Mathematical modeling of the circadian clock of a large hepatocyte cell population.

Keywords : Mathematical modeling of biological processes, dynamical system, partial differential equations, numerical simulation, circadian clock

General information

- **Contract type :** Internship for a Master student
- **Location :** Inrae Jouy (Jouy-en-Josas)
- **Duration of contract :** 6 months
- **Application deadline :** 15/02/2023

About Inrae and the MaIAGE research unit

The Mathematics and Numerics division (MathNum) of INRAE develops research in applied mathematics, statistics, bioinformatics, artificial intelligence and information technology. Based on its 11 research units, the MathNum community comprises more than 350 people, including permanent staff (researchers, lecturer-researchers, engineers and technicians) and more than 160 PhD students, postdocs and other fixed-term-contract staff members. Its collaborations and partnership encompass many institutes and universities in France as well as in Europe and in the world.
The MaIAGE research unit (Jouy-en-Josas) gathers mathematicians, computer scientists, bioinformaticians and biologists to tackle problems from biology, agronomy and ecology. Its teams conduct theoretical, methodological and applied research. You will be recruited in the team BioSys (Systems Biology), which aims at developing mathematical and algorithmic methods to model, analyze and simulate complex biological systems, ranging from the scale of intracellular processes to the scale of an organism in its environment.

Context

The circadian timing system synchronizes the cells' behaviour and physiology with a 24 hours cycle corresponding to Earth's light/dark cycle. The misalignment between body time and external time is a risk factor for cardio-metabolic inflammatory and malignant diseases such as cancer. It is now well established that neurons located in the suprachiasmatic nuclei (SCN) oscillate in synchrony, and it is generally accepted that this central clock drives all scales of the organism, down to cellular clocks, in a master-slave manner. However this view has been recently challenged by both *in vivo* and *in vitro* experiments showing at least some level of communication between neighboring cells in the global synchronization of clocks. In particular, two recent studies highlight two interesting phenomenons : the synchronization of small clusters of neighbouring cells in heterogeneous populations of hepatocytes [4] and the positive correlation between the cell culture density and the synchronization duration [5]. Hence, local couplings among hepatocytes in space and spatial patterns are brought to light.
To tackle this open question, our team aims at building and analyzing mathematical models of the circadian clock at the scale of a population of hepatocyte cells including the spatial dimension and the environment.
This topic is part of the ANR project InSync, gathering two modeling teams: INRAE-MaIAGE BioSys and Inria-BIOCORE (M. Chaves), located in Sophia-Antipolis and one experimental team: Circadian Systems Biology (F. Delaunay), IbV Nice. The Master student will have the opportunity to interact with both teams, notably with biologists with expertise in the mammalian circadian clock. A continuation of

this project under a doctoral thesis may be considered at the end of the internship.

Assignment

First, we will extend the mathematical formalization of the circadian clock to a macroscopic scale. We will use ordinary differential equations to build a minimalistic mathematical model of the circadian clock of a population of hepatocyte cell [3]. It will lead to a compartmental model where each compartment corresponds to a density of cells synchronized on the same stage of the circadian clock. A proper definition of those stages, together with the transition rules from one stage to the next will constitute a key step in the understanding of clock synchronization in populations. For that, two models of cellular clocks are already available [1,2] representing biological phases on a quantitative and qualitative level. Those models will provide valuable information to aggregate the intra-cellular mechanisms into quantities which have a meaning at the macroscopic scale.
The next step will be to add a spatial representation in the population of hepatocytes' oscillators. There are several ways to incorporate the spatial dimension into the mathematical model. Either, a discretization of space is integrated into the compartmental model or the biological process is modeled in a continuous setting leading to a coupled system of partial differential equations. The mathematical analysis of both representations (the compartmental model and the PDE system) and of the relationships between the two will be essential to understand the mechanisms behind circadian synchronization at the population scale.
The step after will be to test different hypotheses in silico. For instance, we will be able to study the model according to different topographies (e.g. monolayer domains 1D, 2D versus multilayer domains 3D), or the effect of modifying the type of exchanges between cells (e.g. adding promoting or inhibiting molecules in the domain). We will also be able to confront the numerical simulations of the models to experimental data in order to understand the mechanisms behind the patterns seen in the experiments.

Required skills

- The candidate is an applied mathematician with some knowledge on ordinary differential equations and/or partial differential equations.
- The candidate should have a good motivation for mathematical modeling of biological system.
- The candidate should be familiar with scientific programming software such as Python (numpy, scipy, etc), Matlab or equivalent.

Benefits package

- Subsidized meals and partial reimbursement of public transport costs
- Leave: 2.5 days/month
- Social, cultural and sports events and activities

Contacts : Mathieu Mezache (mathieu.mezache@inrae), Laurent Tournier (laurent.tournier@inrae.fr), Alain Trubuil (alain.trubuil@inrae.fr)

References

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