Offer #2024-07585

**PhD Position F/M Modeling and Dynamical Analyses of Cell Death Signaling to Understand Tumor Cell Responses to Cancer Therapeutics and the Immune System**

**Contract type:** Fixed-term contract

**Level of qualifications required:** Graduate degree or equivalent

**Function:** PhD Position

**Level of experience:** Recently graduated

**Context**

Tolerant tumor cells can emerge after cancer treatments even when combination strategies are used and contribute to partial treatment efficacy. Identifying the molecular mechanisms involved in cell tolerance is thus an essential task in the rational design of efficacious drug combinations.

One of the major pathways contributing to cell death is the extrinsic apoptosis pathway, which activates a cascade of proteins called caspases, responsible for targeting and cleaving many proteins in the cell, and eventually leading to cell death. However, other components and pathways are known to strongly interact with the extrinsic apoptosis pathway, including both anti-apoptotic (such as FLIP or NF-κB and PI3K/Akt pathways) or pro-apoptotic (such as immune effectors, or p53 and JNK pathways) ones.

Mathematical modeling of these pathways is essential to understand the interaction between the different components and their response to cancer drugs and will help to identify potential targets for drug combinations.

This project is a collaboration between M. Chaves from MACBES team at Inria and the team of J. Roux at IPMC (Institut de Pharmacologie Moleculaire et Cellulaire, CNRS, Sophia Antipolis) to develop a modeling workflow that uses single-cell response data and mathematical models to understand the dynamic interplay between death signaling pathways and its role in tumor cell killing.

Funding for this project will be obtained by applying to PhD fellowships at Inria and/or the doctoral schools of Université Côte d'Azur.

**Assignment**

The two teams have been developing mathematical models for the extrinsic apoptosis pathway (Pere et al, 2020; Chaves et al 2021), with the goal of identifying the molecular mechanisms involved in cell tolerance to cancer treatments. Two directions will be followed in the current project:

The first goal is to develop a minimal system of ordinary differential equations that integrates a reduced model of extrinsic apoptosis (Pere et al, 2020) with a set of both anti- and pro-apoptotic components, such as FLIP and granzyme B, to include the principal components that modulate caspase activation. The model's parameters will be calibrated with single-cell data from the Roux Lab. A special focus will be on model calibration to caspase response during the first hour after treatment, for subsequent use in cell fate forecasting. "Fast" components that are likely to modulate cell response during the first hour will therefore be included in the model: a strong candidate is the granzyme B pathway, since cell death mediated by granzyme B occurs on average about 20 minutes after natural killer cell contact with the tumor cell.

A second direction is to analyze the transcriptomic profiles of single cells. The Roux Lab developed a pipeline that links the predicted drug response of a cell to its own genome-wide transcriptomic profile in single-cells (Meyer et al, 2020). This pipeline uncovered a cell sensitivity signature to TRAIL, composed of a set of genes which were shown to increase cell sensitivity to death receptor agonists. The goal is to investigate and quantify the role of these high-ranking genes on the apoptosis pathway and their effect on cell-to-cell variability in drug response.

**References:**

- M Pere, M. Chaves, and J. Roux. Core models of receptor reactions evaluate basic pathway designs


**Main activities**

- Mathematical modeling and analysis of a signaling network, by application of different techniques.
- Numerical simulations and analysis of the results, combining machine learning strategies for data analysis with methods for simulation of ordinary differential equations.
- Writing scientific papers on the results and their communication at the main conferences in the area.

**Skills**

- Some experience on analysis and simulation of ordinary differential equations
- Good experience using software such as Matlab, Scilab, Python, or equivalent
- Some experience with or willingness to be using and exploring machine learning algorithms.

**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 (after 6 months of employment) 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
- Social security coverage

**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**: 2024-10-01
- **Duration of contract**: 3 years
- **Deadline to apply**: 2024-05-31

**Contacts**

- **Inria Team**: MACBES
- **PhD Supervisor**: 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**

A great motivation to work on mathematical models of biological networks, using a diversity of tools from analysis of dynamical systems, numerical simulations, and comparison between models and experimental data.

**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**

**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.