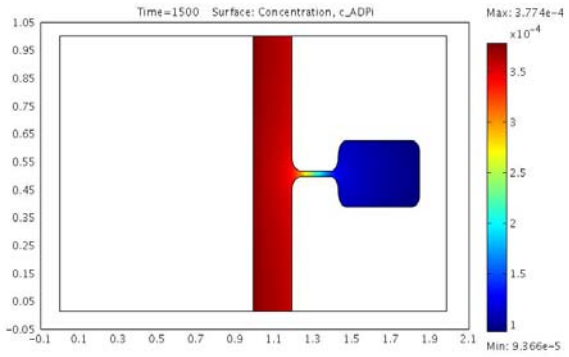






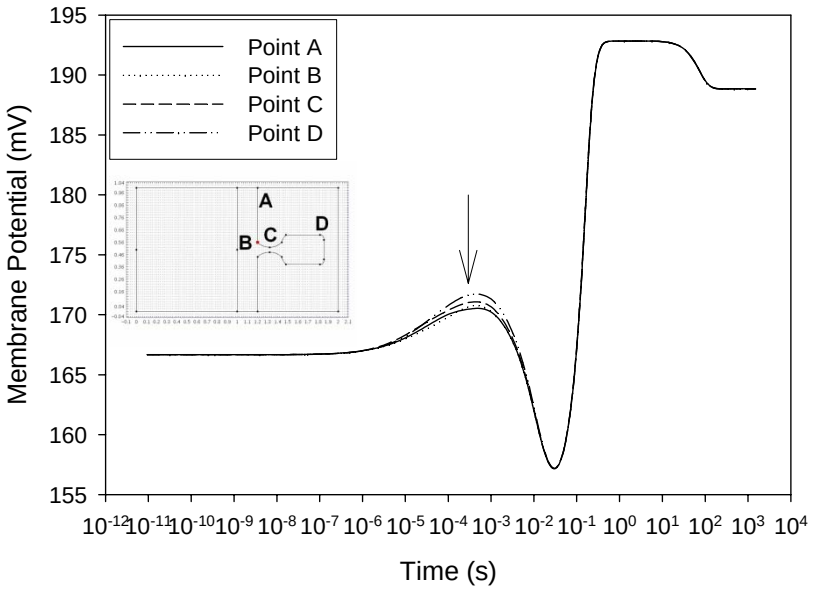
ADP concentration in the cristae is affected by the tubular connection as expected.

Reduction in junction diameter further increases the concentration differences



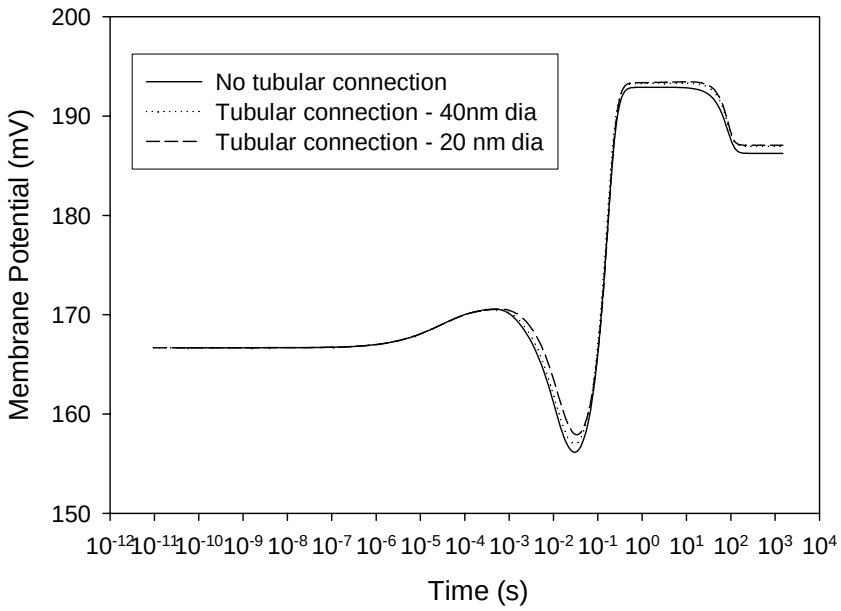
Results – Effect on membrane potential

Potential change at various points on the inner membrane and cristae



Potential does not change along the inner membrane and small changes occur only in time scale of milliseconds

Effect of diameter of tubular connection on potential



The decrease in tubular connection diameter causes only a small delay and slight changes in the response

Conclusion and Further Work

Even though there is ADP concentration changes in the cristae, its overall effect on membrane potential is negligible.

Further Work

- Explore the possibility of diffusion coefficient changes in the tubular connection.
- Optimize the adjustable parameters to get predicted values closer to experimental values.
- Implementing hydrogen ion concentration as a variable in the intermembrane space to study its effect of membrane potential

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Thank You