Towards modeling ROS-induced ROS release in Heart Cells

by
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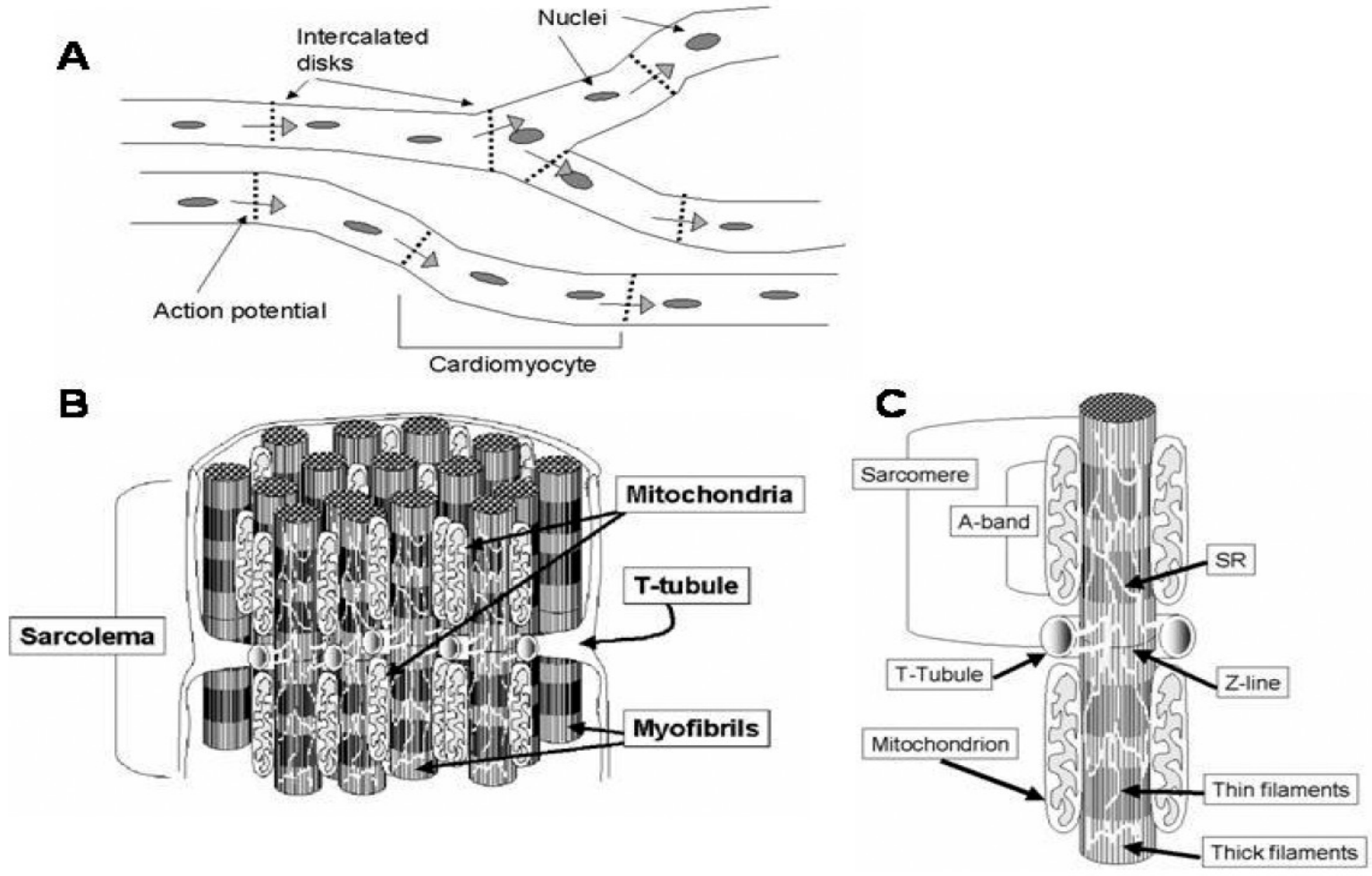
Outline

- Biological problem
- Cardiomyocyte
- Mitochondria
- ROS-Induced ROS release mechanism
- Tentative, qualitative model
- Results

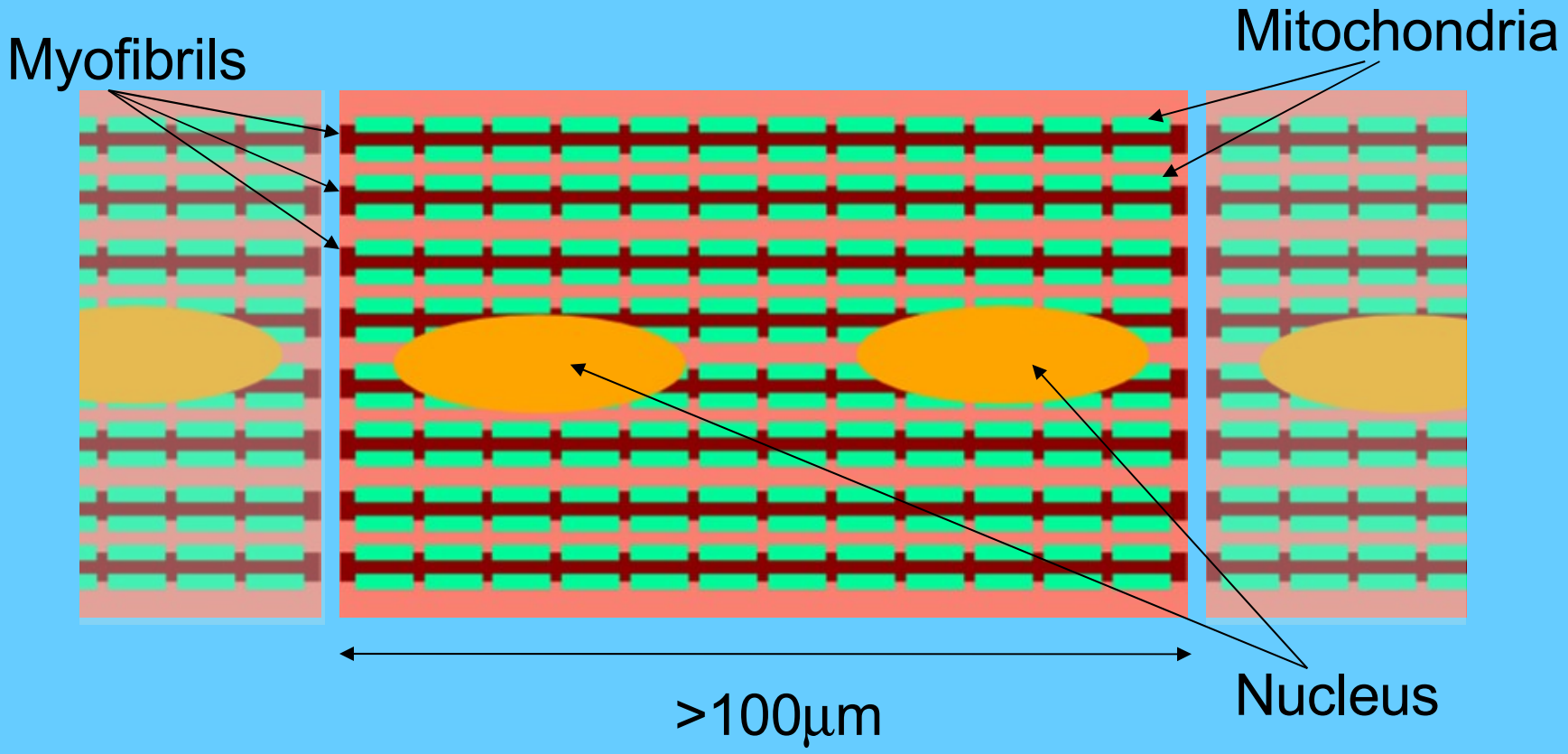
Biological implications

- Cardiomyocite mitochondria – energy sources to heart cells
- Changes in the mitochondrial state can alter the heart beating
- It leads to death

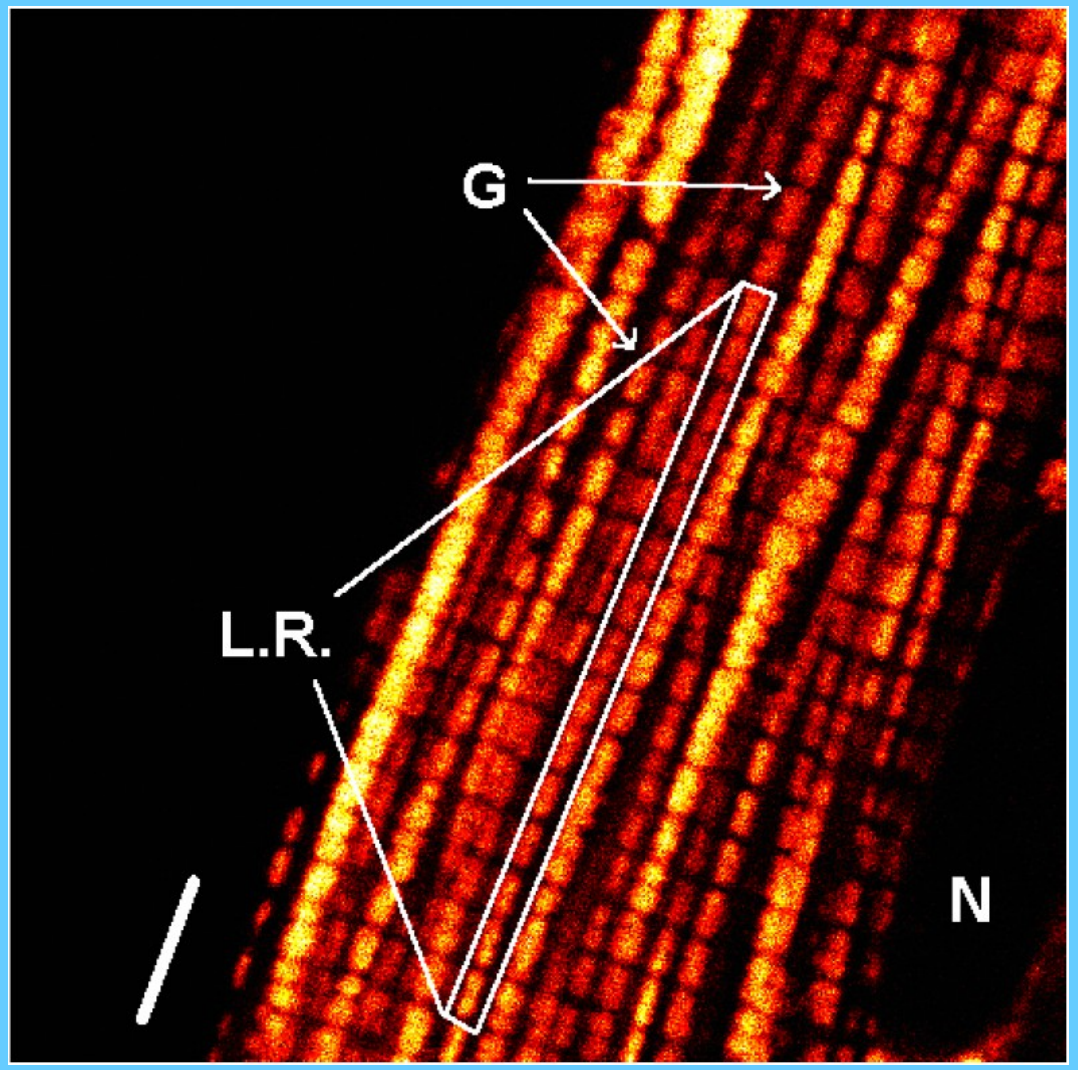
Mitochondria – organization



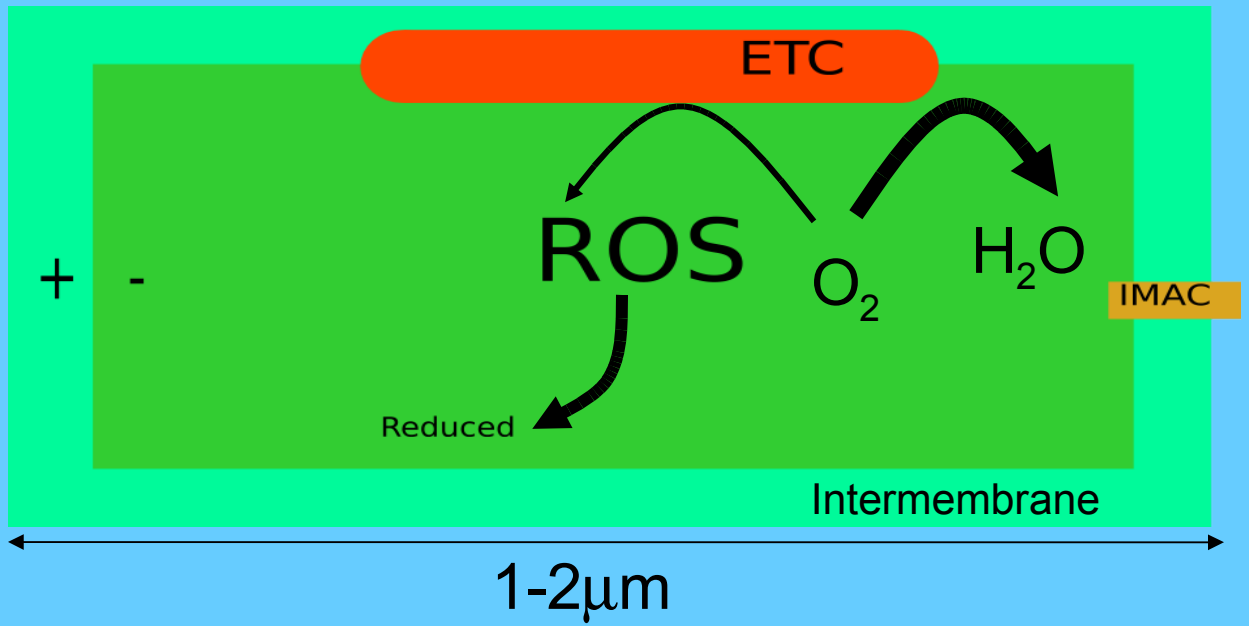
Cardiomyocyte



Cardiomyocyte



ROS production



ROS = O_2^- (3% of O_2)

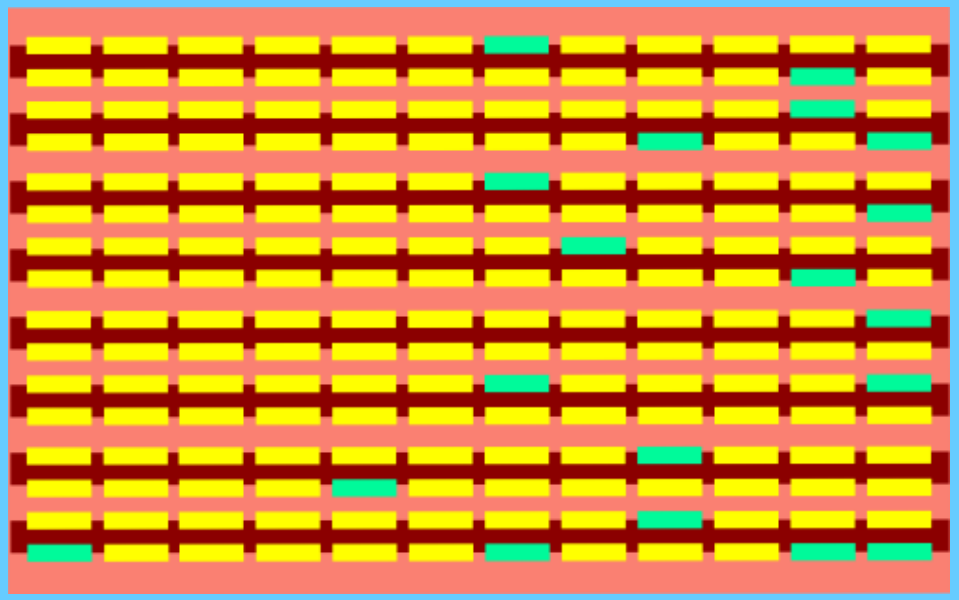
ROS is dangerous!

-Electron Transfer Chain: Generates most of ROS

-IMAC: a pore that open in presence of high conc. mROS and pumps ROS out.

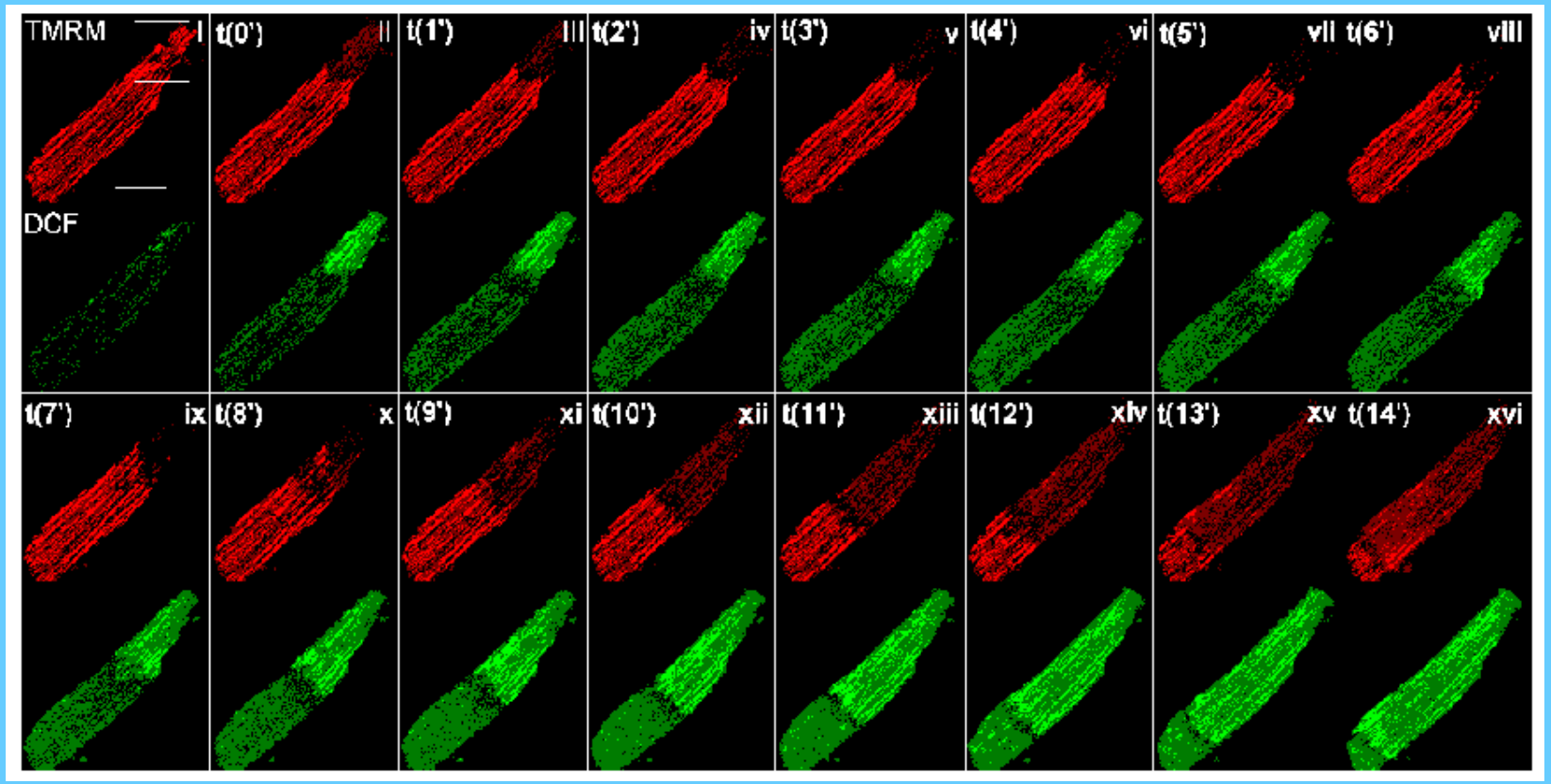
ROS-Induced Ros Release

How is it induced and released?
First the laboratory observations ...



The front travels at about 5μm /min

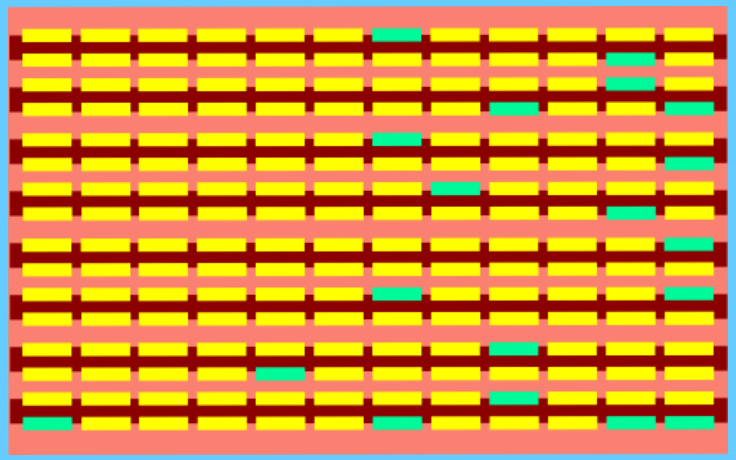
Lab Front Observation



Red: polarization (high intensity)
Green: cytosolic ROS (high intensity)

ROS-Induced ROS Release

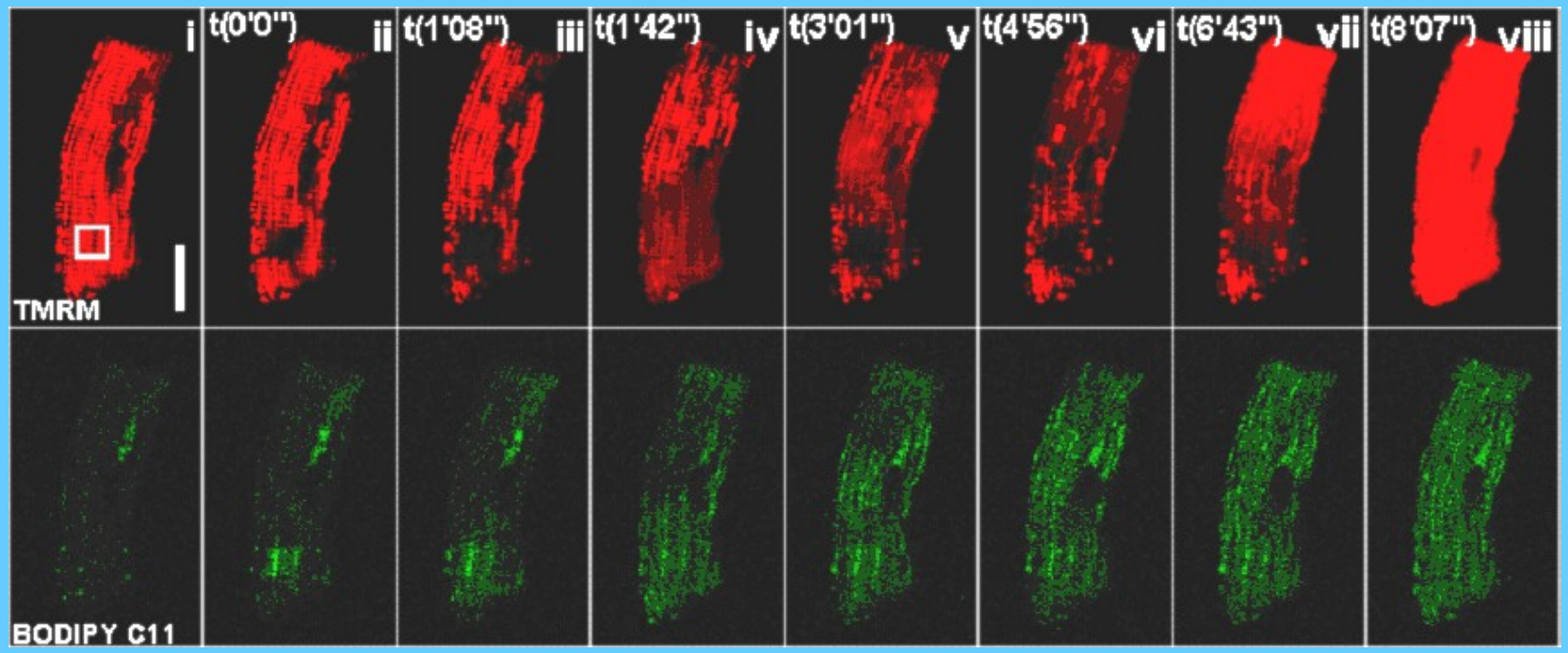
After the whole mitochondria is depolarized...



It repolarizes!

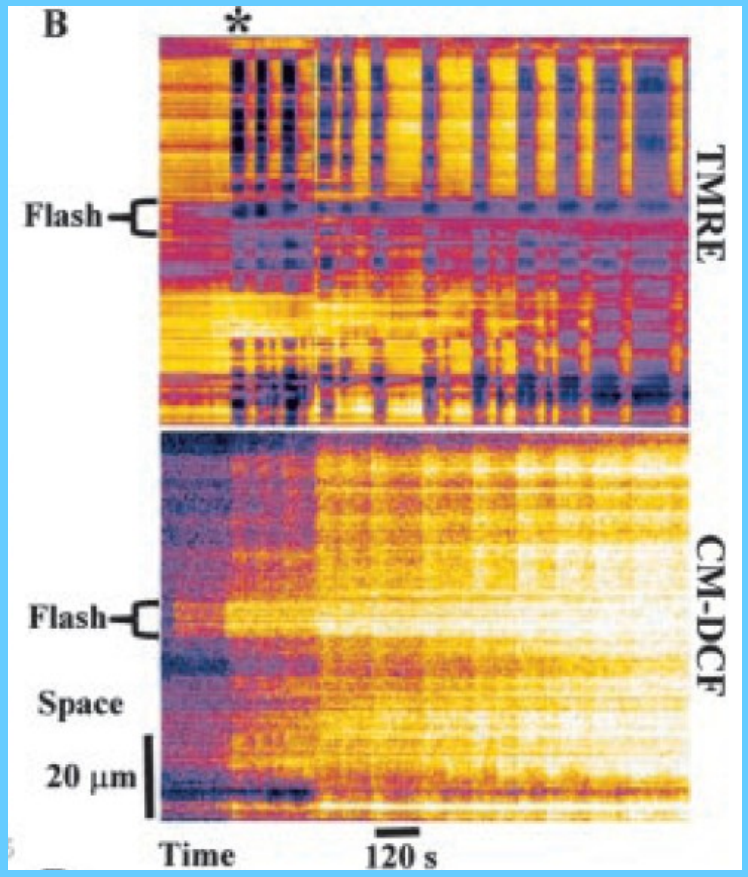
Observation:
-The repolarization wave is faster than polarization.

Lab Observation of Repolarization

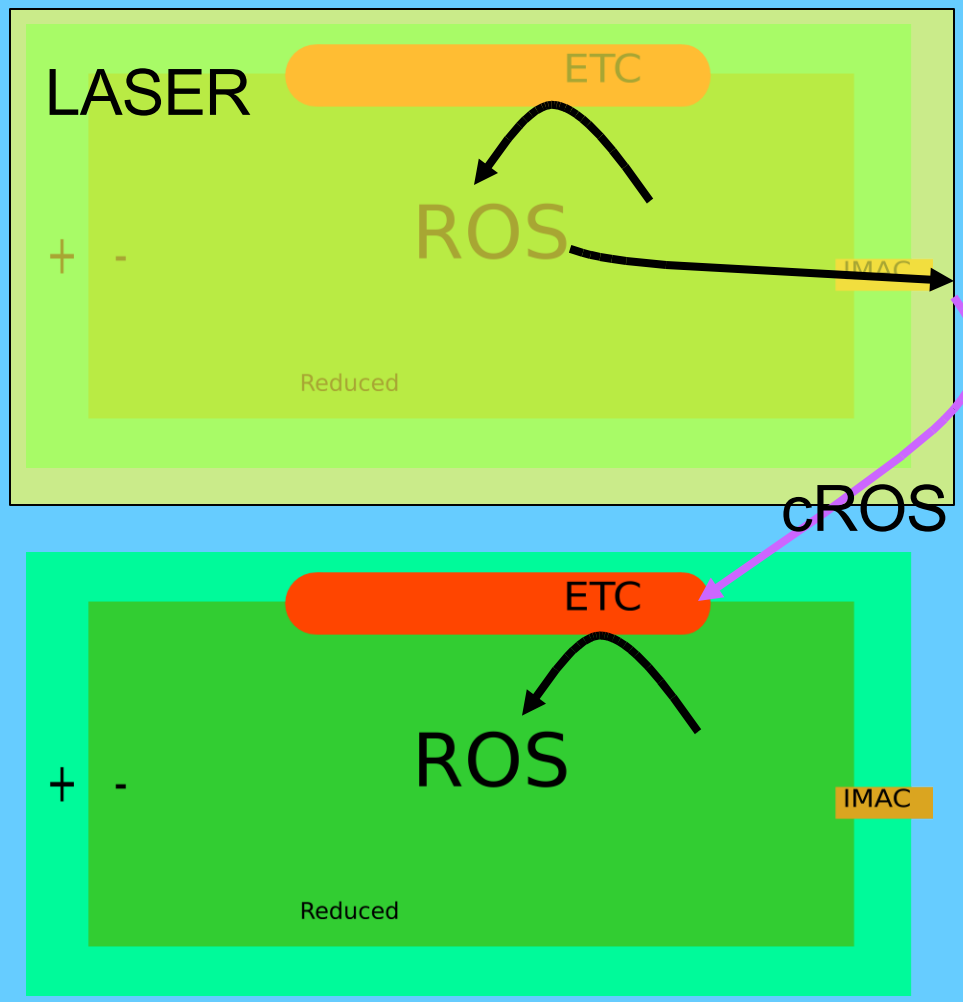


Depolarization front ii-vi
Repolariztion vii-viii (40μm/min)

And Global Synchronized Oscillations



Supposed Mechanism for RIRR



1-mROS production induced

2-IMAC pores open

3-Membrane depolarization

4-mROS pumped to cytosol

5-cROS stimulates ETC

6-mROS is produced in stimulated mitochondria

7-cROS slowly scavenged

8-IMAC pore closes mROS depletion

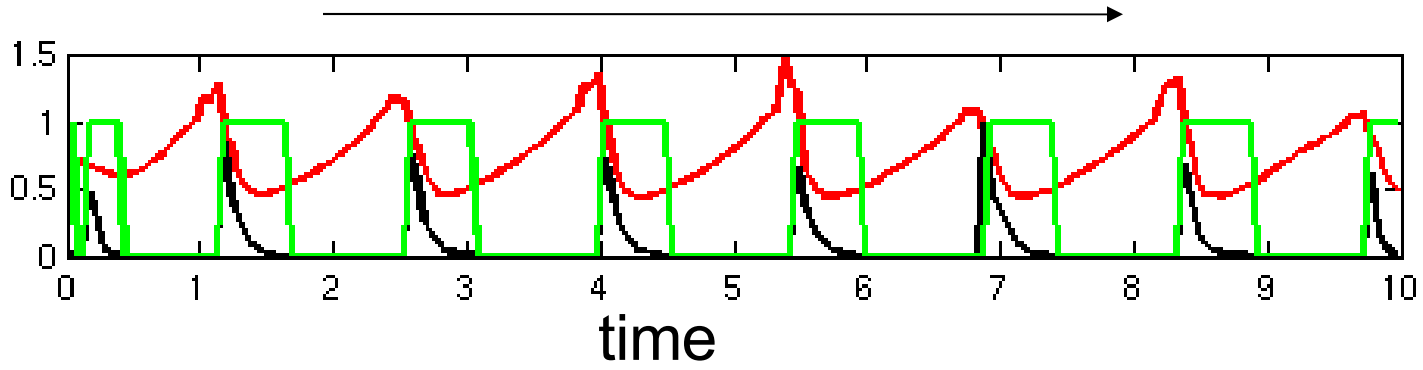
Towards Modeling RIRR

$\Psi = 0$ if mROS > thr, for $t-\tau<s<=t$,
$\Psi = 1$ otherwise

cROS = Diffusion - Scavenging + $(1-\Psi)$ Released
mROS = Internal - $(1-\Psi)$ Release + ΨInduced

This is solved using a 1D partial differential equation

Results



Legend:
Green: Potential Y
Red: Cytosolic ROS
Black: Mitochondrial ROS
(minus background ROS)

- mROS production in polarized mit. and due to RIRR
- Moving front due to initial conditions and cytosolic diffusion and RIRR

Conclusions

-Simplified spatial model of RIRR

-Capable of reproducing the traveling front observed in experiments by Brady and Aon, that lasts about 120s.

-However, the oscillatory behaviour observed by Aon et al. Is not yet fully included (t>120s).

Thanks

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Thanks to you all for your attention

Q&A?