Mitochondrial network structure, bioenergetics and blood pressure variability

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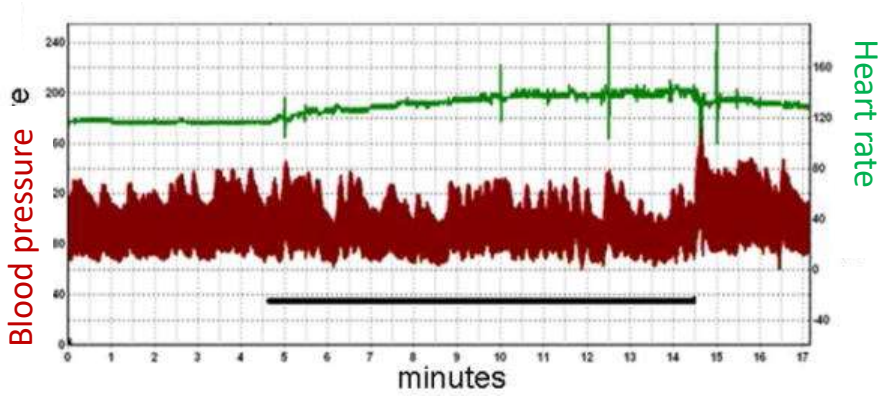
‘‘If the pattern of the heart beat becomes as regular as the tapping of a woodpecker or the dripping of rain from the roof, the patient will be dead in four days.’’

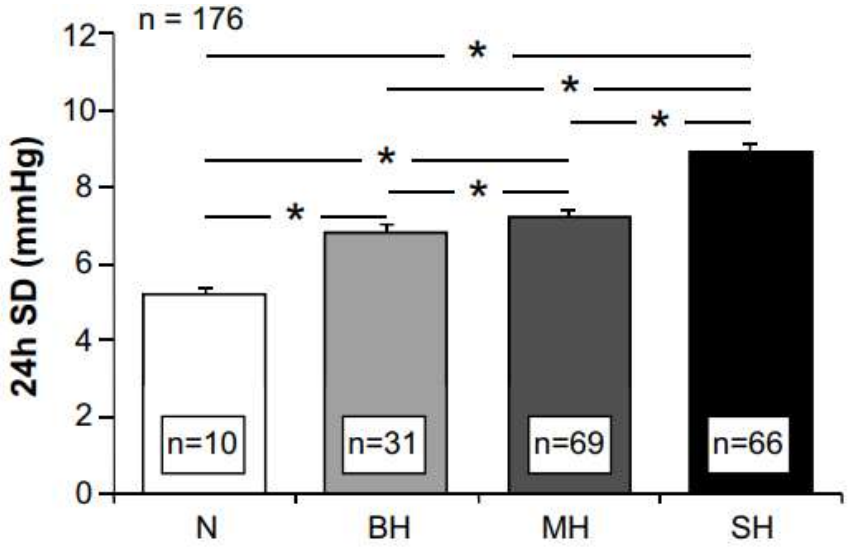
Shu-he Wang (265–317 AD)

(Cardiothoracic surgery in China: Past, Present and Future. Ed, S. Wan and A.P.C. Yim, The Chinese Univ. Press, 2007)

Heart rate and blood pressure variability

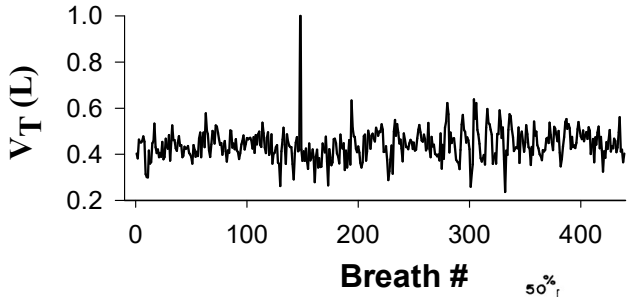


Kimpinski et al. Auton Neurosci. (24;155:130-1, 2010)

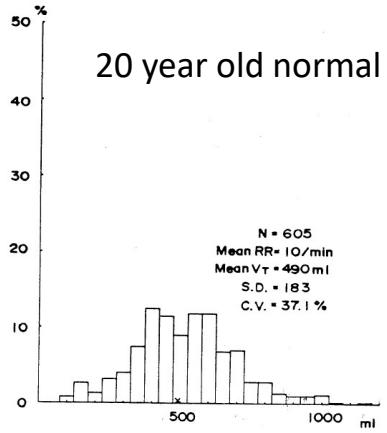


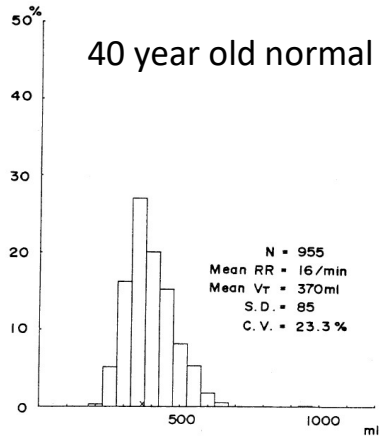
SD of 24 h mean arterial pressure in normotensive subjects (N) and borderline (B), moderate (M), and severe (S) hypertensive (H) patients.
Mancia et al. *Circ. Res.* (1983)

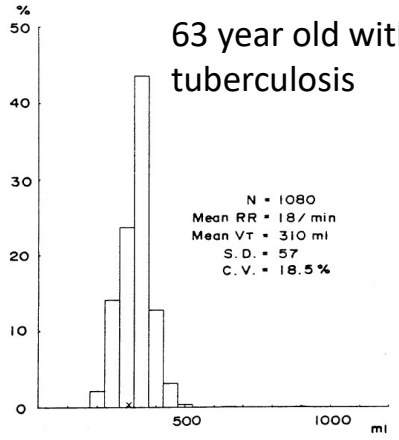
Variability in Tidal Volume

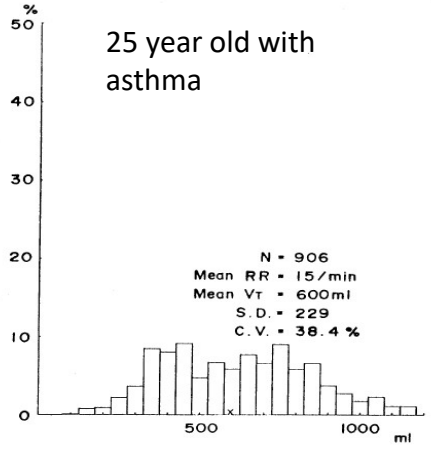


Dellaca et al. (PLoS One, 2015)









Kuratomi et al. *Jap. J. Med.* (1985)

Hypothesis

- Fluctuations accompany life.

- Breathing generates tidal volumes with variabilities; the heart generates fluctuations in blood pressure; muscle contraction and all body movements generate variabilities.

- Stretch/pressure/force amplitudes that all adherent cells are exposed to in the body will show similar variabilities.

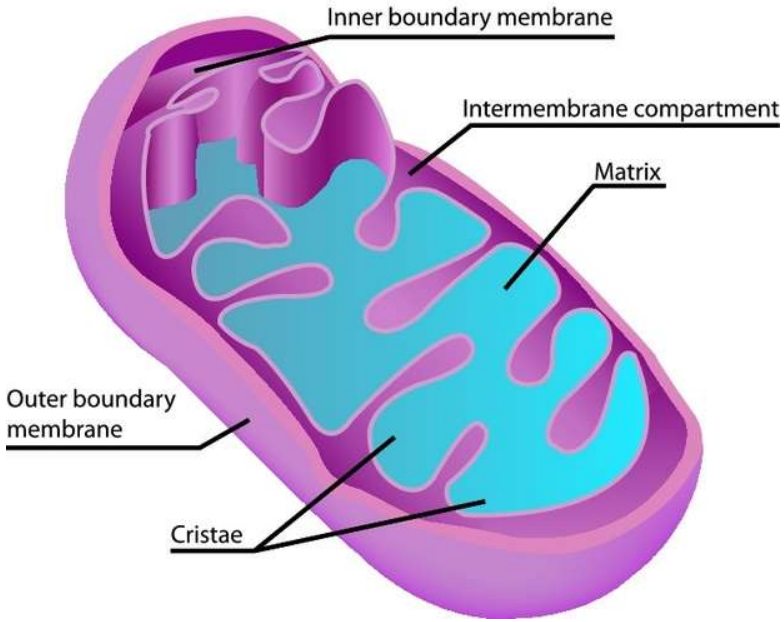
- Over hundreds of millions of years of evolution, cells in the body must have adapted to such variable patterns.

- ***We hypothesize that all cell functions that are affected by stretch/pressure/force will be sensitive to the pattern of mechanical stimuli.***

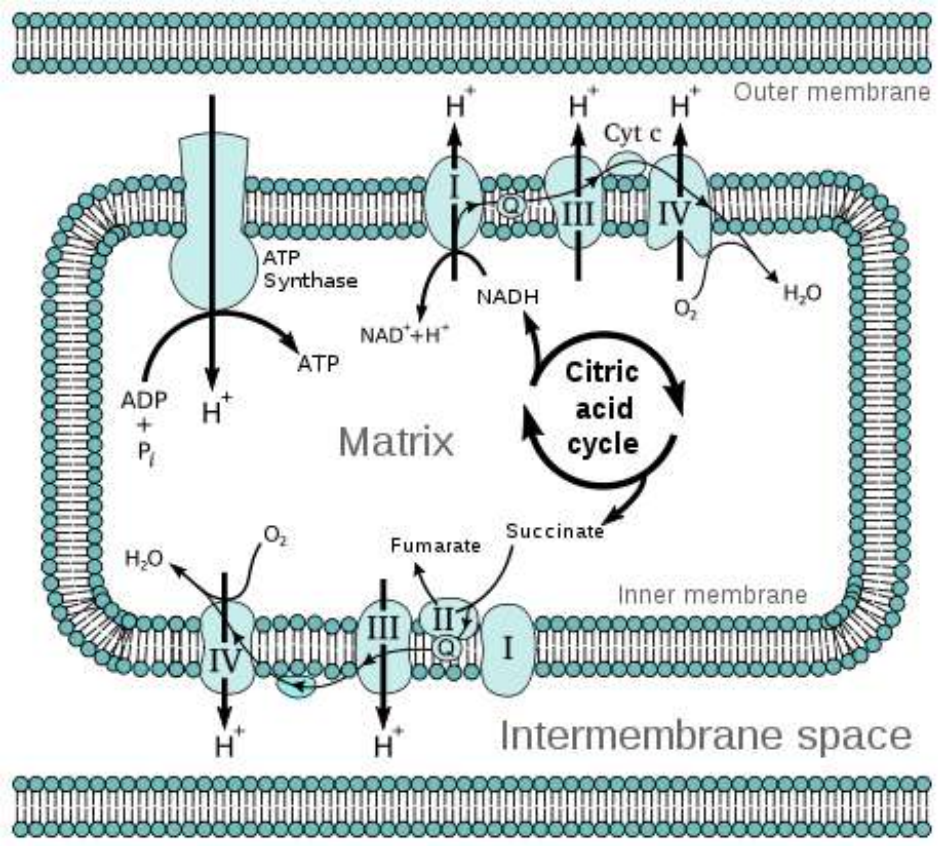
Implications

- If variability indeed was built into cell function when multicellular life evolved about a billion years ago, then variability of mechanical forces acting on cells should affect the most ancient cellular process, the generation of usable energy in the form of ATP!

The mitochondrion

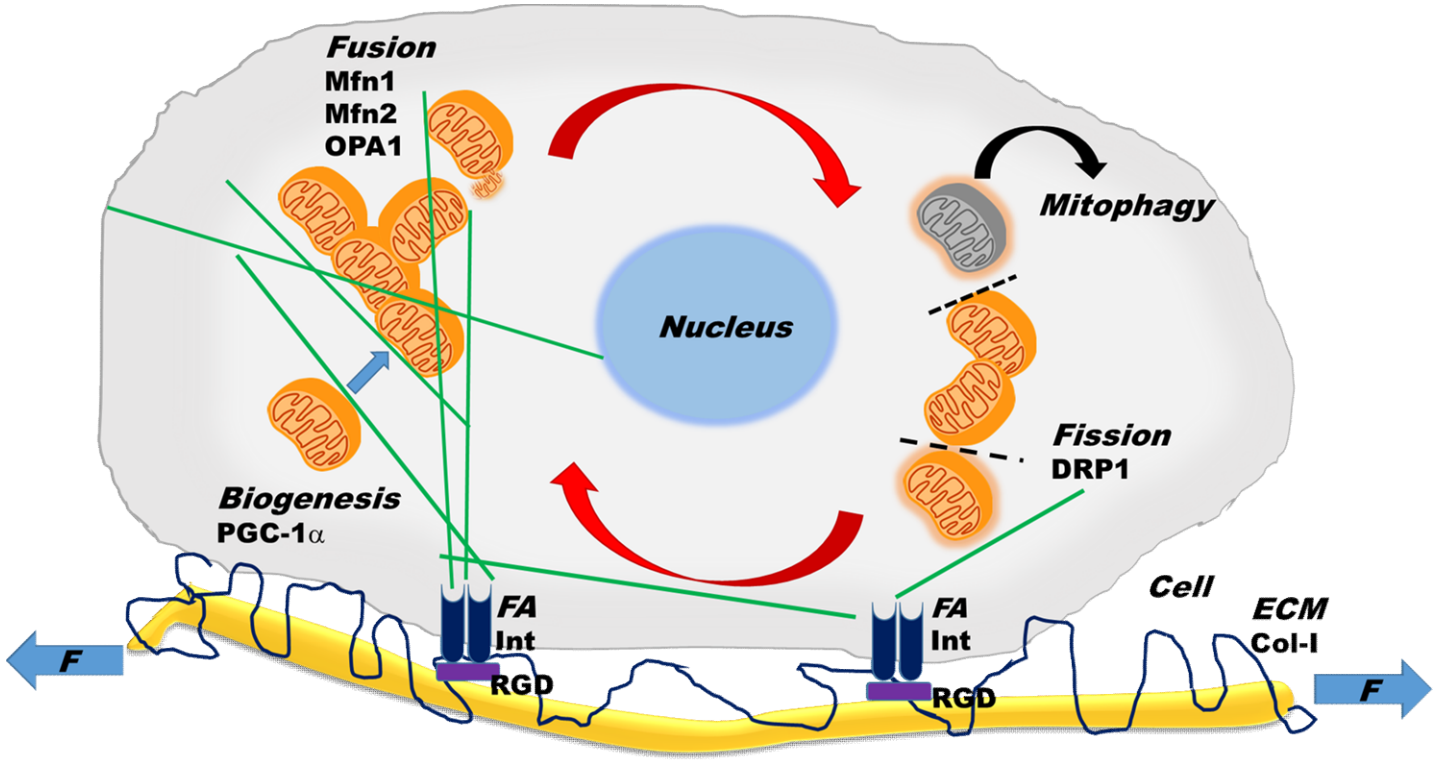


(Wikipedia)



The mitochondria is the powerhouse of the cell. Fat and sugar enter the mitochondria through various channels and the Krebs cycle feeds the chain of respiratory complexes which create an electrical gradient across the inner membrane, called the mitochondrial membrane potential. This potential drives the ATP synthase which in turn generates ATP from ADP.

Mitochondrial network dynamics



Bartolák-Suki et al. (Int J Mol Sci, 2017)

Mitochondria undergo cycles of fusion to form elongated complex networks and fission into smaller individual organelles. During this network formation and breakdown, damaged mitochondria can be separated and designated for autophagy.

Mitochondrial functions

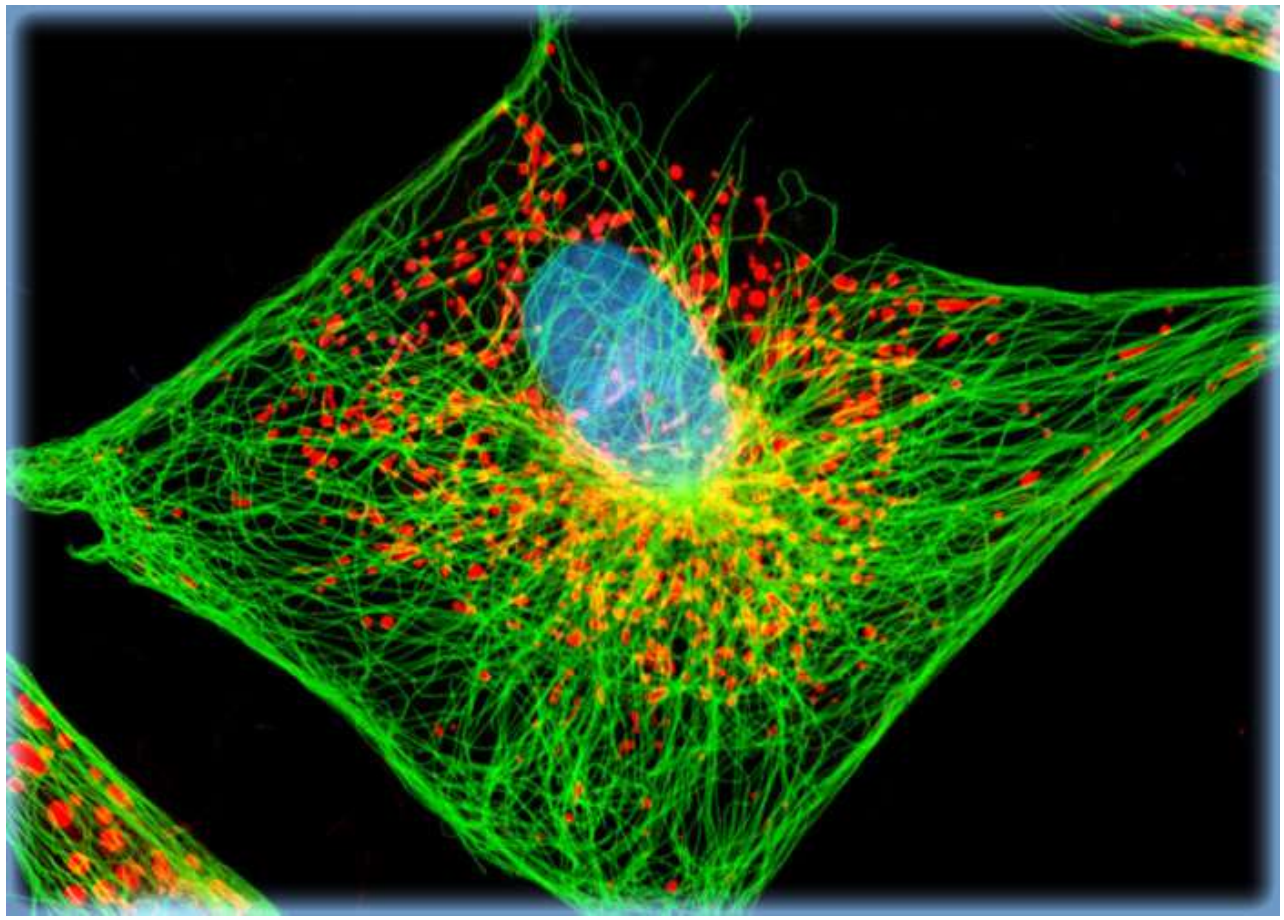
Mitochondrial functions:

- 10^{23} ATP in 2 min
- Calcium buffering
- Apoptosis

Mitochondrial dysfunctions:

- Neurodegenerative diseases
- Alzheimer, Parkinson
- Cardiovascular diseases
- Cancer
- Aging
- Asthma
- COPD
- Fibrosis

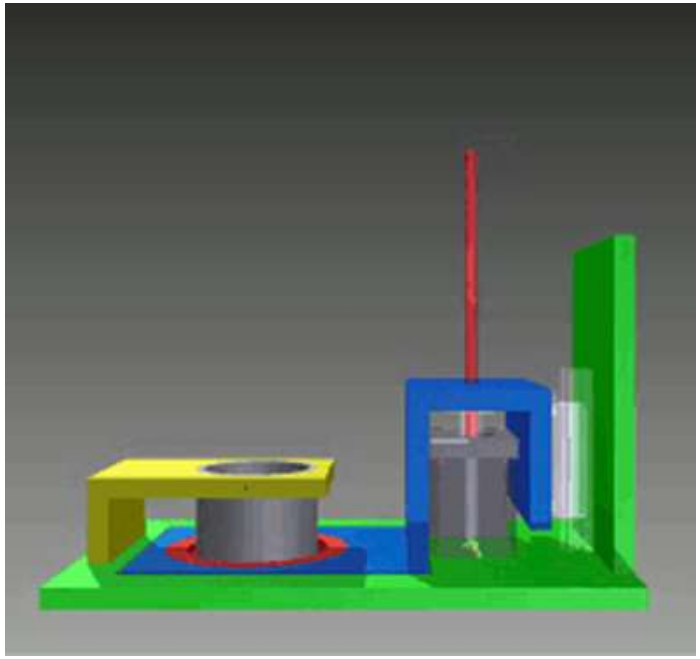
Mitochondria are embedded in the cytoskeleton

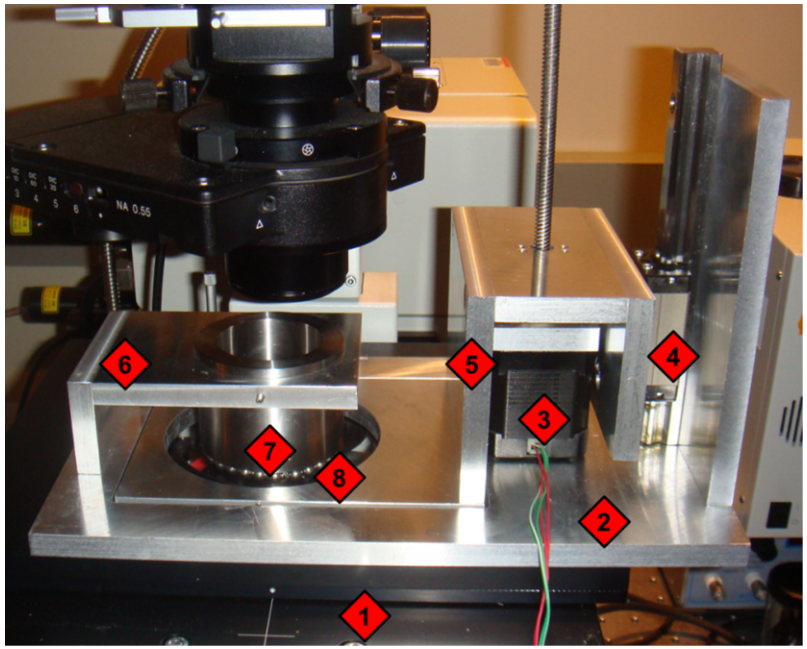


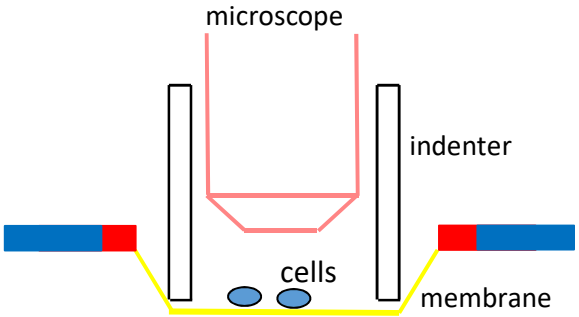
Green: microtubules
Red: mitochondria
Blue: nucleus

Source; www.olympusmicro.com

A Novel Stretching System to Image Cells





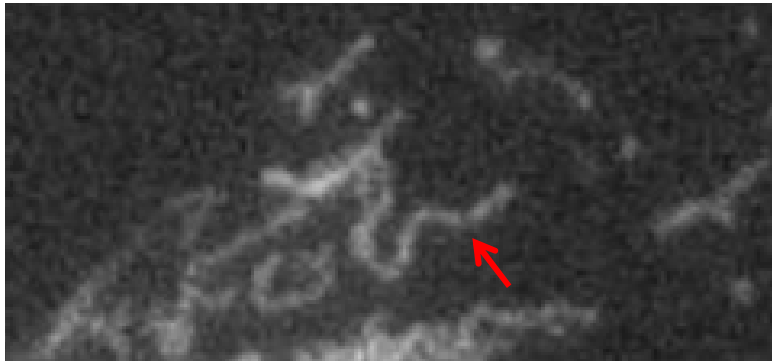


1) Microscope Stage; 2) Stretcher Base; 3) Stepper Motor; 4) Linear Motion Guide; 5) Traveling Stage; 6) Indenter Holder; 7) Indenter; 8) Cell Culture Well

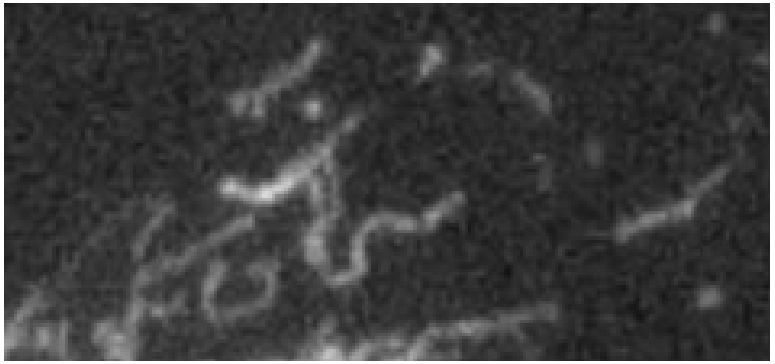
Imsirovic et al. PLoS One (2015)

Single stretch of the mitochondrial network

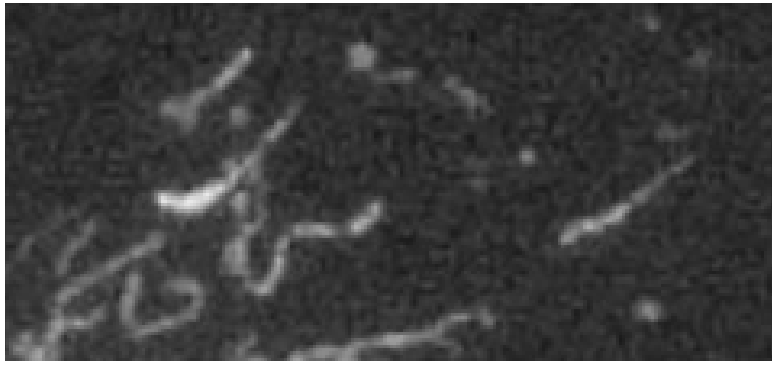
0%



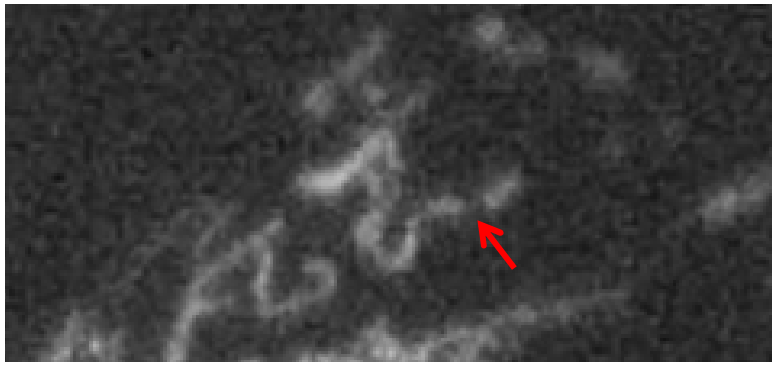
10%



20%

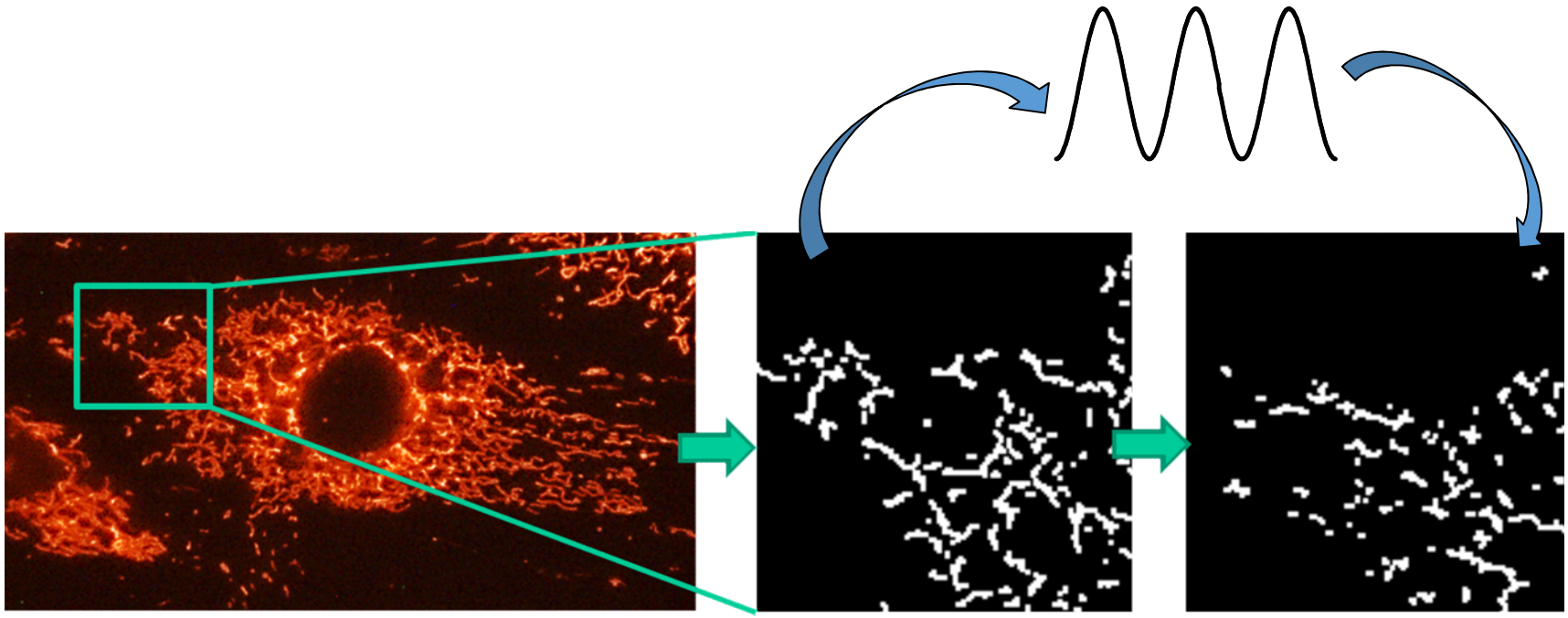


30%



TMRM (tetramethylrhodamine methyl ester) labeling => marker of ATP production

Cyclic stretch of the mitochondrial network

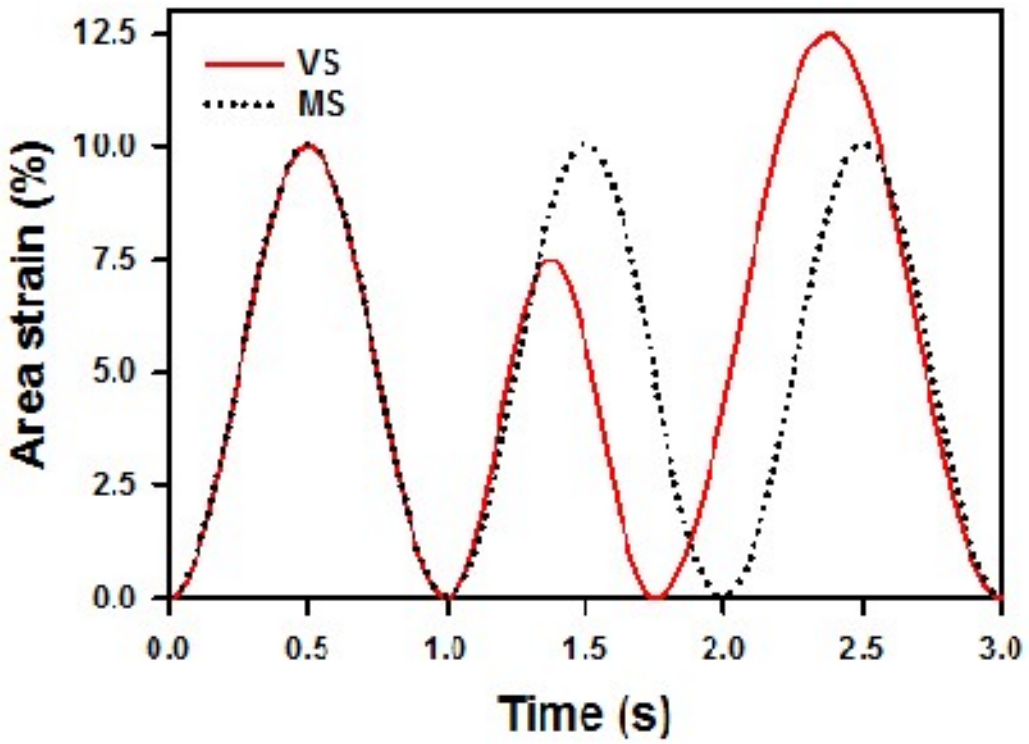


Before

30 min after
sinusoidal stretch

Cyclic stretch remodels the mitochondrial network by inducing fission and fusion!

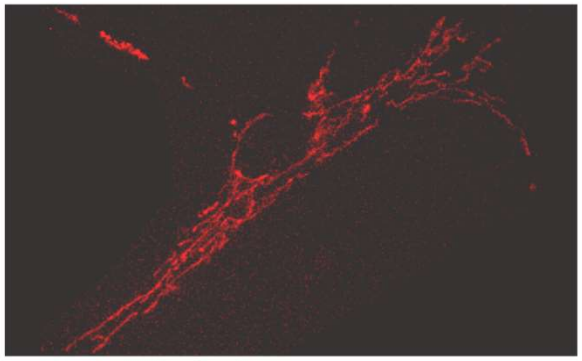
Variable Stretch Pattern



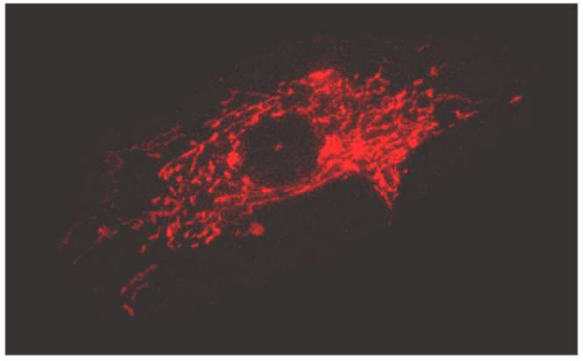
Black: Typical laboratory standard monotonous stretch (MS)

Red: variable stretch (VS) mimicking natural fluctuations in blood pressure in normal subjects

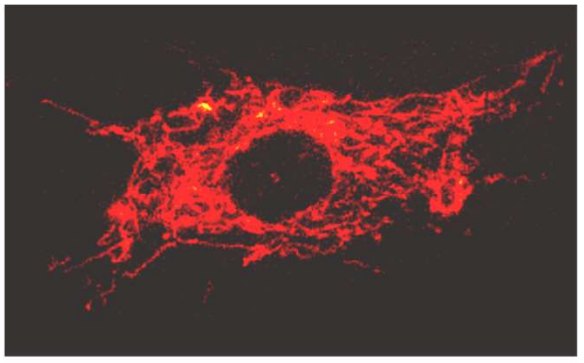
Effects of stretch pattern on mitochondria and ROS



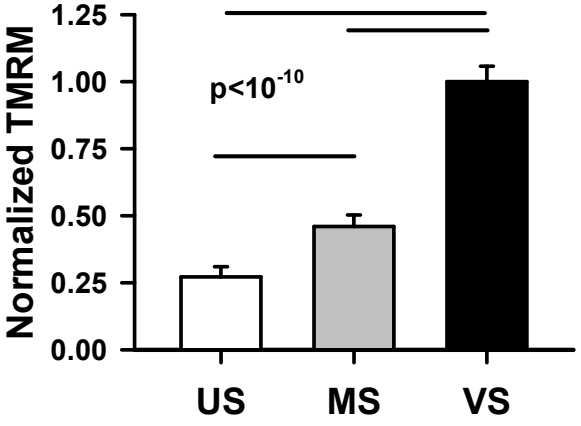
UnStretched (US)

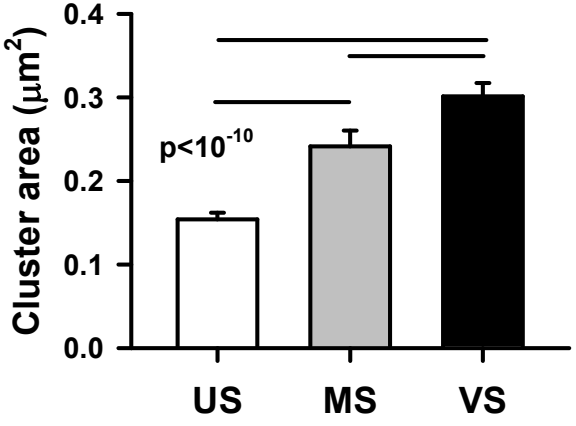


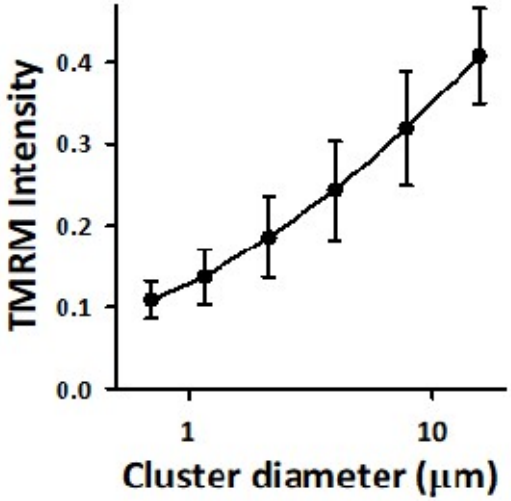
Monotonous Stretch (MS)



Variable Stretch (VS)





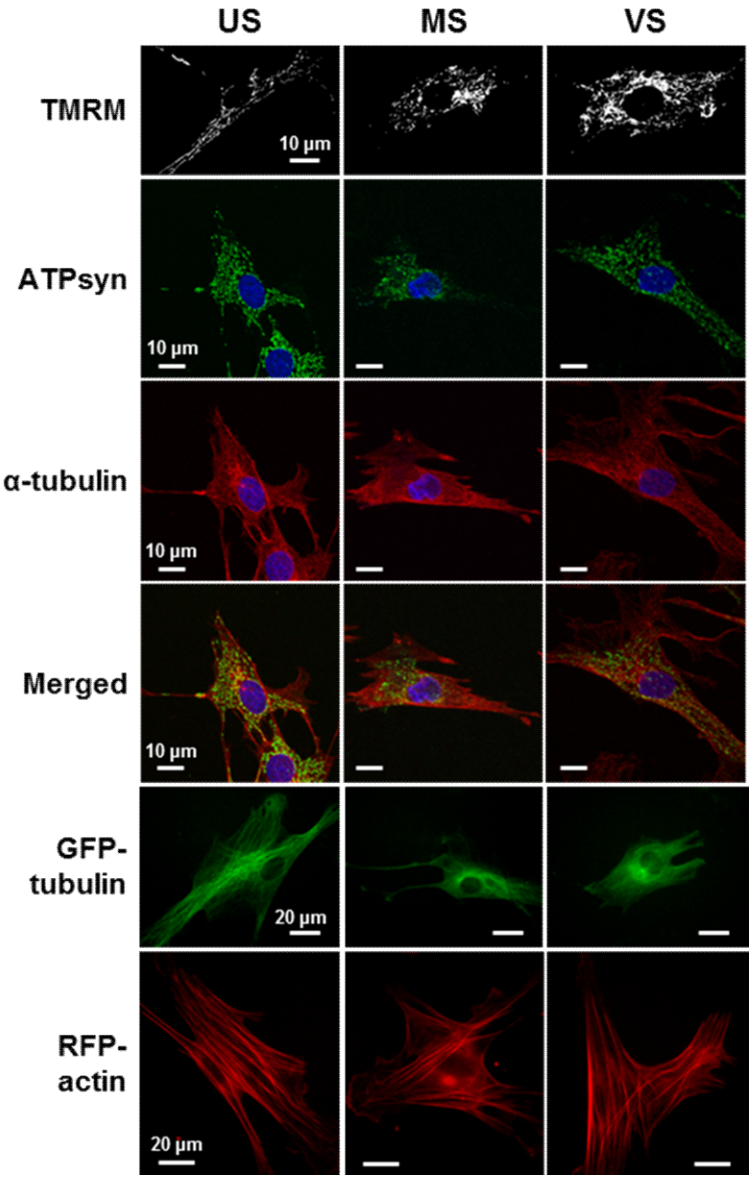


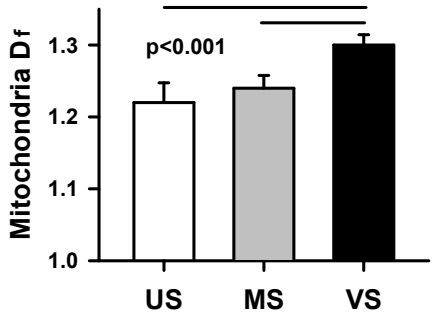
- Mean area strain is 10%
- Frequency: 1 Hz
- Variability: between 7.5 and 12.5%

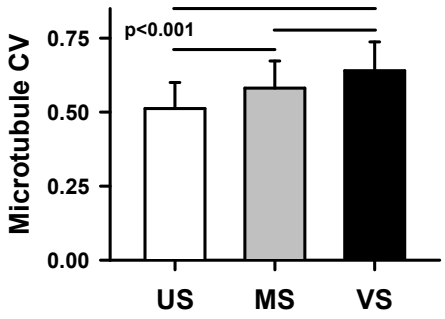
Structure-function relation

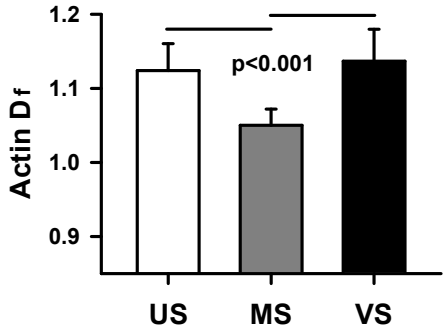
Bartolák-Suki et al. (Nature Materials, 2015)

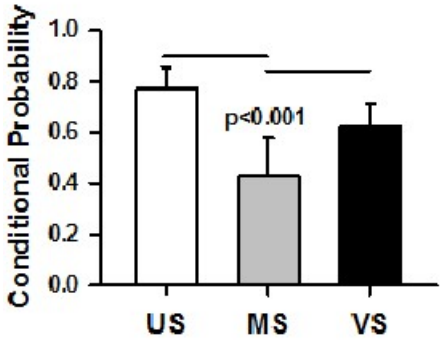
Mitochondrial structure and function









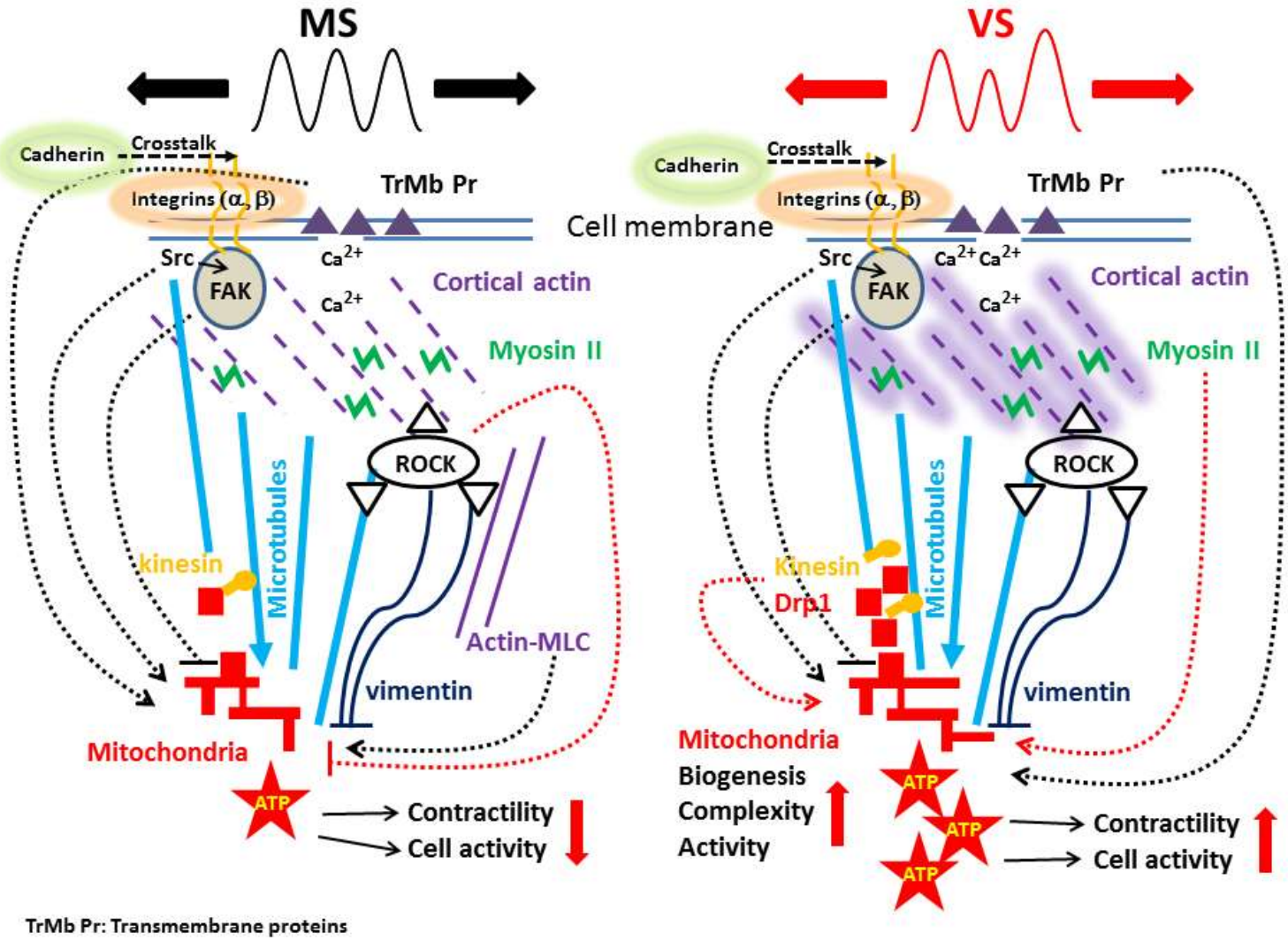


Network-network interactions

US: unstretched
MS: Monotonous stretch
VS: variable stretch
D_f: fractal dimension, structural parameter measuring complexity and space filling
CV: coefficient of variation

Bartolák-Suki et al. (Nature Materials, 2015)

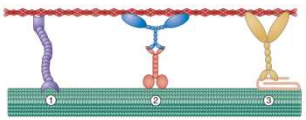
What are the biochemical mechanisms?



Suki et al. (Physiology, 2016)

What are the network-related mechanisms?

VS



Organization of actin

Organization of microtubules

Transport of mitochondria on remodeled microtubules is more efficient

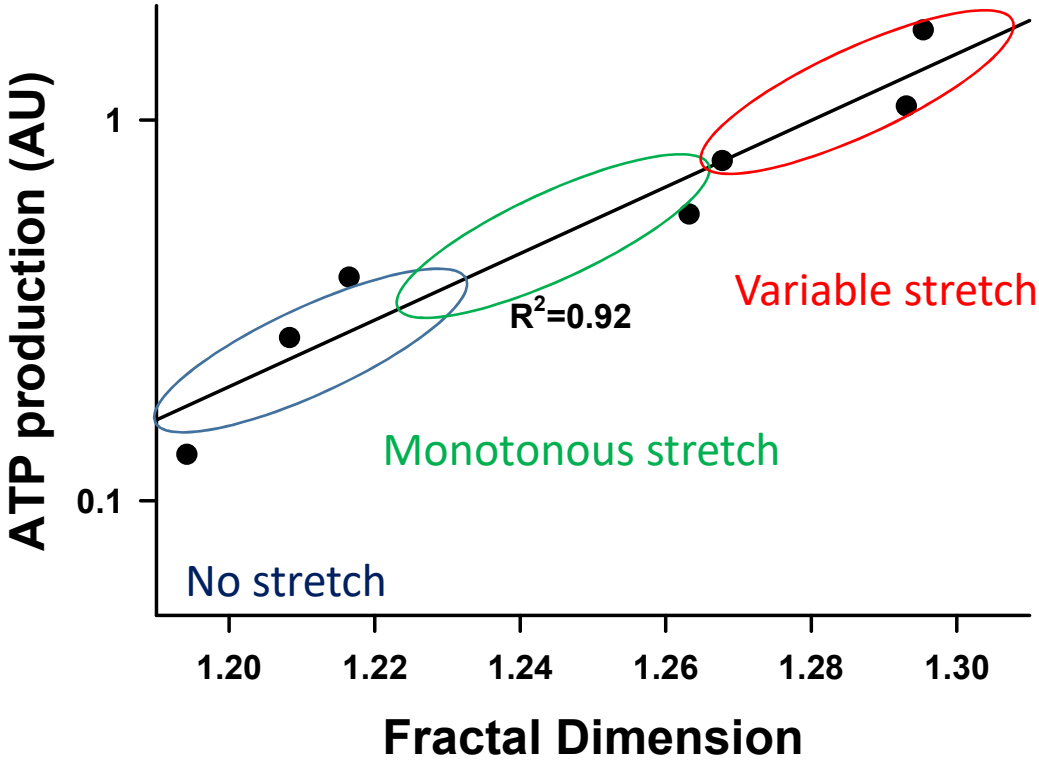
mitochondria form more complex larger clusters (D_f increases)

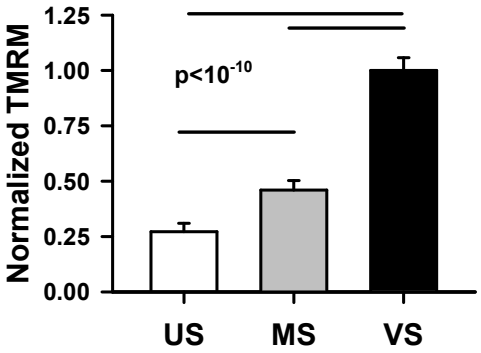
Inner membrane potential increases on larger and more complex network of clusters

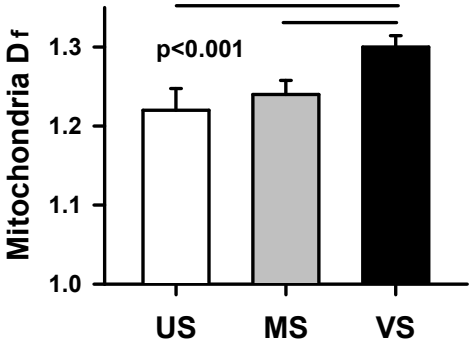
ATP production is upregulated

General cell function is influenced by natural variability!

Bioenergy and complexity

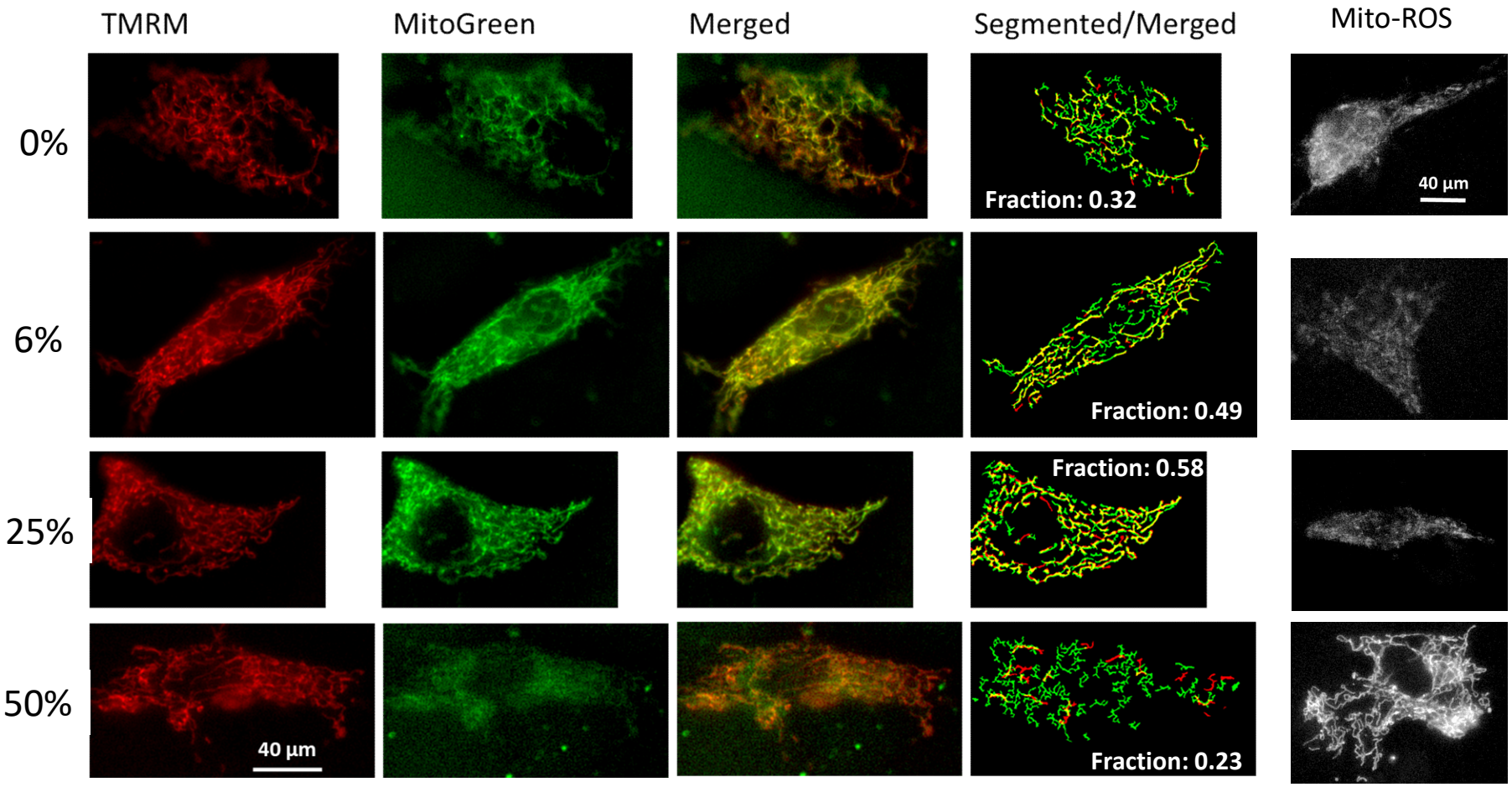






Cells harness energy from fluctuations by charging mitochondria, the battery of life.
Under VS, cells operate far from equilibrium supported by a complex fractal network.

Tuning mitochondrial function



Stretch types:

0%: no variation, same as MS;

6%: ±6% around mean as in anesthesia;

25%: same as VS, normal healthy variability;

50%: ±6% around mean mimics hypertension/aging

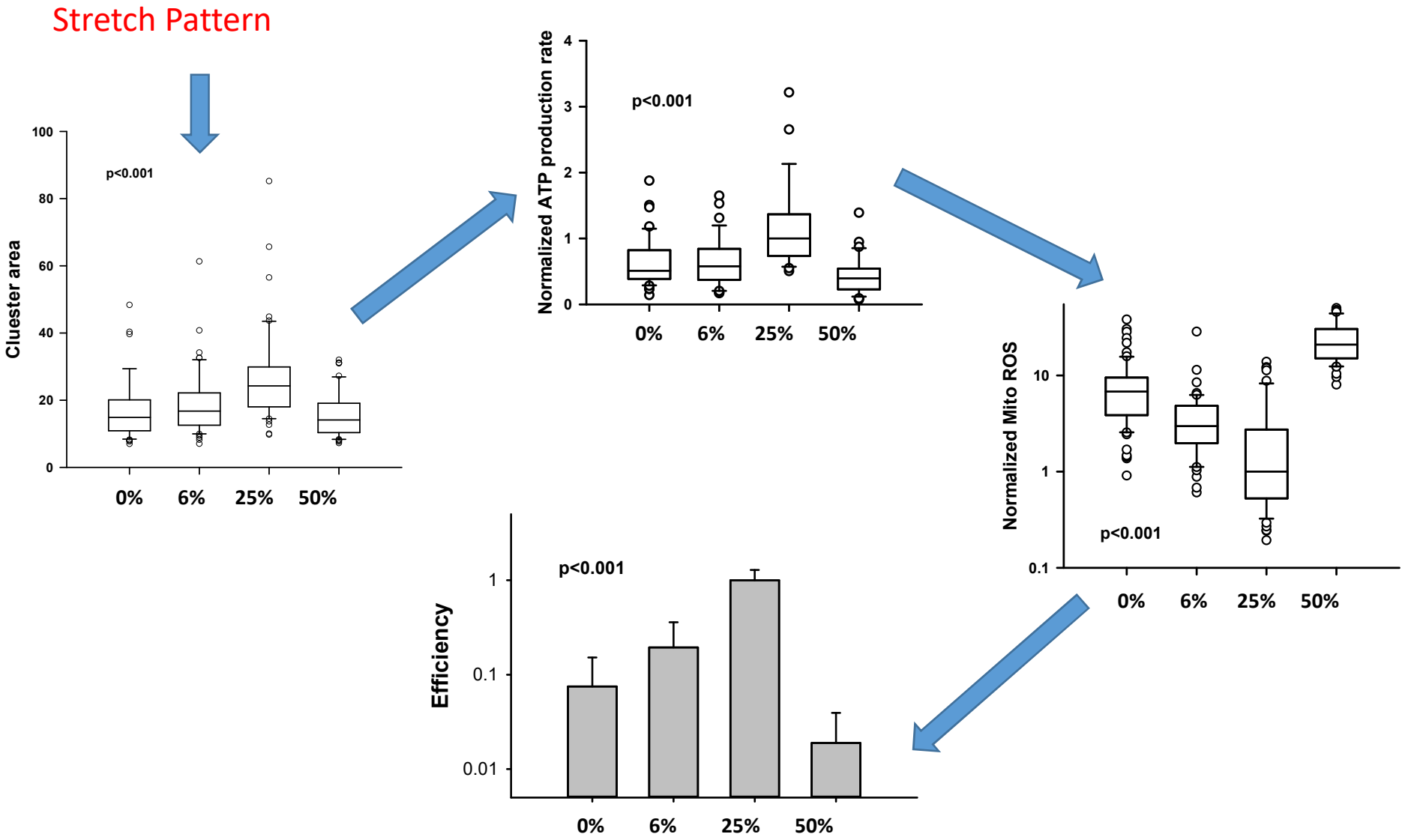
Dyes:

TMRM: ATP production rate on active sites

MitoGreen: all mitochondria

Mito-ROS: ROS level within mitochondria

Mitochondrial efficiency as a function of variability



Summary

- Complexity of mitochondrial network is regulated by normal blood pressure variability.
- Complexity of the mitochondrial network is at the heart of bioenergetics via ATP production.
- Optimal mitochondrial network is achieved by balanced fission and fusion, which maximizes ATP production and minimizes harmful ROS production.
- Mechanical fluctuations will influence many cell function via ATP.
- Laboratory standard monotonous stretch destroys all this!