Machine learning and mathematical modelling for identifying determinants of meiosis maturation

One 6 months internship (starting in the first quarter of 2021) is available at the **University of Montpellier.** We are looking for master or engineering students with excellent skills in mathematical modelling (nonlinear ordinary differential equations, parameter optimization, bifurcation analysis) and computer programming (Matlab and Python); knowledge in systems biology, biochemistry and cell biology will be appreciated.

Context: Normal female fertility relies on proper development of the oocyte. One of the final stages of oocyte development is maturation, defined as meiosis entry. The progression of the oocyte towards maturation is controlled biochemically and involves a balance between factors promoting maturation and maintaining meiotic arrest. The precise mechanism leading to maturation is still unknown and needs to be deciphered. For doing so, we plan to use similarities between meiosis and mitosis: both processes lead to cell division and involve common biochemical determinants. Based on our recent findings that Cyclin A and Bora dependent Plk1 activation is a determinant of mitotic entry and controls G2 phase length, we want to build a mechanistic mathematical model clarifying the role of Plk1 activation in the meiotic maturation [1]. Preliminary results in the team of T.Lorca indicate that in meiosis, Mos is activated upstream and can induce the activity of Plk1 by phosphorylating Bora. Analysis of the mitotic mathematical model [1], using bifurcation diagrams, emphasized the relative roles of different molecules. Thus, Cyclin A was shown to be the mitotic trigger (via Bora and Plk1 activation), whereas the CyclinB/cdk1 complex was shown to play a more passive role, being only a driver [1]. This picture is already different from the traditional one where CyclinB/cdk1 self-activation is sufficient for mitotic entry [2,3]. The working hypothesis of the current project is that meiosis is more complex, having both Mos and CyclinB/cdk1 as trigger determinants. We aim to combine a multidisciplinary approach (cell biology, biochemistry and mathematical modeling) in two model organisms (*Xenopus* egg extracts, Xenopus and Human oocytes) to decipher the mechanism of meiosis maturation.

Problem(s): The project aims at solving two problems. i) using machine learning and mathematical modelling to build a model of meiotic maturation consistent with the experimental data produced in T.Lorca's team. ii) qualify the role played by various factors by using model analysis tools such as bifurcation diagrams.

Solution(s): Mathematical modelling using systems of non-linear differential equations is now a well established method in this field. However, modelling choices will be made concerning which biological details are important and need to be part of the model and which details are minor and can be discarded. These choices will be guided by the results of biological experimentation: we will build the minimal model that is compatible with the full data corpus (Occam razor principle). Depending on the complexity of the model, parameter synthesis will be performed by optimization using gradient descent with random initial data or genetic algorithms. Bifurcation analysis will be performed by tools developed in O.Radulescu's team.

References

[1] Vigneron S, Sundermann L, Labbé JC, Pintard L, Radulescu O, Castro A, Lorca T. Cyclin A-cdk1 Dependent Phosphorylation of Bora Is the Triggering Factor Promoting Mitotic Entry. Dev Cell. (2018) Jun 4;45(5):637-650.e7.

[2] JR Pomerening, SY Kim, JE Ferrel, Systems-level Dissection of the Cell-Cycle Oscillator: Bypassing Positive Feedback Produces Damped Oscillations. Cell (2005) 122:565-578.

[3] S. Mochida, S. Rata, H. Hino, T. Nagai, B. Novak, Two bistable switches govern M phase entry. Curr. Biol., 26 (2016), pp. 3361-3367.

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