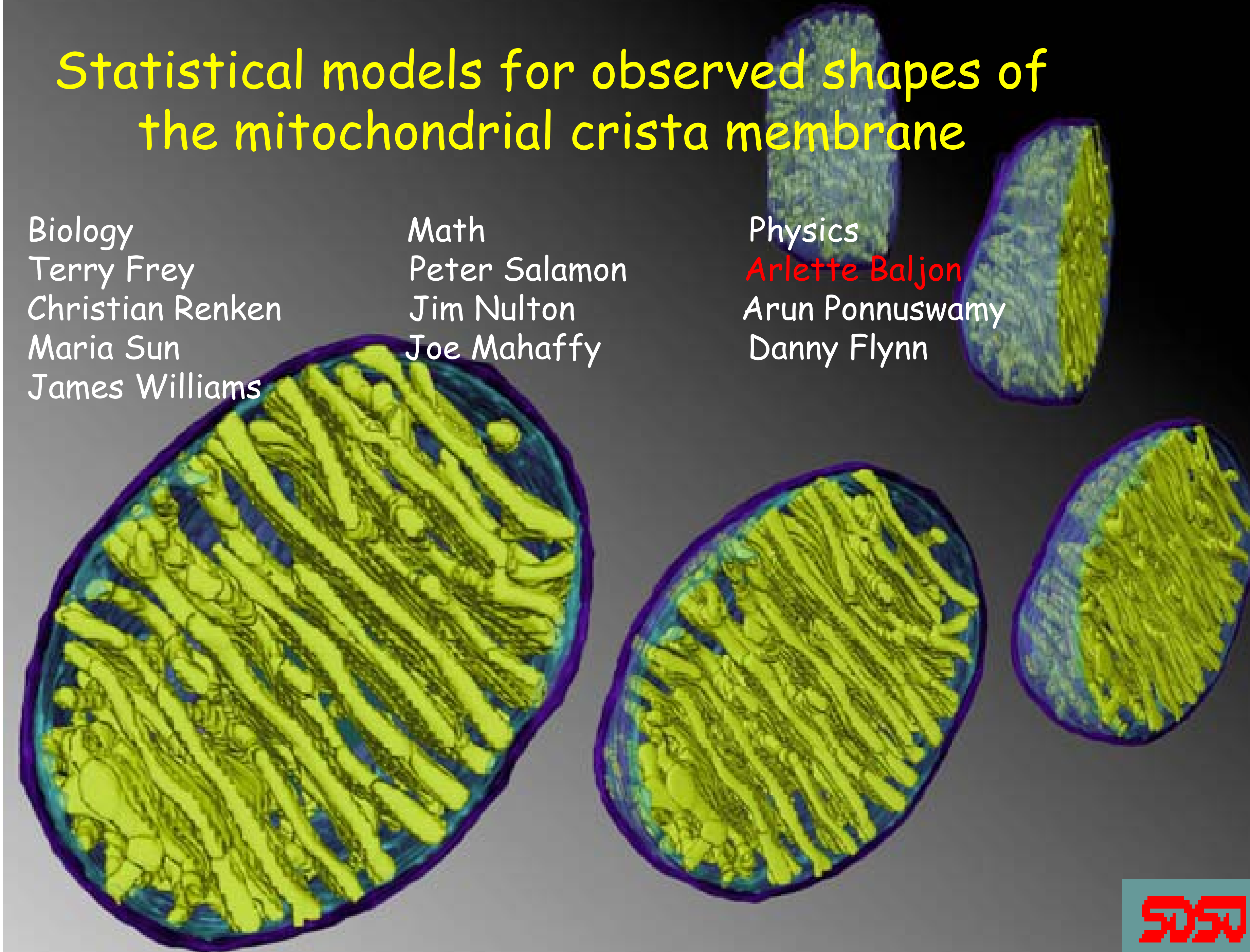
Statistical models for observed shapes of the mitochondrial crista membrane

Biology
Terry Frey
Christian Renken
Maria Sun
James Williams

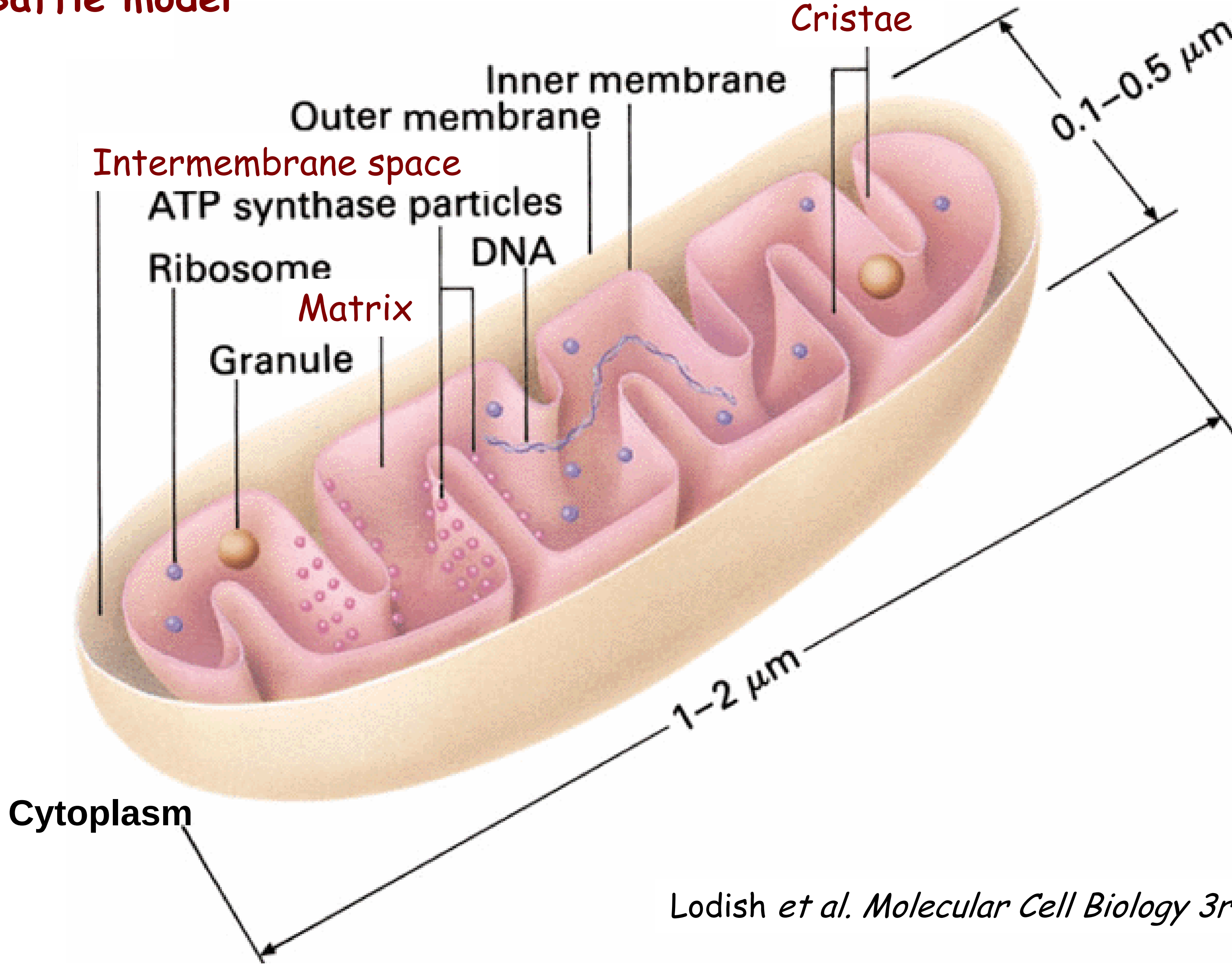
Math
Peter Salamon
Jim Nulton
Joe Mahaffy

Physics
Arlette Baljon
Arun Ponnuswamy
Danny Flynn



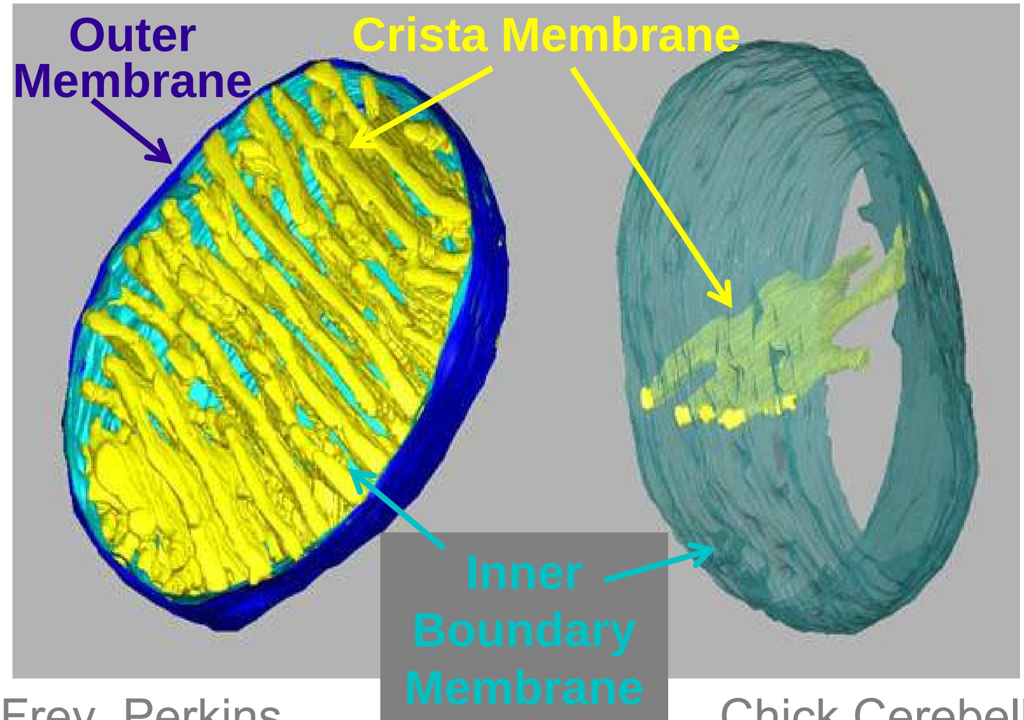
Traditional model of mitochondrial structure

Baffle model

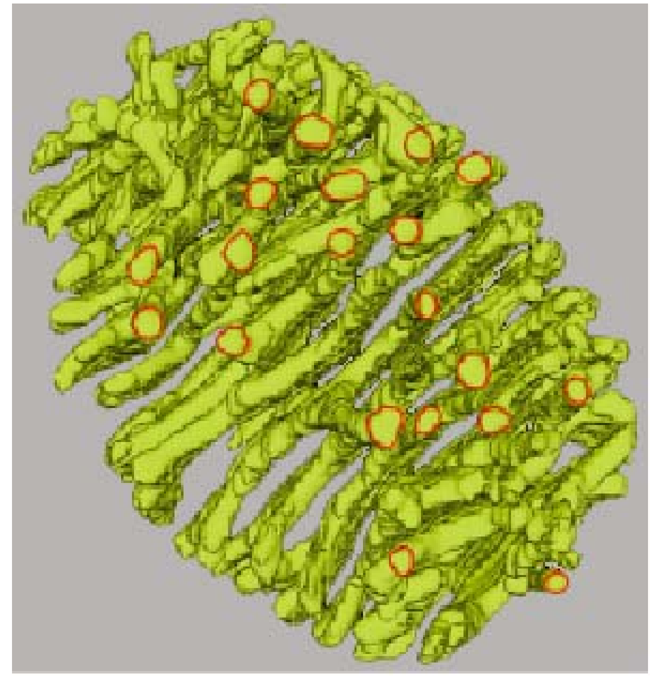


Lodish *et al. Molecular Cell Biology 3rd Ed.*

Corrected model-Crista junction model



Frey, Perkins   Chick Cerebellum



Electron Tomography

Complex topology

- Matrix (connected)
- Intermembrane space
- Cristae

Crista membrane:

- Flat Regions
- Tubular Regions
- Crista Junctions

Junctions are uniform in size:

Radius $\approx$ 10 nm

Alberts *et al. Molecular Biology of the Cell 4th Ed.*

Function

- ATP synthesis
- Regulate cell death

  Development of:

  - Central Nervous System
  - Immune System

- Neural dysfunction ⟷ Defects in structure of inner mitochondrial membrane

Mitochondrial diseases: Altzheimer, Parkisons, Cancer, Heart attacks, Neurodegeneration, Muscle degeneration

Free energy for uniform membrane

$$F = \frac{\kappa}{2}\oint(\frac{1}{R^2})dA + \frac{k^m}{4A}(\Delta A - \Delta A_0)^2$$

Bending

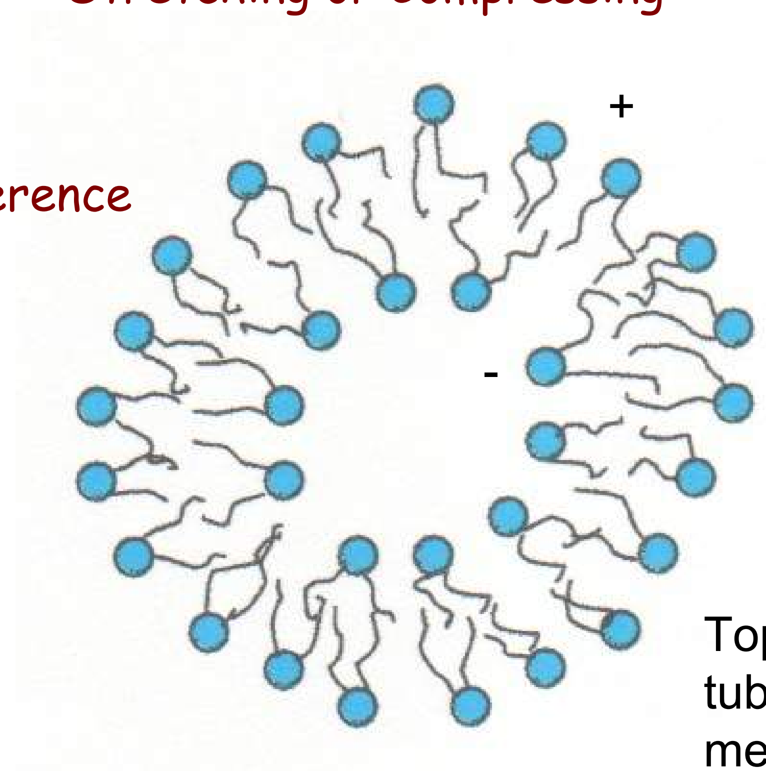
Helfrich   Area Difference

$$+ k^m A\left[(N^+ + N^-)/(2\phi_0 A)\right]$$

Stretching or Compressing

$$+ F_v$$

Osmotic Pressure Difference



Topview tubular membrane

Review:
Seifert, Advances in Physics, 1997

K -bending modulus
k^m-compression modulus

ϕ is the number density of lipid head groups
+,- are actual values in outer, inner leaflet;
0 is the preferred value

Nanoscience

Giant Vesicles (cell membranes) $A=1000\mu m^2$.

- "A simplification arises from the fact that there are two well separated energy scales."
- "Area of membrane is constant because stretching or compressing the membrane involves much larger energies than the cost of bending deformations."
- "Any net transfer of water would generate an osmotic pressure that can not be counterbalanced by the relative weak forces arising from bending the membrane."

Seifert, Advances in Physics, 1997

Crista Structures $A=1000nm^2$

- All terms result in roughly equal contributions

First model

Physical Biology **2, 73 (2005)**

Explain the uniformity in the radius of the tubular portions

- Osmotic pressure difference
- Non-uniform lipid distribution (C_0)

- No stretching or compressing forces

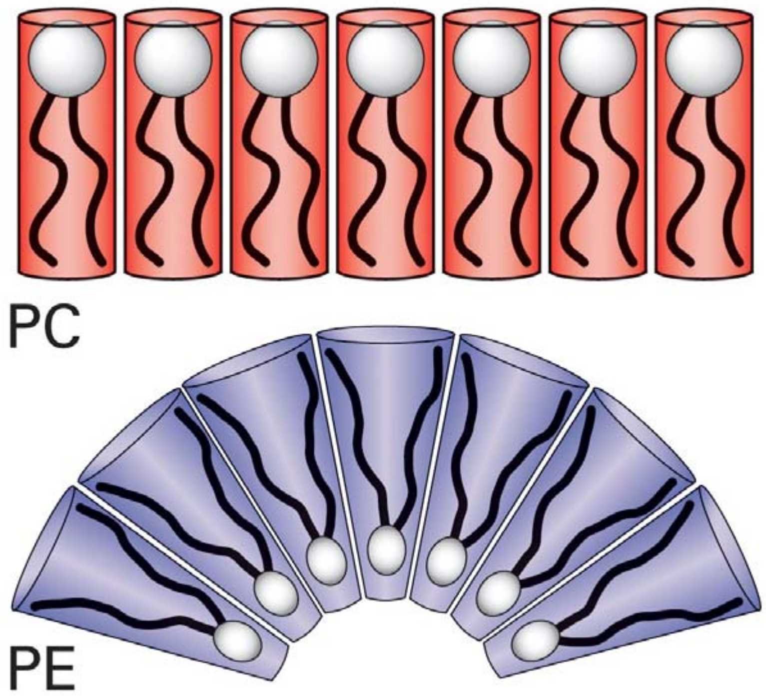
Two-lipid Model

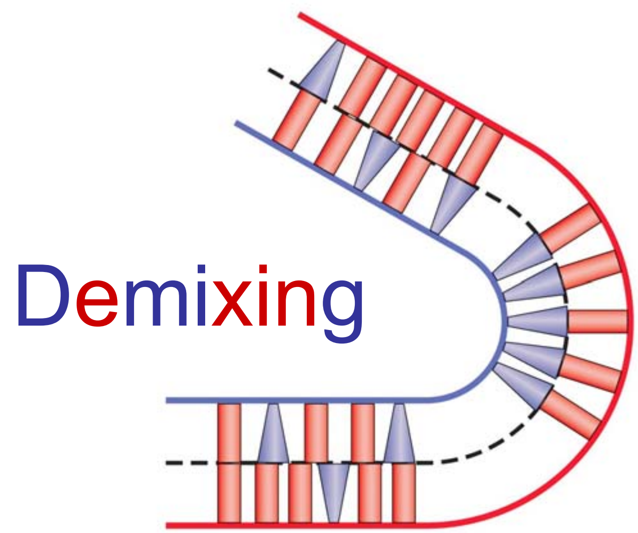
- Lipids
  - Phosphatidyl Choline (PC) – 44.5%
  - Phosphatidyl Ethanolamine (PE) - 27.7%
  - Cardiolipin – 17.4%
  - Others – 10.4%
- Proteins

Free energy of bending

$$F^{bend} = \frac{k^m}{2} \sum_{lipids} a\left(1 - \frac{a_0}{a}\right)^2$$

Israelachvilli
Miao et al.

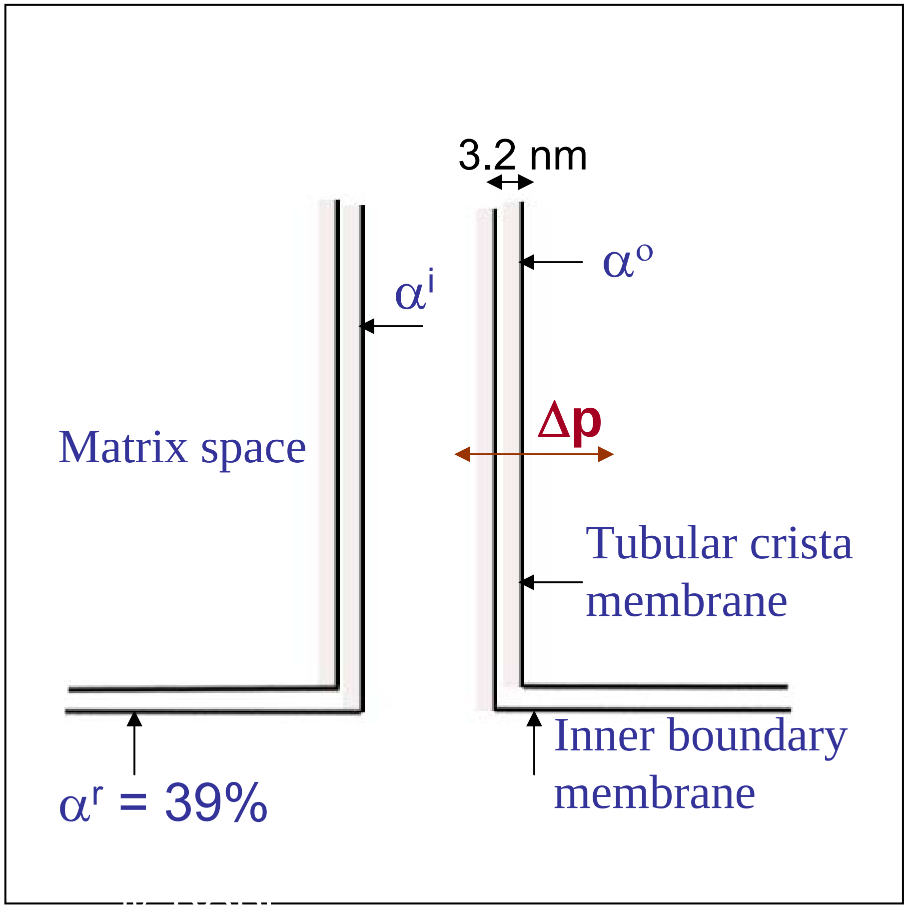




a_0 preferred area per headgroup
a actual area per headgroup

Lodish *et al. Molecular Cell Biology 5th Ed.*, Freeman, 2003
Ding *et al. Langmuir* 21, 203, 2005

Definitions



Bending

$$F^{bend} = \frac{k^m}{2} \sum_{lipids} a\left(1 - \frac{a_0}{a}\right)^2$$

Entropy

$$F^{demix} = T\Delta S$$

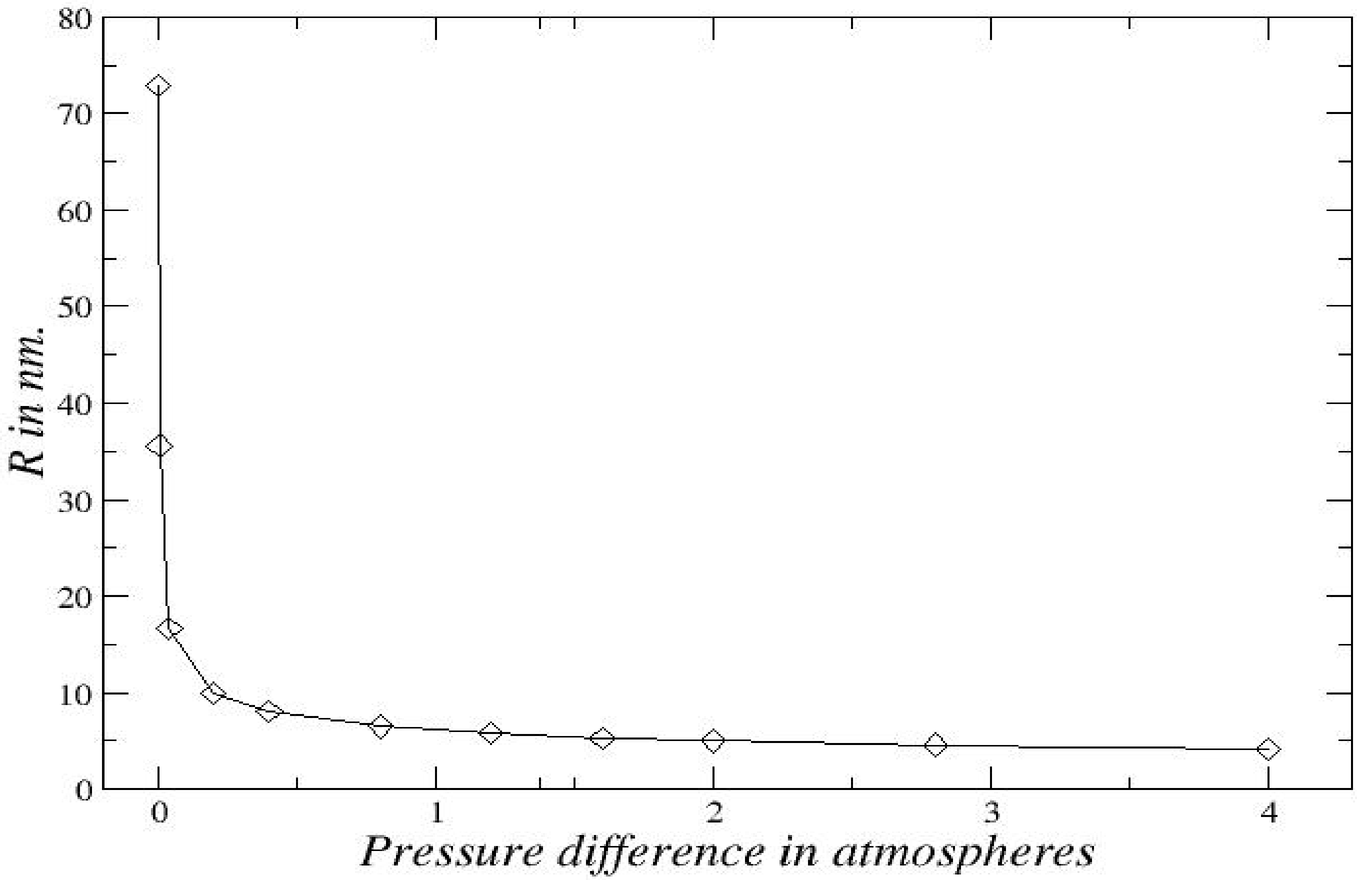
Mechanical Work

$$F_v$$

Given Δp, minimize F(α^i, α^o, R)

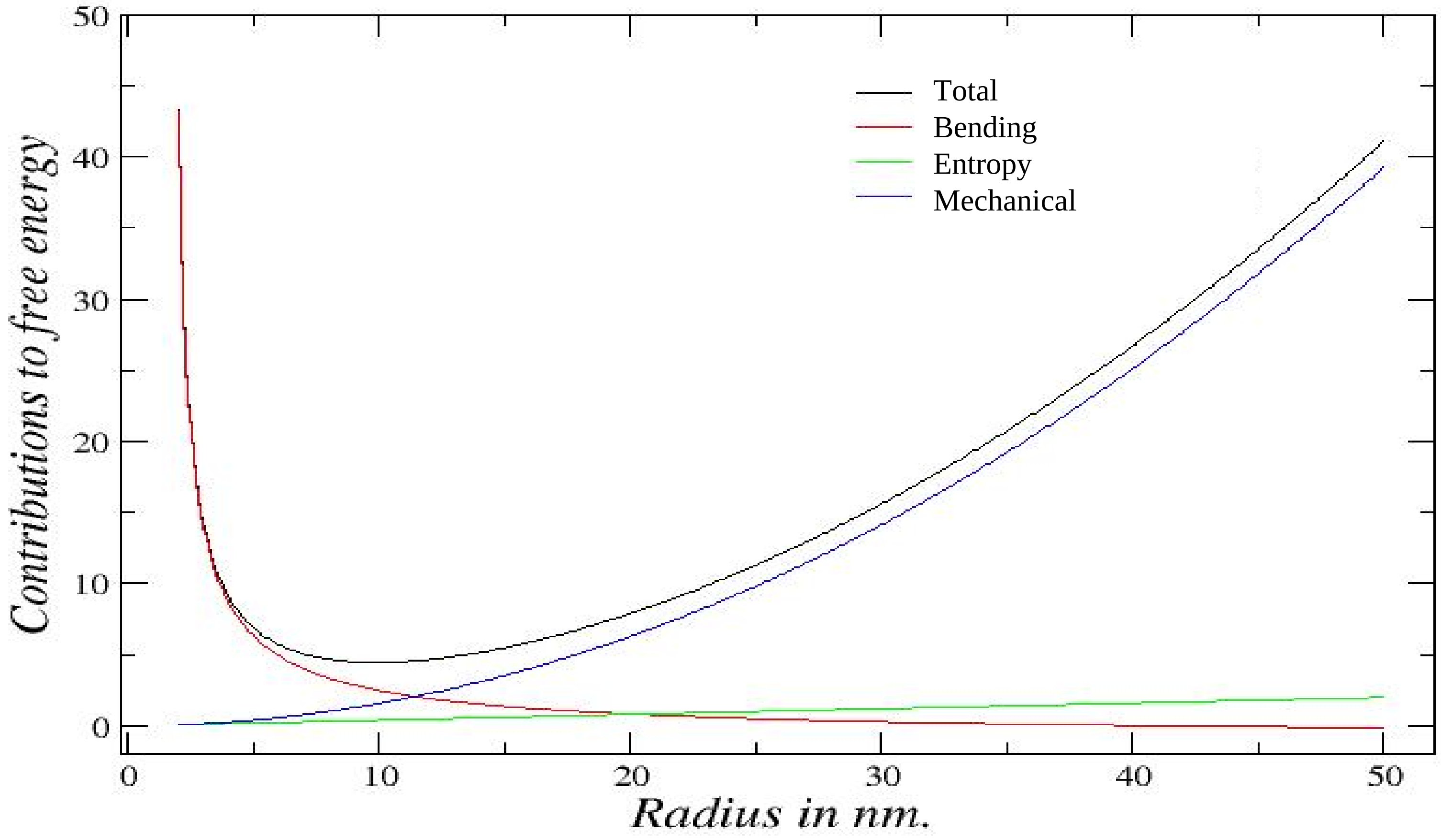
α^i = %DOPE (inner layer) α^o = %DOPE (outer layer) R = Radius tube

Pressure Dependence



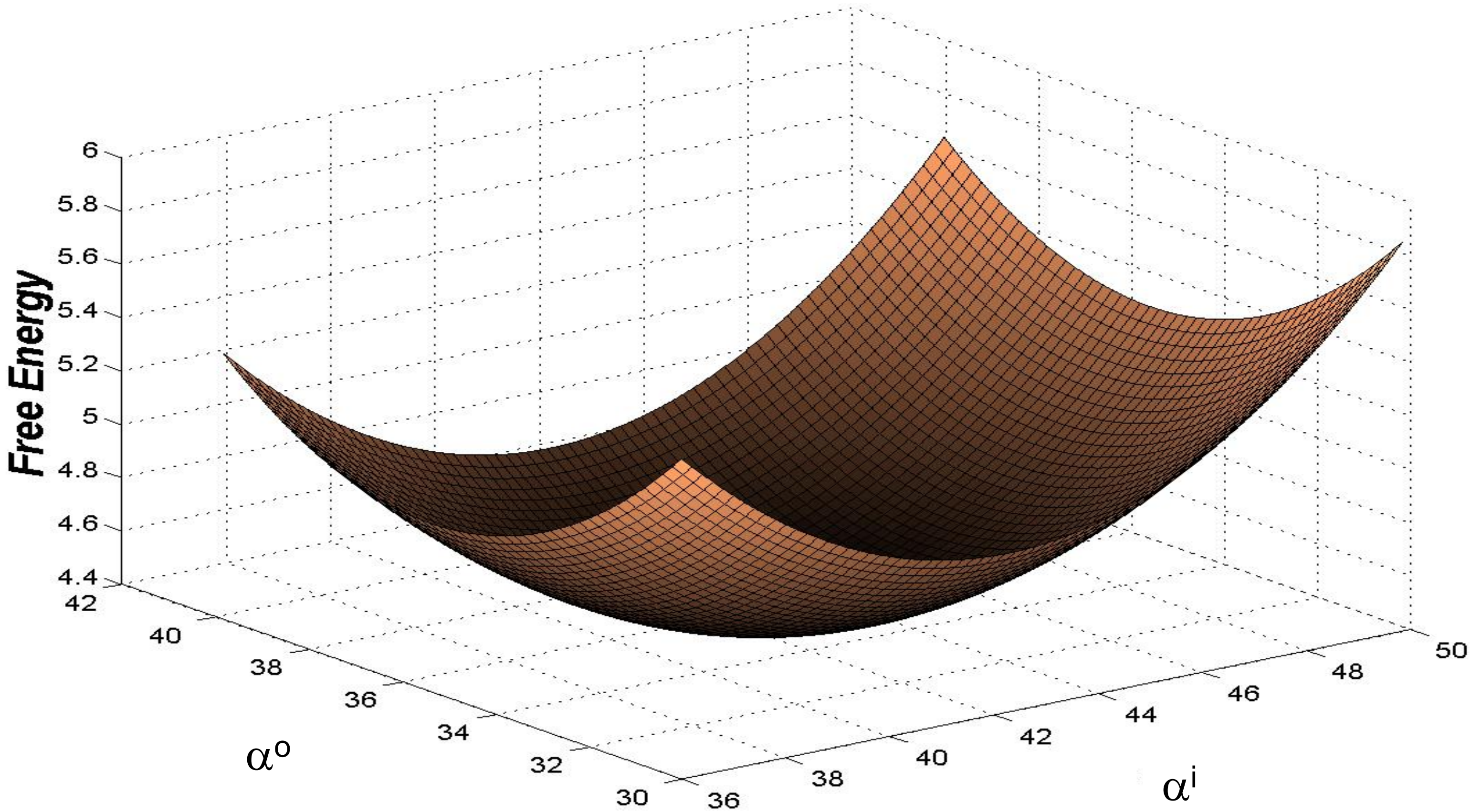
At Pressure difference Δp = 0.2 atm., R = 10nm

Free energy of tubular membrane
(compared to that of flat membrane)



At Δp = 0.2 atm, α^i = 42%, α^o = 35%

Relevance of lipid composition



Δp = 0.2 atm, R = 10 nm

First Model

Given the observed raduis of tubes R=10 nm

- **Predicted pressure difference**:

  $\Delta p = 0.2$ atm

- **Predicted lipid redistribution:**

  α^i = % DOPE (inner layer tube) = 42%

  α^o = % DOPE (outer layer tube) = 35%

Issues

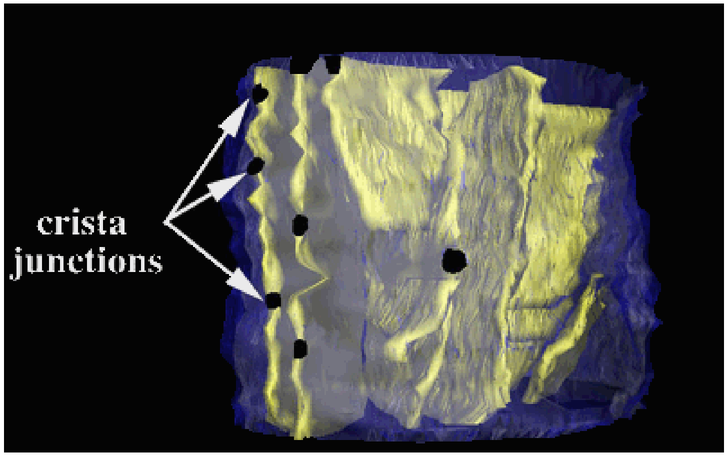
Why do tubular regions and flat regions coexist in mitochondrial crista membrane?
Why do tubes vary in length?
Is there indeed an osmotic pressure difference?
What is role of OPA1?

OPA1

Dynamin-like GTPase
Mechano-enzyme
Intermembrane protein

"Loss of OPA1 Perturbates the Mitochondrial Inner Membrane Structure"
Olichon et all, *JBC* (2002).

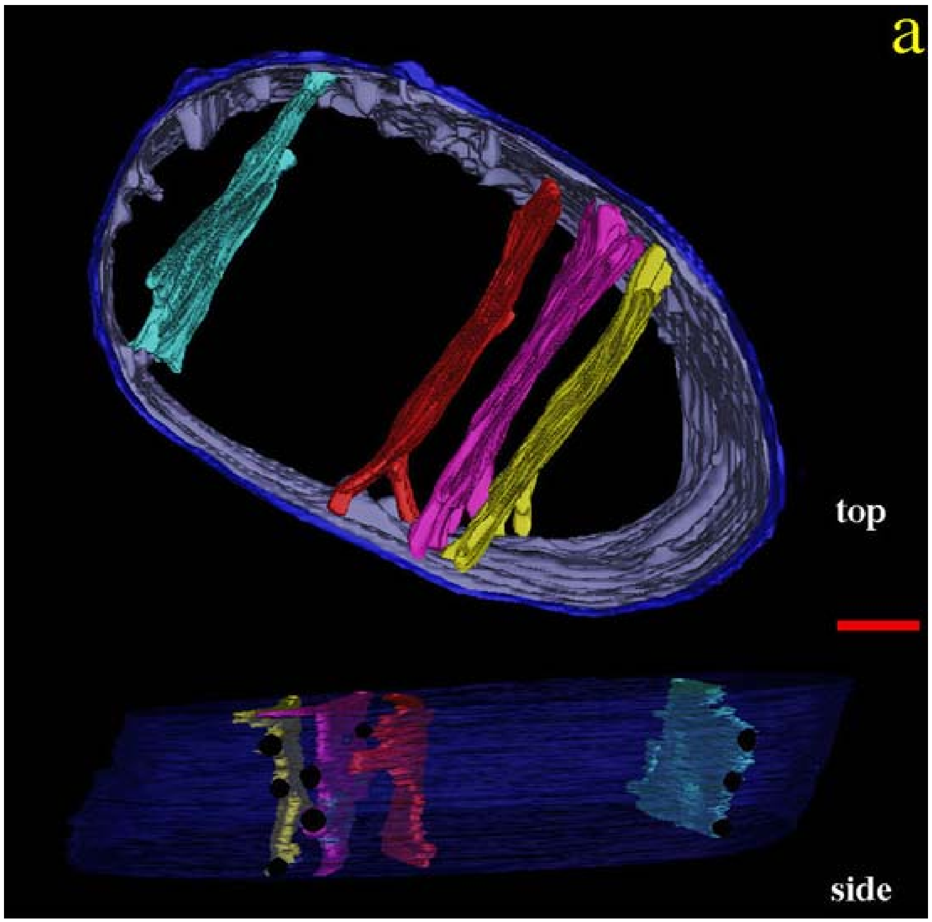
Vestigal crista junctions



Neurospora mitochondrion, Perkins
Brown Adipose Tissue

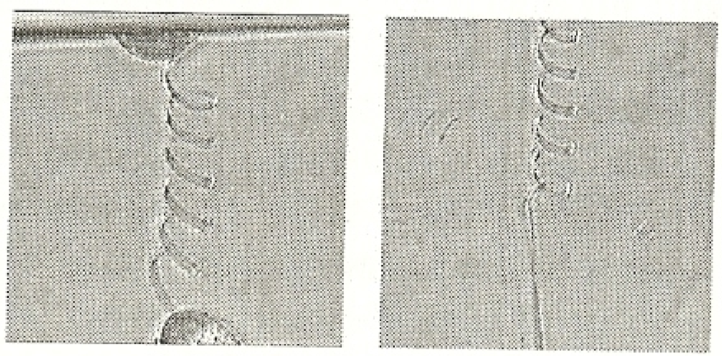
Second Model

- Membrane under compression
- Radii of tubes (R=10 nm) dictated by other mechanism (OPA1)
- No osmotic pressure difference



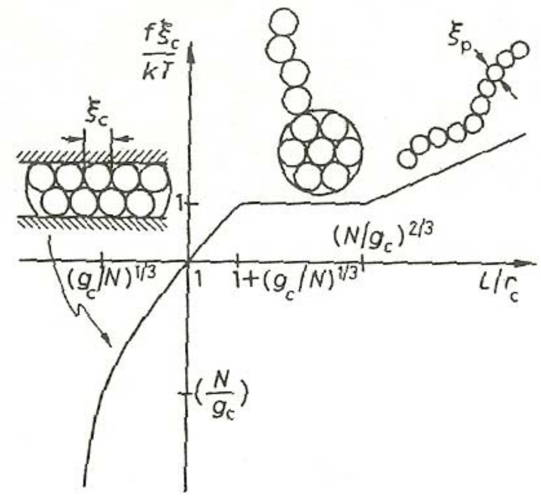
Spacing (D) of tubules is less than πR

Tension induced shape transitions



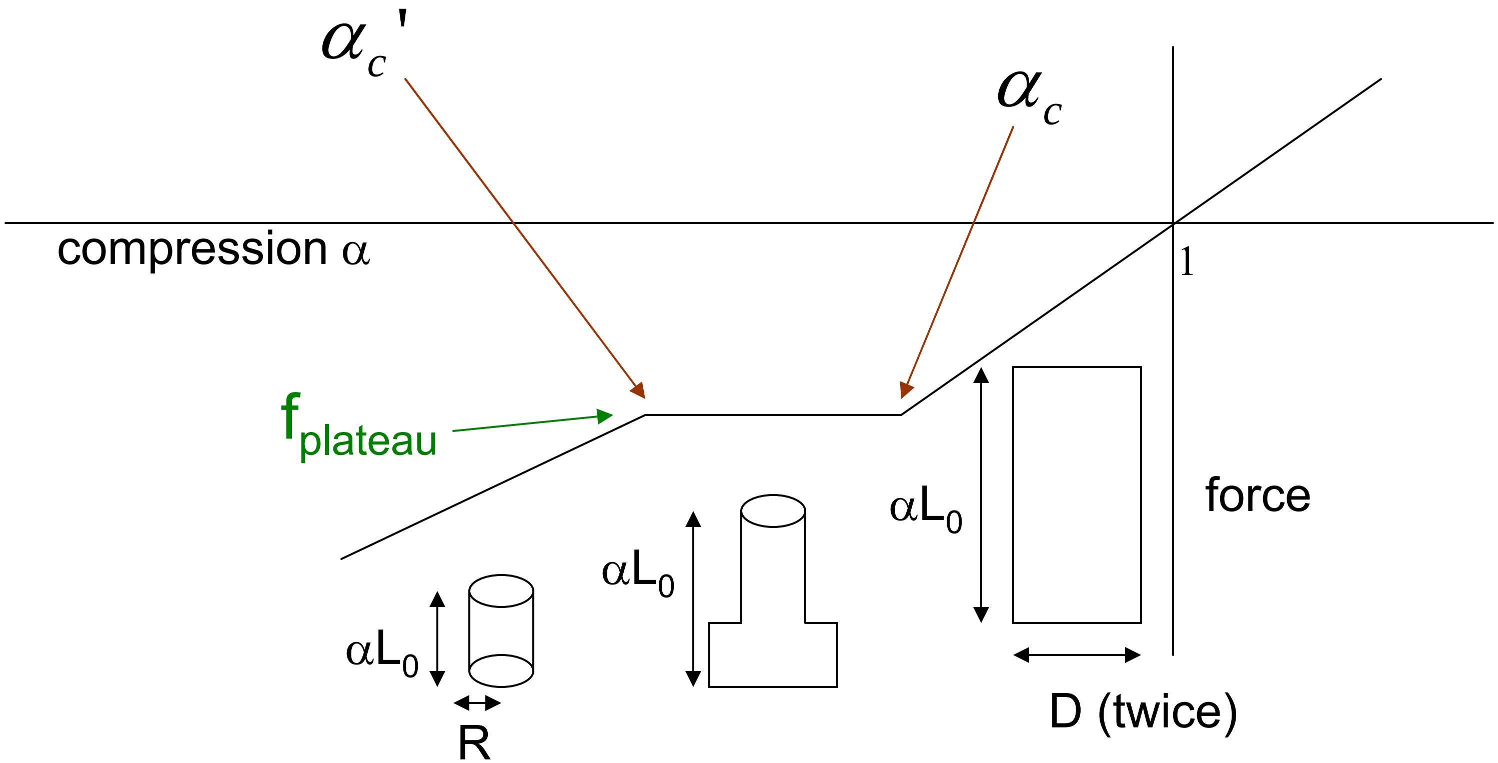
(b) (c)

Helical Ribbon:
Smith at all
Phys. Rev. Lett. 87, 278101, 2001



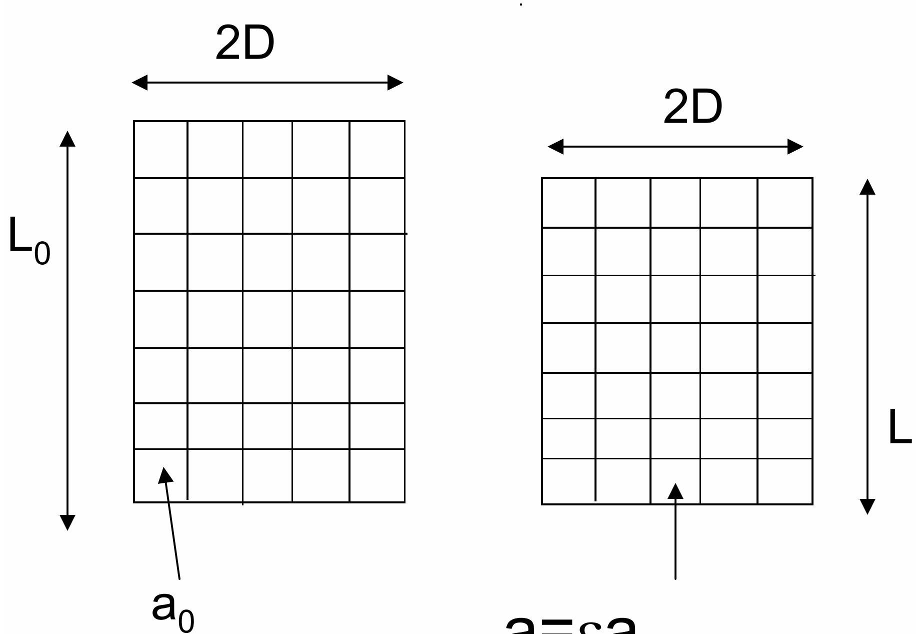
Polymer:
Halperin, Zhulina
Eur. Phys. Lett. 15, 417, 1991

Compression induced shape transition



Coexistence of two "phases"

Compressed flat portions

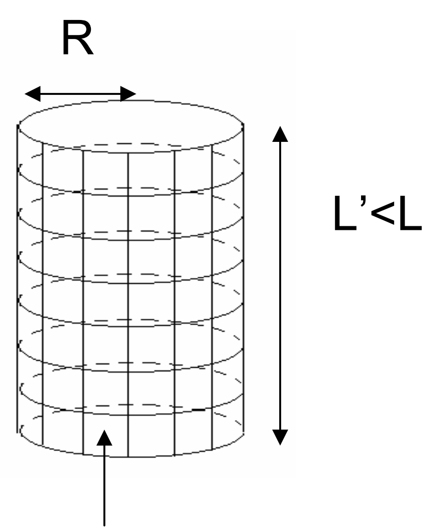


$a=\varepsilon a_0$

$L=\varepsilon L_0$

Assume that $\pi R > D$

Tubular portion at lower compression



$1>\varepsilon'>\varepsilon$

$a'=\varepsilon' a_0$

$$L' = \frac{D}{\pi R}\varepsilon' L_0$$

Conditions

F^{flat} = free energy of plat portion

F^{tube} = free energy of tubular portion

Coexistence implies:

$$\frac{\partial F^{flat}}{\partial N^{flat}} = \frac{\partial F^{tube}}{\partial N^{tube}} =$$ Free energy per molecule

$$\frac{\partial F^{flat}}{\partial L^{flat}} = \frac{\partial F^{tube}}{\partial L^{tube}} =$$ Plateau force

Free Energies

Free energies for flat and tubular parts

$$F^{flat} = k^m A\ (1 - \frac{A_0}{A})^2 = k^m \varepsilon A_0\ (1 - \frac{1}{\varepsilon})^2$$

$$F^{tube} \approx k^m \varepsilon' A_0\ (1 - \frac{1}{\varepsilon'})^2 + \xi k^m A_0$$

where $F^{bend} = \frac{k^m}{2} \sum_{lipids} a(1 - \frac{a_0}{a})^2 = \xi(R) k^m A_0$

for a uniform membrane, R=10 nm, ξ=0.0056

Coexistence

$$\frac{\partial F^{flat}}{\partial N^{flat}} = \frac{\partial F^{tube}}{\partial N^{tube}} \quad \text{gives} \quad \varepsilon\left(1-\frac{1}{\varepsilon}\right)^2 = \varepsilon'\left(1-\frac{1}{\varepsilon'}\right)^2 + \xi \qquad (1)$$

$$\frac{\partial F^{flat}}{\partial L^{flat}} = \frac{\partial F^{tube}}{\partial L^{tube}} \quad \text{gives} \quad \frac{\partial F^{flat}}{\partial \varepsilon} = \frac{\pi R}{D}\frac{\partial F^{tube}}{\partial \varepsilon'} \quad \text{or}$$

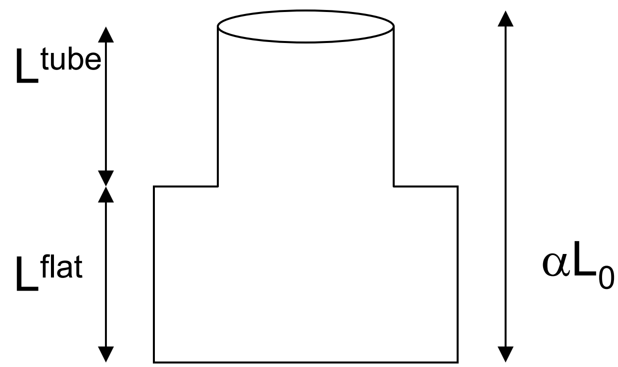
$$\left(1+\frac{1}{\varepsilon}\right)\left(1-\frac{1}{\varepsilon}\right) = \frac{\pi R}{D}\left(1+\frac{1}{\varepsilon'}\right)\left(1-\frac{1}{\varepsilon'}\right) \qquad (2)$$

Using Taylor expansions in (1-ε) and (1-ε') I obtain as solution for (1) and (2)

$$\alpha_c = \varepsilon = 1 - \sqrt{\frac{\xi}{\left(\frac{\pi R}{D}\right)^2 - 1}} \qquad \alpha_c' = \frac{D}{\pi R}\varepsilon' = \frac{D}{\pi R} - \sqrt{\xi\left(\frac{2\left(\frac{D}{\pi R}\right)^2 - 1}{\left(\frac{\pi R}{D}\right)^2 - 1}\right)}$$

Plateau Force Regime

$$\alpha_c' < \alpha < \alpha_c$$



From equations:

$$L^{flat} + L^{tube} = \alpha L_0$$

$$N = N^{flat} + N^{tube}$$

$$N = L_0 D / a_0$$

$$N^{flat} = DL^{flat} / \varepsilon a_0$$

$$N^{tube} = \pi R L^{tube} / \varepsilon' a_0$$

it follows that:

$$\frac{L^{tube}}{L^{flat}} = \frac{\dfrac{1}{\alpha} - \dfrac{1}{\alpha_c}}{\dfrac{1}{\alpha_c'} - \dfrac{1}{\alpha}}$$

Second Model

Compression $\longrightarrow$
- Coexistence of flat and tubular regions
- Variance in length of tubes

How does OPA1 control the radius?

Hypothesize: OPA1 controls Plateau force

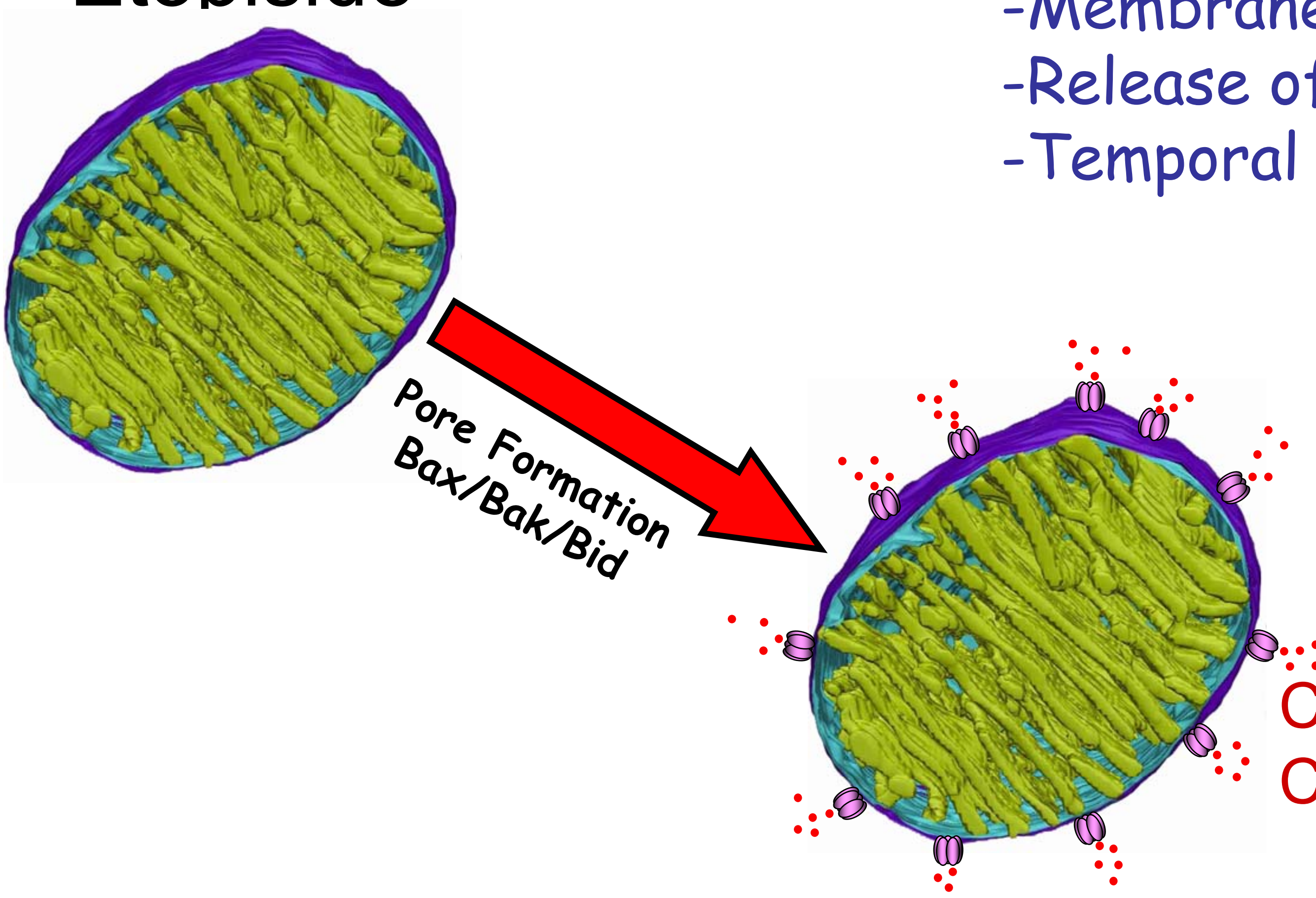
$\Rightarrow$ Radius

$$f_{plateau} = 2Dk^m\left(1+\frac{1}{\varepsilon}\right)\left(1-\frac{1}{\varepsilon}\right) \qquad \varepsilon = 1-\sqrt{\frac{\xi(R)}{\left(\frac{\pi R}{D}\right)^2-1}}$$

Apoptosis

Etopiside

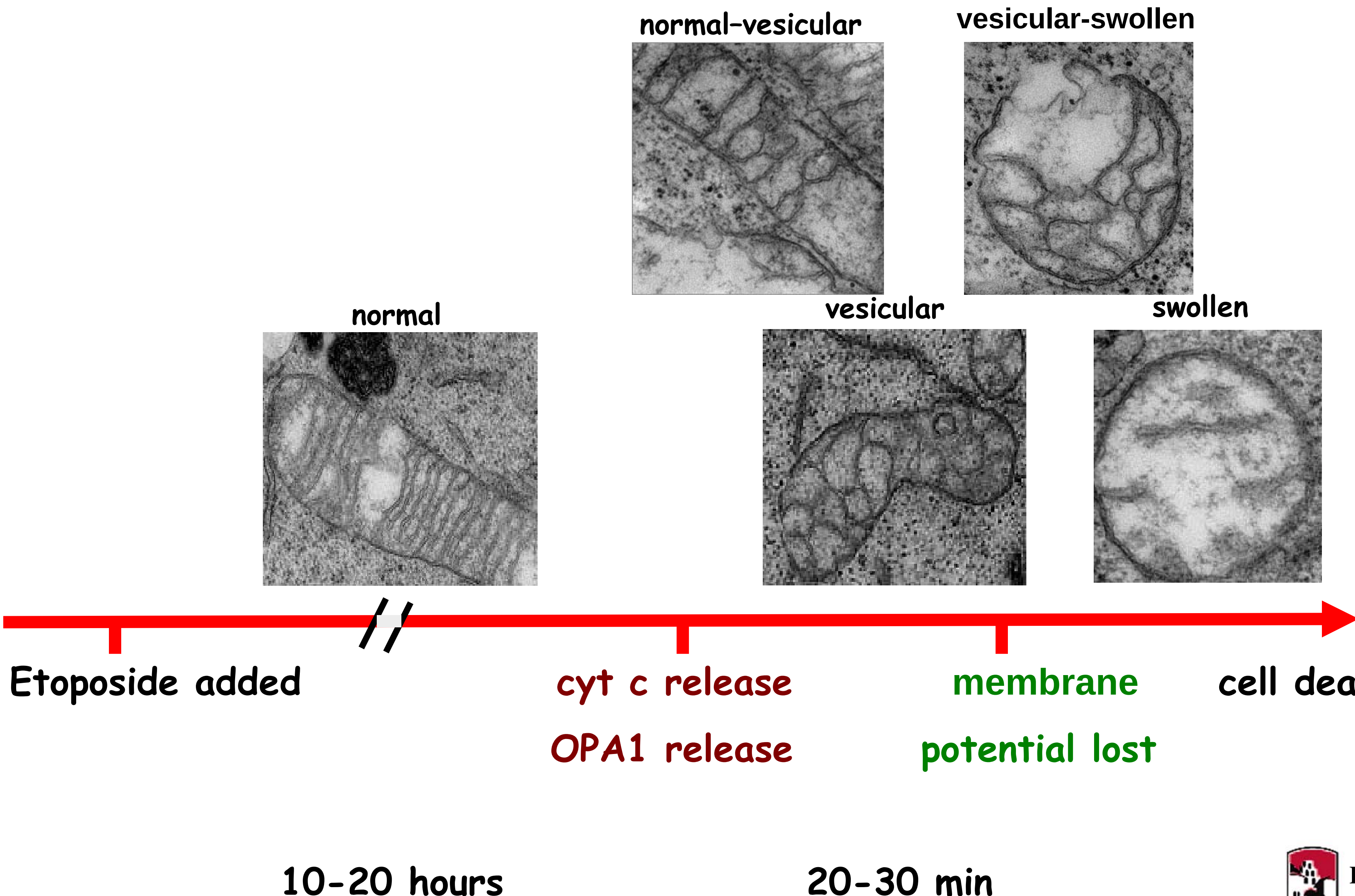
Issues:
-Membrane remodeling
-Release of OPA1
-Temporal order of events



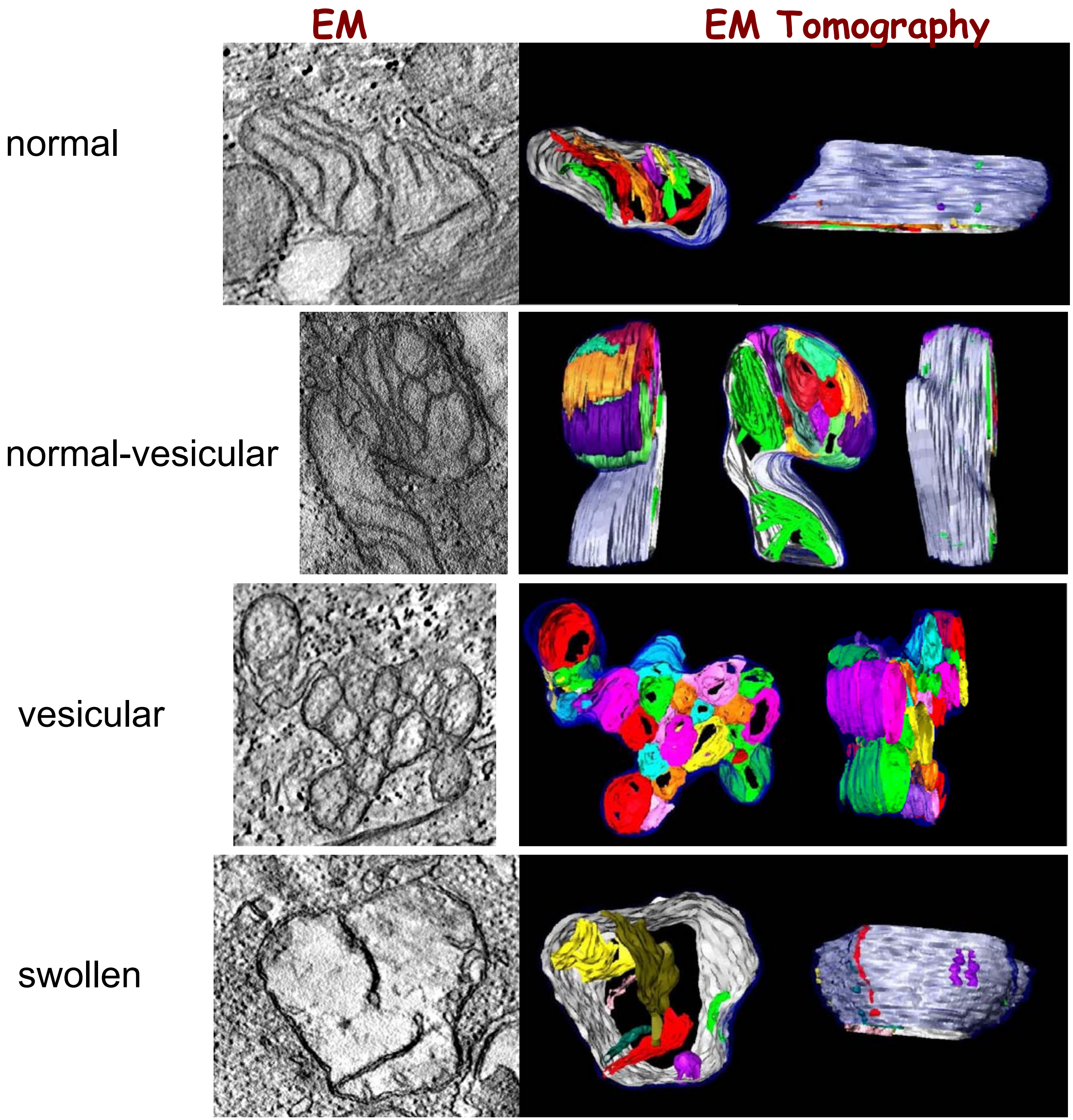
Cyt-c released
Caspases activated

Cell Death

The Progression of Structural Changes in Mitochondria During Apoptosis Initiated by Etoposide



Biology
SDSU



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