Offer #2024-08293

Mathematical modeling and analysis for biological rhythms of 12 hours

Contract type : Internship

Level of qualifications required : Master's or equivalent

Fonction : Internship Research

About the research centre or Inria department

The Inria center at Université Côte d'Azur includes 42 research teams and 9 support services. The center's staff (about 500 people) is made up of scientists of different nationalities, engineers, technicians and administrative staff. The teams are mainly located on the university campuses of Sophia Antipolis and Nice as well as Montpellier, in close collaboration with research and higher education laboratories and establishments (Université Côte d'Azur, CNRS, INRAE, INSERM ...), but also with the regional economic players.

With a presence in the fields of computational neuroscience and biology, data science and modeling, software engineering and certification, as well as collaborative robotics, the Inria Centre at Université Côte d'Azur is a major player in terms of scientific excellence through its results and collaborations at both European and international levels.

Context

Biological rhythms are very frequent in living organisms, such as the well known circadian clock which controls a number of genes that are expressed in an oscillatory way, with a period of 24 hours. However, very recently, new rhythms with a period of 12 hours have been identified in the liver of mice [1]. This is the case of a large group of genes that are mostly involved in proteostasis and metabolism and whose expression oscillates with a period of 12 hours. Even though very little is known about these 12 hour rhythmic processes, the protein XBP1 appears to be at the core of a negative feedback loop circuit [2] which may be generating an ultradian rhythm.

In general, the 12 hour rhythms have two pics during a whole day, coinciding with the day-to-night and night-to-day transitions, but the first studies indicate that the ultradian rhythms are independent of the circadian rhythm. The goal of this project is to construct a first mathematical model of the XBP1 oscillator, calibrate its parameters from biological data, and analyze the main properties of the model, such as existence and stability of a periodic orbit. Studying the mechanisms of ultradian rhythms, as well as their comparison with circadian rhythms, is important to understand adaptation and evolution of organisms, in particular in the context of certain pathologies.

This topic is part of the project OSCILLA12, in the "Masters Environneés" program at Université Côte d'Azur, in collaboration with the Circadian Systems Biology team of Franck Delaunay and Michele Teboul at Institut de Biology de Valrose, who will be performing experiments connected to the ultradian rhythm. The Master student will thus be integrated in an Inria team with large experience in the modeling and analysis of biological oscillators and will also frequently interact with a team of biologists with expertise in the mammalian circadian clock.

Assignment

A mathematical model using ordinary differential equations will be constructed to describe the circuit involving XBP1, a protein related to the immune system. This circuit has two main elements: first, after transcription, the mRNA *Xbp1* may be spliced and giverise to the protein XBP1s which will in turn further promote the transcription of its gene *Xbp1*; second, the mRNA *Xbp1* may be translated directly into the (unspliced) protein XBP1u, which will in turn contribute to the degradation of the (spliced) protein XBP1s. Thus a positive and a negative feedback loop are present in the XBP1 circuit.

To describe such a negative feedback loop we will start by using the Goodwin model [3], which is composed of at least three variables (Pi, i=1,2,3) organized in a cascade where P1 positively activates P2, P2 positively activates P3, and finally P3 inhibits P1. The model proposed by Goodwin contains only linear terms, except for the term describing the inhibition of P1 by P3, and represents a basic circuit required for the existence of oscillatory behavior. Starting from this basic model, we will then add other elements, such as the positive feedback loop represented by the spliced protein, and also add new variables to represent other proteins that are known to participate in the XBP1 circuit.

The parameters of the mathematical model will then be calibrated by comparison of the model to experimental data from Delaunay team. We will simulate and study the model to show that it has a

periodic orbit with a period close to 12 hours. We will also compare the mechanisms of this oscillator with those of a circadian oscillator [4], to detect possible similarities and differences, and identify mechanisms that are more closely related to longer or shorter periods.

Main activities

1. Mathematical modeling and analysis of the 12 hour oscillator system, by application of different techniques.

2. Numerical simulations and analysis of the results.

3. Writing a report on the project.

Skills

The candidate should have some knowledge of ordinary differential equations and be familiar with a software such as Scilab, Matlab, Phyton, or equivalent.

Benefits package

- Subsidized meals
- Partial reimbursement of public transport costs
- Leave: 7 weeks of annual leave + 10 extra days off due to RTT (statutory reduction in working hours) + possibility of exceptional leave (sick children, moving home, etc.)
- Possibility of teleworking and flexible organization of working hours
- Professional equipment available (videoconferencing, loan of computer equipment, etc.)
- Social, cultural and sports events and activities
- Access to vocational training
- Contribution to mutual insurance (subject to conditions)

Remuneration

Traineeship grant depending on attendance hours.

General Information

- **Theme/Domain :** Modeling and Control for Life Sciences
  Biologie et santé, Sciences de la vie et de la terre (BAP A)
- **Town/city :** Sophia Antipolis
- **Inria Center :** Centre Inria d'Université Côte d'Azur
- **Starting date :** 2025-02-01
- **Duration of contract :** 6 months
- **Deadline to apply :** 2025-01-31

Contacts

- **Inria Team :** MACBES
- **Recruiter :**
  Chaves Madalena / Madalena.Chaves@inria.fr

About Inria

Inria is the French national research institute dedicated to digital science and technology. It employs 2,600 people. Its 200 agile project teams, generally run jointly with academic partners, include more than 3,500 scientists and engineers working to meet the challenges of digital technology, often at the interface with other disciplines. The Institute also employs numerous talents in over forty different professions. 900 research support staff contribute to the preparation and development of scientific and entrepreneurial projects that have a worldwide impact.

The keys to success

If understanding, simulating and analyzing the dynamics of oscillatory systems appeals to you, and If, in addition, you are curious about the workings of biological systems and would like to be involved in interdisciplinary work with a great team of circadian system biologists, then this is right internship for you!

Warning : you must enter your e-mail address in order to save your application to Inria. Applications must be submitted online on the Inria website. Processing of applications sent from other channels is not guaranteed.

Instruction to apply

Applications must be submitted online on the Inria website. Collecting applications by other channels is not guaranteed.

Defence Security :
This position is likely to be situated in a restricted area (ZRR), as defined in Decree No. 2011-1425 relating to the protection of national scientific and technical potential (PPST).Authorisation to enter an area is granted by the director of the unit, following a favourable Ministerial decision, as defined in the decree of 3 July 2012 relating to the PPST. An unfavourable Ministerial decision in respect of a position situated in a ZRR would result in the cancellation of the appointment.

Recruitment Policy :
As part of its diversity policy, all Inria positions are accessible to people with disabilities.