Master 2 internship – Spatio-temporal dynamics of signaling networks

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Background and objectives

Intracellular signaling networks are complex systems, orchestrated by extracellular signals such as hormones. Understanding cell signaling events and their spatio-temporal dynamics is a key stage for the development of innovative pharmacological, hence therapeutic, approaches. This is particularly the case for signaling networks induced by G protein coupled receptors (GPCRs), which are preferred targets for pharmacological agents.
The dynamic properties of the biochemical reactions operating within signaling networks are difficult to capture. They are both kinetically regulated and constrained by intracellular space. GPCRs transduce signaling mechanisms not only from the plasma membrane, as it has been known for a long time, but also from intracellular vesicles in which they are transported. Signaling from inside vesicles has been revealed very recently and completely renews the strategy to explore GPCR pathways. The vesicles are themselves subject to dynamic processes, which determines their numbers, sizes and functions.
The discovery of a dynamic regulation of signaling pathways by active receptors within the cell itself is of paramount importance because it allows to consider graduated physiological regulations [3]. Ultimately, it encourages a reconsideration of traditional pharmacological approaches that target only receptors located on the plasma membrane.
Modeling / analysis approaches have an obvious interest as a complement to experimental approaches, to dissect the different pathways and mechanisms involved from a limited number of measurements, and to test different functional hypotheses (kinetic constants, nature of molecular transfers and transport, relative abundances ...) [6, 4, 7].
The objective of the internship is to characterize the spatial and temporal dynamics of GPCRs and their signaling pathways, from experimental data on signaling events, which can be collected simultaneously at the level of the plasma membrane and intracellular vesicles (endosomes).

Work program

The internship will be dedicated to the formulation, mathematical study and numerical simulation of spatio-temporal models of the intracellular traffic of GPCRs and induced signaling pathways.
The work will consist in developing a dynamic model of the population of endosomes together with their molecular content, coupled with a model of biochemical reaction networks representing the signaling cascades induced by GPCRs.
During the internship, we will use an ordinary differential equation (ODE) formalism to represent discrete compartments corresponding to different types of endosomes (early endosome, late endosome ...) and their signaling activity [5]. This model will account for the phenomena of internalization and spatial distribution of receptors in the cell, as well as their recycling to the plasma membrane. Within each compartment, the biochemical reactions will be formulated by ODEs based on the law of mass action. We will aim to characterize the influence of the kinetic constants at work

(traffic of receptors, signaling cascade ...) and of the temporal encoding of the stimulus acting on the receptor (e.g. continuous, intermittent, periodic).
The objective will be to study how the timescales of the different steps of receptor trafficking impact the spatio-temporal dynamics of activation of signaling pathways, and, *in fine*, to link these dynamics with more integrated cellular events such as proliferation or differentiation. The outputs of the model will give information on the duration of a receptor recycling cycle, from the stimulation until the return to the membrane, on the transit times within the compartments, and on the importance of functional heterogeneity between compartments.

The master internship will lead to a PhD thesis, whose objective will be to characterize more precisely the distribution of endosomal compartments. To this end, we will use a formalism of partial differential equations of the coagulation-fragmentation type, and structure the population of endosomes in size / content as well as in space [2]. Such a formalism will enable one to analyze the existence of concentration gradients for diffusible molecules, and to fully exploit cutting-edge experimental data, including quantitative imaging of intracellular microscopy [1].

References

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