Predictive Modelling of Mitochondrial Spatial Structure and Health

Arne T. Bittig[1], Florian Reinhardt[2], Simone Baltrusch[2], and Adelinde M. Uhrmacher[1]

[1] Institute of Computer Science, University of Rostock
Albert-Einstein-Straße 22, 18059 Rostock, Germany
[2] Department of Medical Biochemistry and Molecular Biology, University of Rostock
Schillingallee 70, 18057 Rostock, Germany

Background

Mitochondria are mobile organelles that exist in living cells as a tubular network. They continuously join the mitochondrial network by fusion and divide by fission events. Mitochondrial fission is mainly regulated by two nuclear-encoded proteins, fission protein 1 (Fis1) and dynamin related protein 1 (Drp1). Mitochondrial dynamics have been shown to be an essential quality control mechanism in order to maintain mitochondrial health. A proxy for mitochondrial health and integrity is the mitochondrial membrane potential [5]. Recent wet-lab studies have shown that the mitochondrial membrane potential is disturbed by an imbalance of the mitochondrial fission proteins. It is therefore the objective of this study to develop an in silico prediction model for the influence of Fis1 and Drp1 on mitochondrial spatial structure and health.

Our Approach

We here take an existing model of mitochondrial health maintenance [3], where mitochondria move in a random direction for random intervals of time (i.e. along not explicitly included microtubules) in an otherwise (for purposes of the model) empty 2D cell. Abstract health units mimic the functional state of mitochondria by representing the membrane potential. Mitochondrial fusion allows mitochondria to exchange components (here: health units) in order to maintain health.

Our model is implemented in ML-Space [1], which combines an attributed rule-based language for describing cell biological processes and a simulator for these in continuous or discretised (i.e. grid-based) space or a hybrid thereof. We modified the existing model by incorporating attributes representing the number of bound Fis1 and Drp1 molecules of mitochondria. In our simulations, only fused mitochondria facilitate Fis1 and Drp1 recruitment. Certain thresholds, namely 8 Fis1 and 2 Drp1 molecules, must be reached to trigger subsequent fission events.

Results and Outlook

Related wet-lab experiments have shown that cells with reduced Fis1 or Drp1 expressions exhibited a significantly lower membrane potential and a heterogenic mitochondrial network [4].

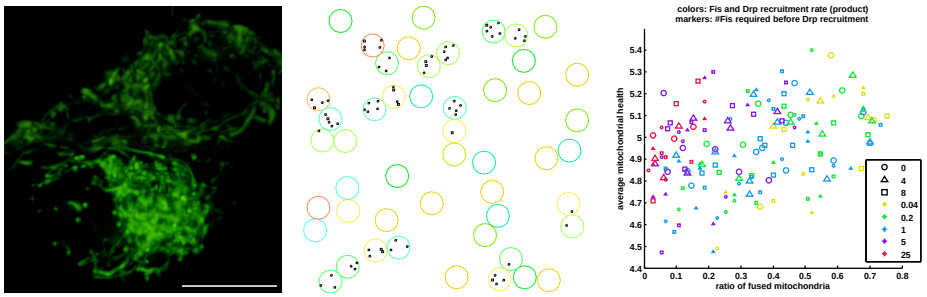

Fig. 1. Left: Microscopic image of the mitochondrial network in a glucose-responsive MIN6 beta cell. Scale bar 20 µm. Middle: Simulation screenshot (cyan/green: healthy mitochondria, red: damaged; tiny circles/squares: recruited Fis1/Drp1 molecules of fused mitochondria) Right: Results of parameter scan experiments.

In our simulations, the parameters representing Fis1 and Drp1 are negatively correlated with the ratio of fused against free mitochondria (the closest analogy to network structure in the simulation results). The Fis1 recruitment parameter is positively correlated with mitochondrial health. Triggering mitochondrial fission, and thus turnover of mitochondrial components within the network, improves overall membrane potential. This is in agreement with wet-lab data. However, the effect on health is still quite small. Interestingly, the Drp1 recruitment parameter did not significantly affect mitochondrial health.

Recent studies indicate that adaptor proteins, namely Mff, MID49 and MID51 are important for Drp1 regulated mitochondrial fission. Thus, future research in this direction will include not only expanding the model by explicit fission protein entities whose spatial distribution may not be homogeneous, but also incorporating new wet-lab findings regarding mitochondrial fission. Once this model has been validated, ROS-related mechanisms for oxidative stress response [2] and adaptive processes to mitochondrial damage shall be simulated.

References

1. A. T. Bittig, F. Haack, C. Maus, and A. M. Uhrmacher. Adapting rule-based model descriptions for simulating in continuous and hybrid space. In *Proc 9th CMSB*, CMSB '11, pages 161–170, New York, NY, USA, Sept. 2011. ACM.
2. J. Park, J. Lee, and C. Choi. Mitochondrial network determines intracellular ROS dynamics and sensitivity to oxidative stress through switching Inter-Mitochondrial messengers. *PLoS ONE*, 6(8):e23211+, Aug. 2011.
3. P. K. Patel, O. Shirihai, and K. C. Huang. Optimal dynamics for quality control in spatially distributed mitochondrial networks. *PLoS Comput Biol*, 9(7):e1003108+, July 2013.
4. F. Reinhardt, J. Schultz, R. Waterstradt, and S. Baltrusch. The mitochondrial fission proteins Fis1 and Drp1 are important for glucose-induced insulin secretion in glucose-responsive INS1 832/13 cells. *Exp Clin Endocrinol Diabetes*, 121(10):P17+, Nov. 2013.
5. H. Schmitt, S. Lenzen, and S. Baltrusch. Glucokinase mediates coupling of glycolysis to mitochondrial metabolism but not to beta cell damage at high glucose exposure levels. *Diabetologia*, 54(7):1744–1755, July 2011.