Physics of biological signal multiplexing

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Ce stage peut être poursuivi en thèse : OUI

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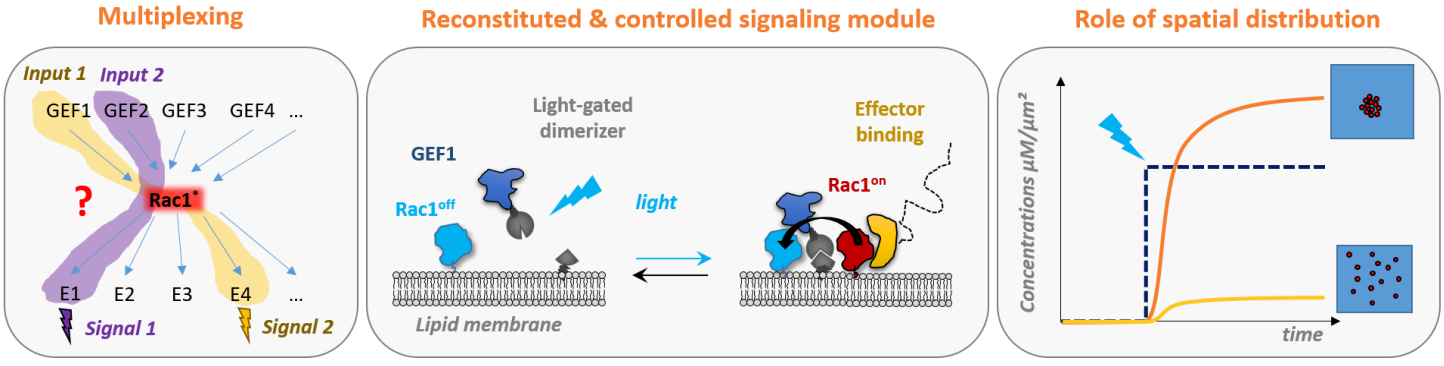
SUJET du stage:

The behavior of cell is controlled by a complex molecular circuitry of proteins in interaction. Signaling pathways, cascade of biochemical reactions, are transducing and processing information about the outside world to the cell interior. Interestingly, **a small set of signaling proteins are "hubs"** of this flow of information. Many incoming signals converge toward these hubs, which in turn control a large variety of responses. How can a single protein encode several messages and transmit them robustly? This problem is called **multiplexing of signals** and is a challenge in modern biology.

We are using the **small GTPase Rac1** as an archetypal hub able to multiplex signals. Rac1 is a membrane bound molecule that switches between "on" and "off" states thank to its interactions with GEF and GAP. In its "on" state, it recruits effector proteins specific of a given cellular function. To understand how Rac1 encodes different signals, we are combining *in vitro* and *in vivo* approaches. **We want to measure signal specificity** by quantifying the kinetics of core signaling modules (one given GEF, GAP and effector cocktail, as in [1]). Our rational is that **the spatial distribution of Rac1 may play a critical role** there. Indeed, we recently showed [2] that in live cells Rac1 forms nano-clusters of few tens of molecules ("signaling quanta"). High local concentrations could enhance drastically the reaction rates and provide a mean to tune the response.

In the context of the internship, we propose to measure the kinetics of Rac1 activation using ***in vitro* reconstituted membrane systems and fluorescent imaging**. Signal activation will be controlled with state-of-the-art **optogenetic** tools. The aim will be to assess the role of Rac1 spatial distribution on quantitative input-output relationships. Our colleagues (Cherefils lab, ENS cachan) will provide the purified components. The intern will prepare the samples, perform experiments with fluorescent TIRF microscopy, develop routines to process and quantify images, and build simple physical models to interpret data.



References: [1] Coyle and Lim, eLife 2016. [2] Remorino et al, Cell Reports 2017.