PhD offer INRAE – Paris-Saclay University

Title: Mathematical modeling of peripheral circadian clock in a population of hepatocytes.

Disciplinary field: Applied mathematics.

Laboratory: INRAE-MaIAGE "*Applied Mathematics and Informatics from Genome to the Environment*", Jouy-en-Josas.

Keywords: Dynamical systems; Ordinary differential equations; Partial differential equations; Mathematical modeling; Numerical simulation; Circadian clock; Multiscale model.

Biological context: synchronization of cellular circadian clocks

An organism's circadian clock regulates its different functions on a 24 hour cycle, aligned with the day/night rhythm. In mammals, it is well established that multiple clocks exist at different levels. The synchronous oscillation of neurons in the suprachiasmatic nucleus, situated in the brain, is responsible for the central clock. Peripheral clocks then operate at different scales, from organs to individual cells. At the cellular scale, rhythm is imposed by a molecular clock, regulated by a network of transcriptional regulations [1]. It is generally agreed that the central clock synchronizes peripheral clocks in a one-way direction. However, recent studies emphasized inter-cellular synchronizations suggesting a more complex coupling. Thus, [2] shows that synchronized oscillations persist in a population of hepatocytes cultivated in a gel *in vitro*, and [3] exhibits synchronization of small clusters of hepatocytes in mice lacking a functional suprachiasmatic nucleus.

The ANR project InSync[1] provides the funding for the proposed PhD. It started in December 2022 and is centered on the analysis of the coupling and synchronization between cellular clocks. This project gathers two teams of modelers including the team BioSys in the MaIAGE laboratory of INRAE, and a team of biologists experimentalists: "Biologie du système circadien" in Nice. Its main objective is to combine mathematical modeling with experimental data production to analyze the emergence and maintenance of synchronization within a population of cells.

Description of the PhD

The proposed PhD is in applied mathematics, with a specialty in **dynamical systems analysis** and a strong interdisciplinary component around the modeling of biological systems. Its main objective is to **produce** and **analyze a mathematical model** of circadian clock within a **population of cells**. We have at our disposal several dynamical models of the regulatory network responsible for circadian oscillations at the cellular scale [4], [5]. These single-cell models can be used to analyze interconnections of a small number of cells, however they are not suitable to study a whole population (beyond hundreds or thousands of cells). The PhD will be aimed at the construction and analysis of a model representing circadian oscillations *at the scale of a population of cells*.

The model can be based for instance on a system of partial differential equations (PDE), structured in age (the age being here the advancement in a given stage of circadian oscillations) as in [6]. The constructed model should take into account as much information as possible from the scale of individual cells in order to represent accurately inter-cellular communications. Information that can be used to connect the two scales can be varied: for instance, some parameters of the population model can be estimated from quantities calculated in single-cell models (*eg.* average duration of a given stage, production of a component above a given threshold...). This type of "multiscale" approach, where two different scales communicate within a single model, is especially relevant when modeling biological systems where multiple scales (both temporal and spatial) coexist. The proposed PhD is aimed at applying such strategy to the particular problem of the synchronization of biological oscillators. The analysis of the produced model will provide a mean to address complex questions about the relationship between the clock of a population and the clocks of individual cells. We give two examples: *(i)* the *in silico* evaluation of different hypotheses about the type of inter-cellular communication and their impact on the synchronization: diffusion of a signaling molecule, or more global signals such as temperature (related to cell metabolism); *(ii)* the synchronization (or lack thereof) between two sub-populations with two versions of the cell model (for instance the wild type and a "mutant" strain with degraded circadian oscillations), in function of different coupling terms.

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[1] Project ANR-22-CE45-0012 "Intercellular coupling and synchronization between peripheral circadian clocks", 2022–2027.

Expected work.   The produced model(s) will be analyzed theoretically and implemented on a computer. The mathematical analysis includes the existence of solutions, their local and global properties, the impact of coupling terms, *etc*; and the numerical simulations will be confronted to biological knowledge. In a first step, data and knowledge from the literature can be used then, with the advancement of the project, experimental data produced by biological partners will become available. Those data consist in hepatocyte cultures in **spheroids** (with hundreds/thousands of cells), in which it will be possible to observe different clock regulators in 3D + time. Theoretical results will then be confronted to these experimental data in order to refine the model. In particular, *in silico* hypotheses evoked earlier will be gradually amended as the project advances. This second half of the PhD will strongly benefit from the presence of biologist within the corsortium.

Desired profile.   Master 2 (or equivalent) in applied mathematics, with a specialty in dynamical systems. Programming skills will be strongly appreciated (scientific computing). No prerequisite in biology is demanded, nevertheless the candidate should have a strong taste for the modeling biological systems.

Working environment.   The work will take place in laboratory MaIAGE of INRAE Institute in Jouy-en-Josas. The supervision will be ensured by Laurent Tournier and Mathieu Mezache, researchers at INRAE. Monthly salary is 2044 euros (as of May 2023). Regular contacts with consortium partners in Nice are planned (both remotely and in person). Within MaIAGE, the candidate will have access to the Bioinformatics platform Migale, with a computing cluster.

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Références bibliographiques

[1]   J. S. Takahashi, "Transcriptional architecture of the mammalian circadian clock," *Nature Reviews Genetics*, vol. 18, no. 3, pp. 164–179, 2017.

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[3]   F. Sinturel, P. Gos, V. Petrenko, *et al.*, "Circadian hepatocyte clocks keep synchrony in the absence of a master pacemaker in the suprachiasmatic nucleus or other extrahepatic clocks," *Genes & development*, vol. 35, no. 5-6, pp. 329–334, 2021.

[4]   S. Almeida, M. Chaves, and F. Delaunay, "Transcription-based circadian mechanism controls the duration of molecular clock states in response to signaling inputs," *Journal of theoretical biology*, vol. 484, p. 110 015, 2020.

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[6]   R. El Cheikh, T. Lepoutre, and S. Bernard, "Modeling biological rhythms in cell populations," *Mathematical Modelling of Natural Phenomena*, vol. 7, no. 6, pp. 107–125, 2012.