Stage Master 2 - 2019
Coupling biochemical reaction networks with cell population dynamics: application to reproductive biology

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One of the main challenges of Multiscale Systems Biology consists in coupling the dynamics of intracellular networks with the dynamics of cell populations underlying tissular and organic functions. On a generic ground, there are numerous methodological challenges associated with this issue (such as model or graph reduction, theoretical and computational connection between different modeling formalisms, integration of heterogenous data, or exploration of the whole parameter space ...), which are far from being overcome at the moment. To bridge the gap, one key point is to understand how intracellular networks translate different signaling inputs into biological outcomes (e.g. cell fate, cell-to-cell communication). These biological outcomes can then be embedded in a multicellular framework, impacting the tissular level. In turn, the dynamics emerging on the whole cell population level feedback onto the individual cell level by tuning the signal inputs qualitatively and quantitatively.

Ovarian follicles are the basic anatomical and functional units within the ovary. A single follicle is composed of many somatic cells surrounding the germ cell. The fate of the follicle is intrinsically related to the changes in its cell number and cell maturity. To describe the terminal stages of follicular development, we have developed a multiscale model describing the cell density in each follicle within a cohort of growing follicles [1]. Each follicle is represented by a non-conservative transport PDE, whose structuring variables are associated with the cell status. The outputs of the intracellular network dynamics enter the formulation of the transport velocities, thereby establishing the coupling of the intracellular scale with the cell population scale.

During this project, the main objective is to describe more mechanistically the biochemical bases underlying this coupling. To this end, we will study the qualitative behavior of the main signaling network involved in follicle selection, namely the Follicle Stimulating Hormone (FSH) signaling network [5]. We will focus on the mathematical properties of specific input-output relationships that are critical for the establishment of the follicle selection process. We will study how different network topologies and/or external perturbations may modify these relationships, and impact the selection. For instance, we will discriminate, among different intracellular biochemical pathways, the most relevant for the control by FSH of the cell decision making.

Based on our biological and modeling expertise on cell signaling [6, 2], we will design dynamical models of the FSH signaling network (Figure 1) in the framework of biochemical reaction network theory [7] and ordinary differential equations. We will study stationary states and bifurcations properties to characterize the qualitative behavior of the FSH network. Using timescale separation techniques [3, 4], we will tackle the model reduction to extract the key properties of the signal networks such as input-outputs relationships. These relationships will then be used to refine the formulation of the transport velocities in our multiscale model. If time permits, we will simulate the refined PDE model to investigate the impact of the FSH intracellular biochemical network on the cell population dynamics. This will be a first step towards the possibility to account for new control points in the multiscale model, corresponding to well-specified nodes in the biochemical network, with the ultimate goal to reproduce and/or investigate the action of drugs targeting these nodes and their impact in reproductive medicine.

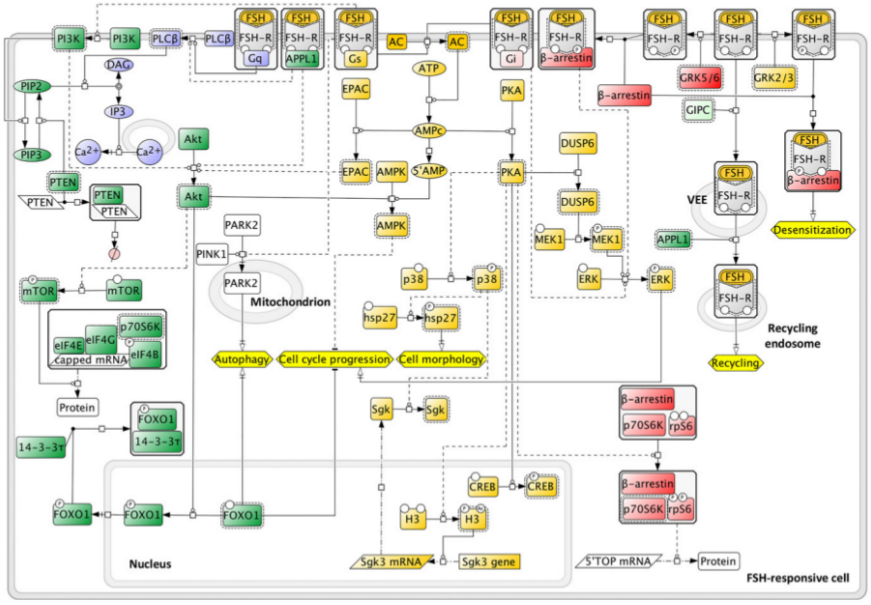

FIGURE 1 – Main components of the FSH signaling network, from [5]

Specific skills and profile A general background in Applied Mathematics is required, including solid notions in ordinary differential equations, and familiarity with numerical simulations. An experience in the study of either stochastic processes and/or partial differential equations would be appreciated. A strong motivation for applications in biology is mandatory.

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References

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