From data to model: mitochondrial transport in living cells

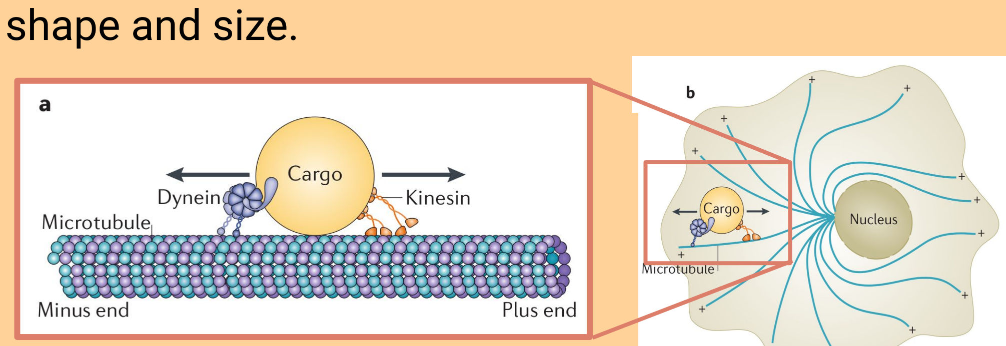
Agustina Fernández Casafuz[1]*, M. Cecilia De Rossi[2], Luciana Bruno[1]

[1] Instituto de Cálculo, UBA - CONICET, [2] Departamento de Química Biológica, UBA - Argentina

*afcasafuz@gmail.com

Abstract

Mitochondria are fundamental organelles for the correct function of eukaryotic cells. Several studies show that mitochondria are transported preferentially to areas with high metabolic demand. In order to achieve their precise location, mitochondria undergo bidirectional transport along cytoskeleton filaments driven by molecular motors, *i.e.* kinesins and dyneins, which are also relevant in regulation of mitochondria shape and size.



From Hancock, Nat. Rev. Mol. Cell Biol. 15, 615 (2014)

It is well documented that mitochondrial dysfunction and changes in mitochondrial dynamics and mobility are involved in the pathology of some major neurodegenerative and neurological disorders, thus the need of understanding the underlying mechanisms in mitochondrial transport.

In recent studies [1] in *X. laevis* melanophore cells we have observed that mitochondria change their shape to rod-like when being transported along microtubules and that they change their length in correlation with the direction of motion: Mitochondria tend to retract during anterograde transport performed by dynein motors, whilst they maintain their length in retrograde transport mediated by kinesin motors. We also observed that slow mitochondria preferably stretch when moving.

In order to explain these effects we proposed a novel one-dimensional model for intracellular transport of smooth flexible organelles based on a Langevin equation of motion in the overdamped limit. We ran numerical simulations to study the behavior of the cargo for different motor teams in competitive and noncompetitive scenarios, focusing on the transport properties observable in the experiments, e.g. cargo speed and length. Our results [2] suggested that active motors adopt opposite configurations depending on the resisting load: For low loads motors push the cargo and the organelle contracts, while when the resisting load is large (e.g., in very competitive tug-of-war), motors pull the cargo and the organelle stretches. With these results we interpret the complex behavior of mitochondria transport observed in *X. laevis* cells.

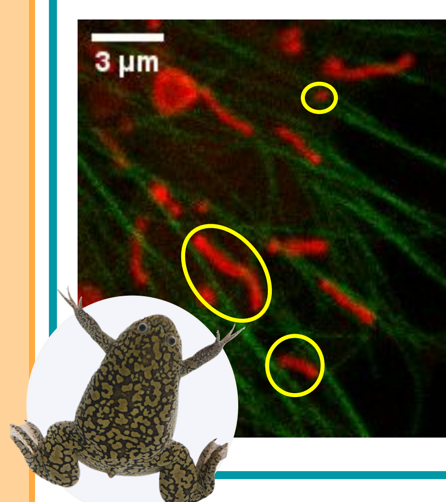
References:

[1] M. C. De Rossi, V. Levi, and L. Bruno, Biosci. Rep. 38,BSR20180208 (2018)

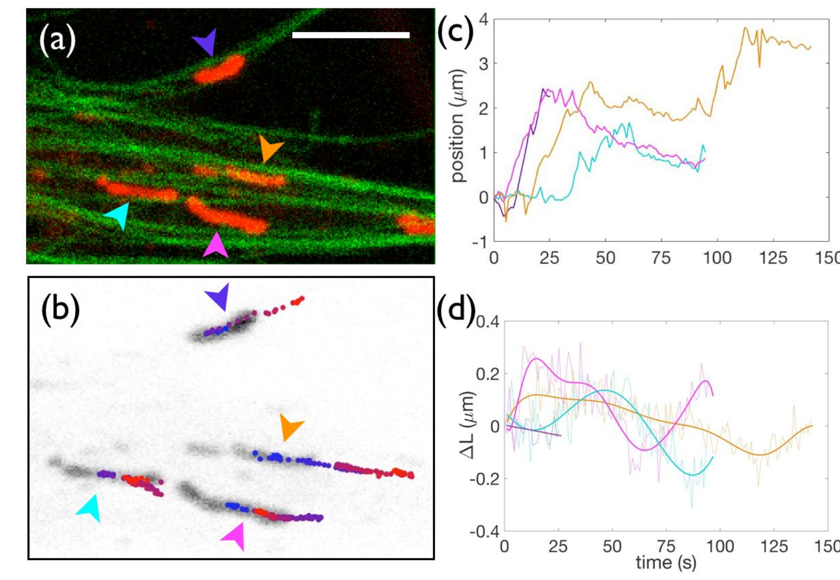
[2] Fernández Casafuz, A., De Rossi, M. C., & Bruno, L. (2020). PRE, 101(6), 062416.

Experimental data

We study the bidirectional transport of mitochondria along microtubules (MT) mediated by teams of molecular motors in living melanophore cells of *Xenopus laevis*. We analyze confocal microscopy images of Mitochondria labelled with Deep-Red Mitotracker (in red below) and MT expressing XTP-GFP (green below).

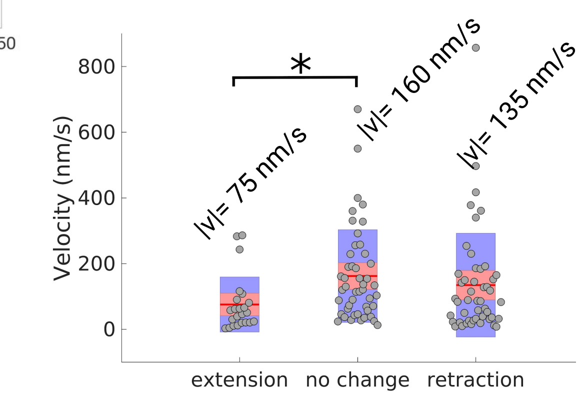


One of the many interesting things about mitochondria is that they have different shapes and sizes, as one can see on the figure to the left

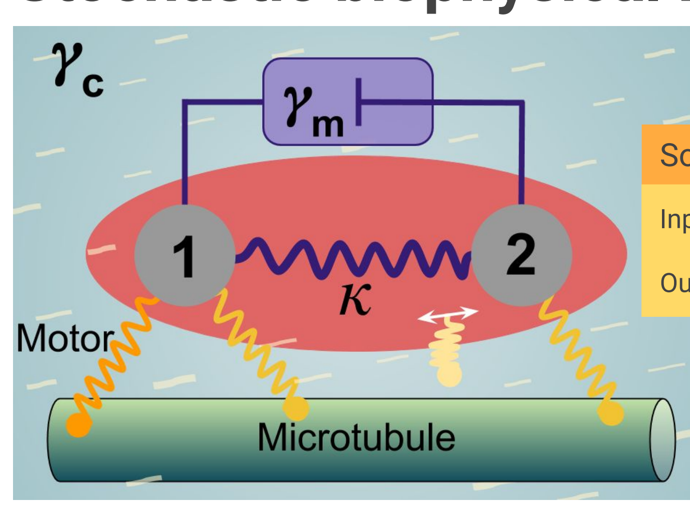


We perform single-particle tracking experiments of rod-like mitochondria (panel a) in which we track each mitochondrion's center mass to recover its trajectory (b and c) and at the same time we can obtain its length variation for each frame (d). Spoiler alert: it changes over time!

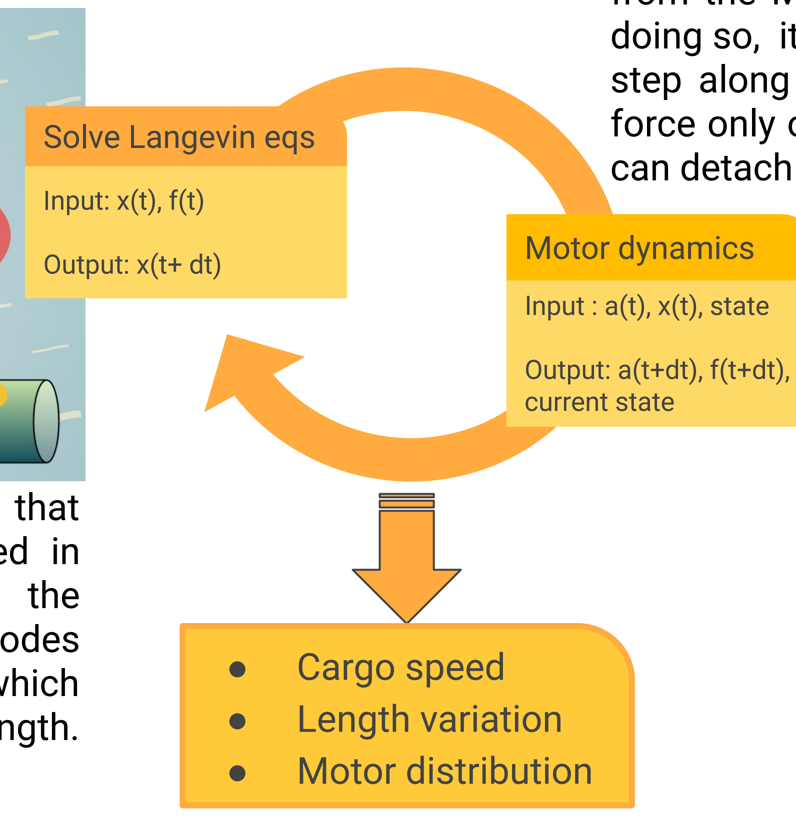
We found that mitochondria can change up to 30% of their length during transport, either elongating or retracting. What is more, there is a correlation between the speed of the organelle and the change in their length. According to a Kruskal Wallis test, the mitochondria that extend move at slower speeds (fig below)



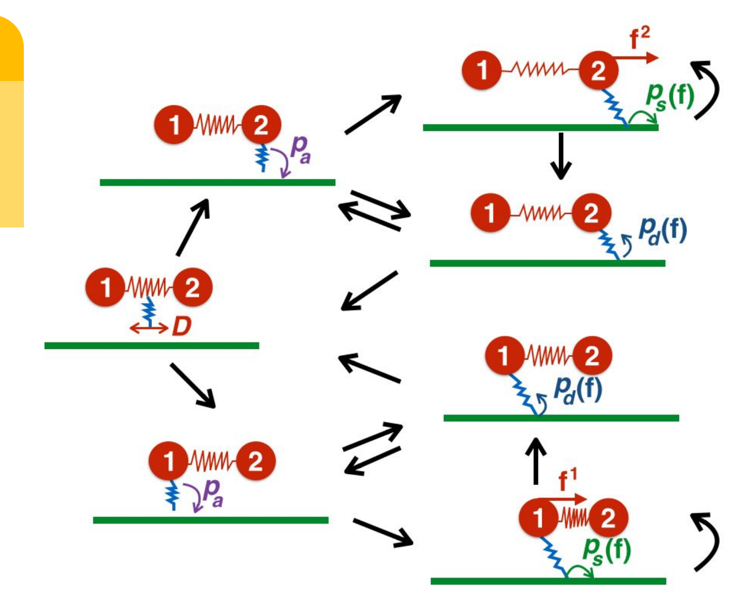
Stochastic biophysical model



We propose the simplest model that could mimic the behavior observed in the experiments. We consider the organelle as composed of two nodes coupled by an overdamped spring, which gives it the flexibility to change length. Motors link the cargo to the MT.

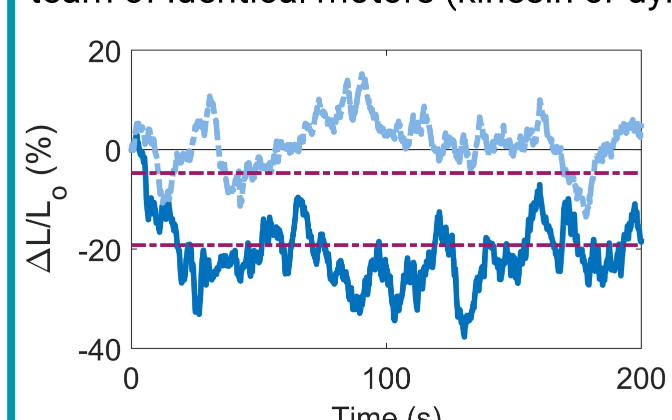


Each motor diffuses along the cargo membrane unbound from the MT until it attaches to it with probability p_a. In doing so, it links one of the nodes to it, so that if it takes a step along the MT (with probability p_s) it exerts a local force only on that node (f^i). After a few steps (or none) it can detach from the MT and go back to diffusing.

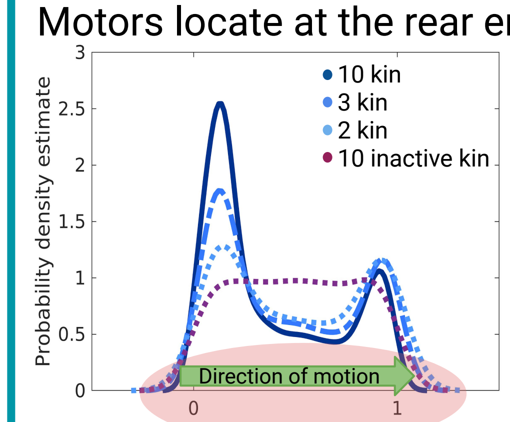


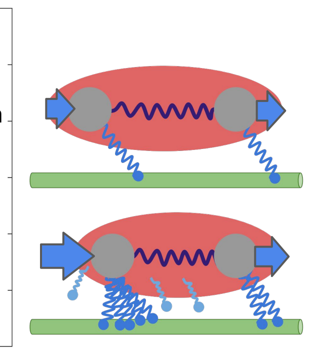
Single polarity team → Retractions

In the simulations in which the cargo is transported by a team of identical motors (kinesin or dynein), the cargo length fluctuates relative to the natural length, presenting periods of stretching and retractions, with a tendency to contract during transport for large number of motors in the team.



Motors locate at the rear end of the cargo!

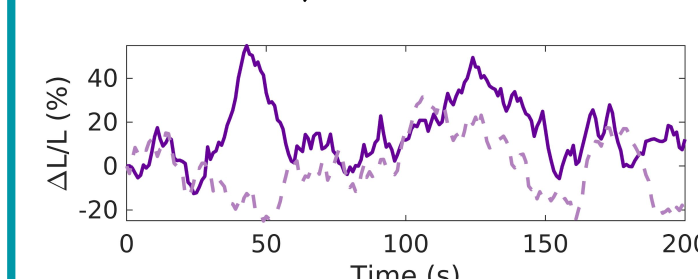


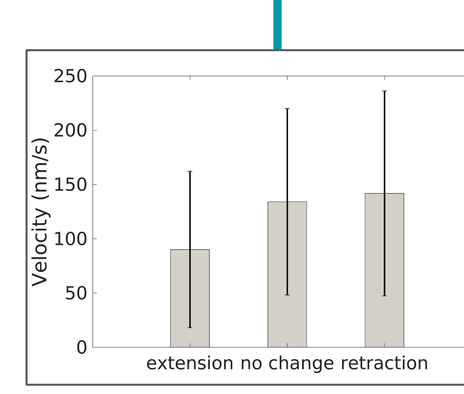


Opposite polarity teams → Extensions

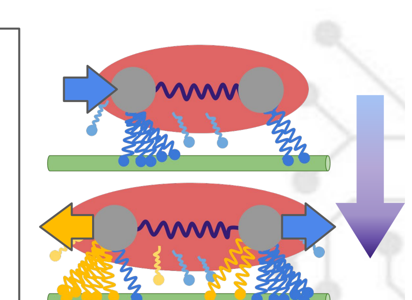
In a tug-of-war scenario, we have competing teams of kinesins and dyneins. As before, the cargo presents periods of stretching and retracting, but now we see a predominance of stretching.

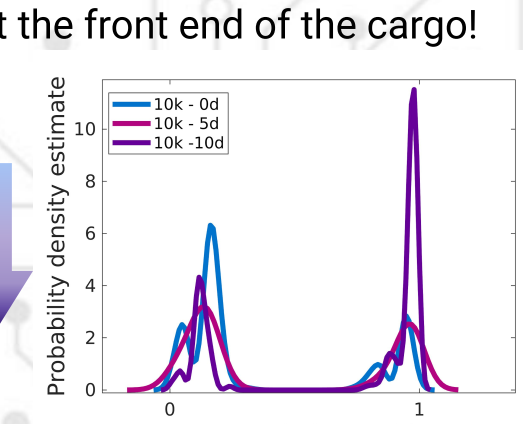
We observe that, as the number of motors in the opposite team grows, the distribution of motors inverts and so we have a transition from pushing to pulling the organelle.





Motors locate at the front end of the cargo!





We infer that cargoes that undergo retractions are probably carried by one kind of motors, and cargoes that extend are probably in a tug of war scenario