



Neuronal Mitochondrion Trafficking

BCH441 Project: Defining a System

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*The source code, notebook, and data pipeline can be found at github.com/thejmazz/biologicalsystem.
Cover image (mitochondrion in Purkinje neuron) by Atlas of Ultrastructural Neurocytology¹*

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1 Introduction

The “powerhouse of the cell” as it is so commonly called, the mitochondria is one of the most vital organelles in eukaryotes. This structure is thought to have developed through a symbiotic relationship among engulfed prokaryotic cells and their hosts. As such, it is rooted quite deeply evolutionarily, and one might expect its proper functioning to be absolutely vital, that is, knock-out mutants will not survive. This is true - but as we will see, it is not just the performance of this organelle which is centrally important, but where it is localized within the cell as well.

¹synapses.clm.utexas.edu/atlas/1_1_2_8.stm

Images of isolated mitochondria were first observed in 1979 by Johnson et al.:

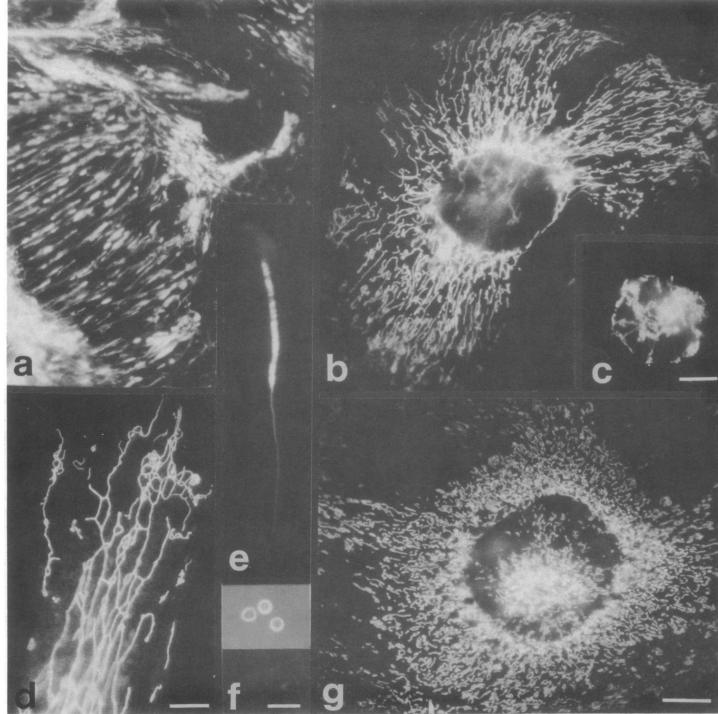


FIG. 5. Living cells stained with rhodamine 123: (a) rat cardiac muscle; (b) Pt KI marsupial kidney; (c) mouse B lymphocyte; (d) mouse 3T6; (e) mouse sperm; (f) human erythrocytes (phase-contrast above and rhodamine 123-treated but unstained below); (g) rat embryo fibroblast. Bar represents: 15 μm in a, b, e, and g; 10 μm in c; 8 μm in d; 10 μm in f.

The variety of mitochondrion shape and size is clear, ranging from globular to filamentous to networked structures. As well, the authors observed movement during 15-30 sec intervals, between fluorescent and phase-contrast photographs.

The primary role of a mitochondrion is to supply energy to the cell in the form of ATP units, through the electron transport chain among the cristae. Where is that energy needed? Consider highly polar and elongated cells such as neurons. The cell body of a neuron is distant from its synaptic endings, where as it happens, large amounts of energy are required for neurotransmitter release and absorption. Following, we will investigate the **system** whose **functional role** is the **localization of mitochondrion within neurons**.

2 The System

<i>Name</i>	Localization/Trafficking of mitochondrion within neurons
<i>Description</i>	The collective of functional units represented by genes which process signals, transduce these events, initiate, and maintain the actions necessary to transport mitochondrion to distal points along the axon of a neuron.
<i>Associated GO Terms</i>	GO:0051646 (mitochondrion localization)

- GO:0051659 (maintenance of mitochondrion localization)
 - GO:1990456 (mitochondrion-ER tethering)
- GO:0034643 (establishment of mitochondrial localization, microtubule mediated)
 - GO:0034642 (mitochondrial migration along actin filament)
 - GO:0034643 (establishment of mitochondrial localization, microtubule mediated)
 - * GO:0034640 (establishment of mitochondrion localization by microtubule attachment)

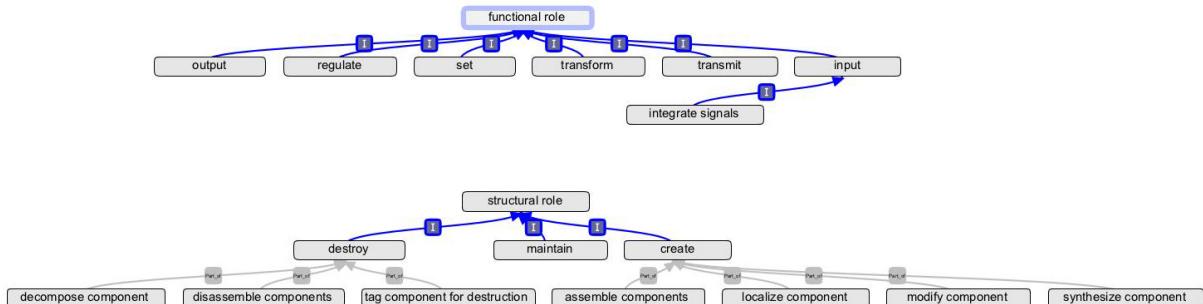
- * GO:0047497 (mitochondrion transport along microtubule)
- GO:0090146 (establishment of mitochondrial localization involved in mitochondrial fission)
- * GO:0090147 (regulation of establishment of mitochondrion localization involved in mitochondrial fission)
- GO:0048311 (mitochondrion distribution)
 - GO:0048312 (intracellular distribution of mitochondria)
 - GO:0000001 (mitochondrion inheritance)

Why this system? Originally I was looking into “mitochondrial localization.” Amongst the genes returned by the ontology, there appeared those related to mitochondrial localization during cellular reproduction, transport, microtubules, tethers, mRNA-binding, and various “popular” genes such as ubiquitins, serum albumin, leucine-rich repeat serine/threonine-protein kinase, basic helix-loop-helix protein. There was a fair amount of variety. In order to gather together a structured list of genes I would need to filter these out, and to filter these out I would need a functional goal. I decided to choose the neuronal process because it is one of the most extreme cases of mitochondrial movement in all cell types, there was a decent amount of related literature available, some elements of its processes had been recently elucidated, and it has important neurophysiological consequences. A review by Reis et al. (2009) explored the atypical Miro GTPases and their role in transporting mitochondria in neurons. The authors note that abnormal mitochondrial dynamics can contribute to Amyotrophic Lateral Sclerosis (ALS), Huntington’s, Parkinson’s, and Alzheimer’s diseases. A more recent experiment by Loss and Stephenson (2015) examines the role of TRAK1 and TRAK2 kinesin adaptor proteins which link mitochondria to kinesin motor proteins. Furthermore, Miro proteins are expressed in a large variety of cell types, potentially extending this current analysis to new domains (Reis et al., 2009).

2.1 Systems Role Ontology

To define this system in a structured manner, I considered its functionality in the context of the Systems Roles Ontology, which can be found at github.com/hyginn/SyRO:

SyRO – Systems Role Ontology (2015-10-27)



Name	ID	Context Within Neuronal Mitochondrion Localization
input	16	compounds or signals prompting the directed movement of mitochondrion
integrate signals	22	machinery which directs input signals/compounds to the system
output	21	mitochondrion transport towards synaptic endings
regulate	20	components which ensure regular mitochondrial motility
set	19	preparing the functional units, “setting the stage” as it were
transform	18	altering the system status so that it may be reversed, stopped, reinstated
transmit	17	the physical machinery to move mitochondria

These functions collaborate to produce the **functional role** of localizing mitochondria **for the proper functioning of neural communication**. I will define the bounds of this system as any genes which can be annotated with the functional role annotations above. Structural role annotations will be considered second

to function, and will be used largely to describe how that component physically determines its function. With this goal in mind, I fetched and filtered data from the Gene Ontology Consortium, QuickGO, UNIPROT, IntAct, and STRING. Those genes which did not make the cut can be seen through the *Summary of first pool* in my notebook.

3 Gene Collection

References

- Lincoln V. Johnson, Marcia L. Walsh, and Lan Bo Chen. Localization of mitochondria in living cells with rhodamine 123. *Proc. Natl. Acad. Sci. USA*, 77:990–994, 1979.
- Omar Loss and F. Anne Stephenson. Localization of the kinesin adaptor proteins trafficking kinesin proteins 1 and 2 in primary cultures of hippocampal pyramidal and cortical neurons. *Journal of Neuroscience Research*, 93:1056–1066, 2015.
- Katarina Reis, Asa Fransson, and Pontus Aspenstrom. The Miro GTPases: At the heart of the mitochondrial transport machinery. *Federation of European Biochemical Societies Letters*, 583:1391–1398, 2009.