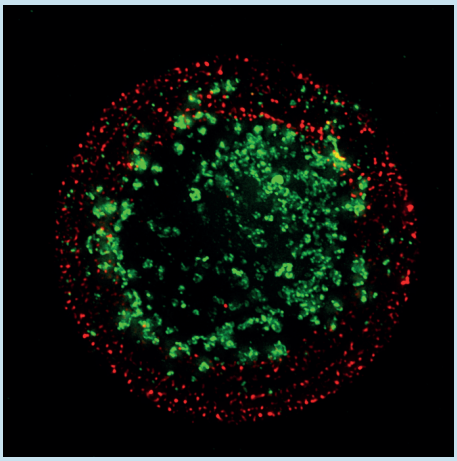
M2 project: Analysis and modelling of lysosomal distribution and dynamics

Lysosomes are essential organelles of the eukaryotic cell responsible of lytic activity. Usually, an eukaryotic cell has several hundreds of lysosomes with a non-random spatial distribution (Ba et al., 2018). Lysosomes are mainly clustered in a fairly immobile perinuclear cloud whereas a minority of mobile lysosomes are moving at the cell periphery (Cabukusta and Neefjes, 2018). It is now clear that this positioning is tightly regulated, especially by motor proteins the establishment of membrane contact sites with the endoplasmic reticulum (Pu et al., 2016; Bonifacino and Neefjes, 2017; Cabukusta and Neefjes, 2018). This distribution may vary in response to various stimuli such as the cholesterol concentration (Rocha et al., 2009), pH (Walton et al., 2018) and extracellular matrix elasticity (Wang et al., 2018).

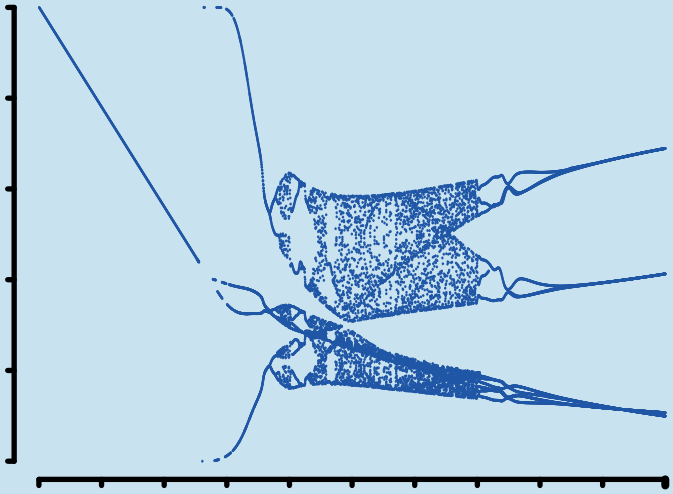
However at resting state, lysosomal distribution is a non-equilibrium steady state (NESS), whichmeans that the global distribution does not changed while lysosomes continue to move individually. As a first approximation, it suggests that centrifuge flux is equal to the centripetal flux. In addition, the lysosomal distribution problem is complicated by two other factors: their biogenesis and their secretion. Moreover, after a perturbation, it seems that there is a spontaneous recovery of the steady state distribution (Guardia et al., 2019).



How do lysosomes spontaneously go back to their steady-state distribution after a perturbation?

First, the project will focus on the characterization of lysosomal dynamics in order to evaluate the centrifuge and centripetal flux, as well as exocytosis rate (preliminary characterizations have already been done in our team) and biogenesis rate. We will assess these issues using a confocal spinning disk microscope available at the Institut Curie imaging platform that is specialized for live-imaging. Cells will be seeded on micropatterns in order to normalize their shape (Schauer et al., 2010), to make them comparable and to ease the subsequent mathematical modelling. Moreover, lysosomal positioning will be perturbed by an optogenetic system coupling lysosomes to molecular motors using light (Duan et al., 2015). This system will allow us to observe how the cell comes back to its steady state. Second, we will model lysosomal distribution. Especially, this question will be addressed thanks to dynamic systems theory in order to write mathematical model and simulate it. We aim at determining whether a stable/attractive fixed point exists for the modelled system and at comparing the dynamics after a perturbation between the model and the observed data.

The student will benefit from a state-of-the-art laboratory with innovative techniques (optogenetic, micropatterning, etc.) and a top-notch infrastructure (microscopy, etc.). In addition, the Curie institute environment, and more specifically our multidisciplinary team, is an ideal setting for a student wishing to learn about cell biology problems with an innovative perspective. The candidate may be trained in code (R), cell culture and microscopy. Nevertheless, preliminary knowledge in these areas is desirable. The essential qualities for this project remain a strong curiosity and a great enthusiasm.



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