PhD PROJECT PROPOSAL

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TURING CENTRE FOR LIVING SYSTEMS

Modeling tumor innervation: impact on immune cells and anti-cancer treatment

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Abstract
The recruitment of new neural projections through a process called axonogenesis is today recognized as a critical step in tumor development, which fundamentally influences tumor growth in a positive or negative way, depending on the type of neurons or cancers considered. The neuronal influence on cancer growth is mediated by local neurotransmitter release that regulate anti-tumor immune responses. We will develop mathematical models of pancreatic tumor innervation at the tissue scale taking into account tumor growth, axon densities, tissue stiffness and immune cells infiltration. Deep learning based Bayesian inference algorithms will allow us to calibrate those models on data. These will allow us to perform in silico experiments that will help to the emergence of some rules and principles of the neurobiology of pancreatic cancer. In addition, it will allow us to test the effect of a chemotherapeutic treatment - that has been shown to reduce tumor growth but promote axonogenesis, increasing the risk of disease recurrence - or chemo-immunotherapy combination.

Keywords
Pancreatic cancer, nervous system, axonogenesis, immune system, tumoral microenvironment, mathematical model, partial differential equation, structured population equation, mixture model, Bayesian statistics, deep learning, normalizing flows.

Objectives
The objective of this PhD is to develop new mathematical models to highlight some rules and principles of the neurobiology of pancreatic cancer and to simulate the effect of anti-cancer treatments. The models need to be properly calibrated from the experimental data. A full Bayesian answer for inference on such complex mathematical models requires the development of machine learning based algorithms, relying on the training of normalizing flows on simulated processes.

Proposed approach (experimental / theoretical / computational)

We previously developed a first mathematical model based on ordinary differential equations (ODE) to mimic the synergy between the anti- and pro-tumoral effect of the axons on the tumor progression [2]. To better understand the possible impact of the timeline of denervation, we have improved the first model by coupling partial differential equations (PDE) to ODE. The PDE is a structured type equation that models more precisely the progression of the pancreatic lesions. To take into account tissue stiffness and immune cell infiltration, new models are required. We will first extend the PDE/ODE model, adding the space dependency to better represent tissue thickness. Mixture models will then be used to take into account the interaction with the immune infiltrate. The mathematical models will be calibrated by data obtained from murine tumor models to understand axonogenesis, depending on the tumor size, tissue stiffness, immune cells infiltration and in response to chemotherapy. The complexity of the new mathematical models will require likelihood free or simulation based inference algorithms to enrich the calibration of the model. To this aim, we will adapt deep learning methods, in particular normalizing flows trained on simulated data. This process will also allow us to understand the amount of information we recover from various experimental designs and to select the most accurate one.

Interdisciplinarity

The project is based on a tight collaboration between the groups of Florence Hubert, specialist of mathematical modeling in biology at I2M, Fanny Mann and Sophie Chauvet, experts in cancer neurobiology at IBDM, and includes a collaboration with Pierre Pudlo, statistician at I2M and Mathieu Mezache, former post-doctorant of the consortium and now CR at INRAE. The collaboration started 4 years ago with a PAIR Pancreas grant, financial support for the experiments and for the post-doct of Mathieu Mezache.
The project involves mathematical model design, calibration of the model thanks to experimental data already existing or produced by the IBDM team, and development of deep learning techniques to enrich the confrontation between experimental data and in silico outputs. Once the model is established, numerical simulations will provide new knowledge in cancer biology. This will allow us to design new experimental plans to test and validate the model predictions experimentally.

PhD student's expected profile

The PhD candidate should preferentially be a mathematician with a strong knowledge in statistics and in partial differential equations and basic knowledge in biology. She or he must be motivated to work at the interface of mathematics and biology as she/he will interpret biological experimental outputs, translate them into mathematics and may propose new experimental protocols. Previous experience in modeling tumoral progression and its interaction with the microenvironment will be appreciated.

Is this project the continuation of an existing project or an entirely new one? YES
In the case of an existing project, please explain the links between the two projects
Two articles came out from this collaboration started four years ago. In [1], advanced statistical tools were used to better interpret the experimental impact of denervation in a PDAC development in mice. In [2] and in an ongoing work, a model has been conjointly designed to study the synergy between the anti- and pro-tumoral effect of the axons on the tumor progression. The new project will now focus on mathematical models that will take into account tumor growth, tissue stiffness, neuro-immune interaction and chemotherapeutic treatment. The calibration of these models on data will require approximate inference methods, and we will focus on the most recent algorithms based on deep learning methods such as normalizing flows.

2 to 5 references related to the project

[1] J. Guillot, C. Dominici, A. Lucchesi, H. Nguyen, A. Puget, M. Hocine, M. Rangel-Sosa, M. Simic, J. Nigri, F. Guillaumond, M. Bigonnet, N. Dusetti, J. Perrot, J. Lopez, A. Etzerodt, T. Lawrence, P. Pudlo, F. Hubert, J.-Y. Scoazec, S. van de Pavert, R. Tomasini, S. Chauvet*, and F. Mann*. *co-last author. *Sympathetic axonal sprouting induces changes in macrophage populations and protects against pancreatic cancer,* Nature Communications, **15**(1985), 2022.

[2] S. Chauvet, F. Hubert, F. Mann, M. Mezache *Tumorigenesis and axons regulation for the pancreatic cancer: a mathematical approach.* To appear in Journal of Theoritical Biology, Volume 556, 2023.

3 main publications from each PI over the last 5 years

Florence HUBERT

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Pierre PUDLO

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G. Aufort, L. Ciesla, P. Pudlo, V. Buat. Constraining the recent star formation history of galaxies: an approximate Bayesian computation approach. *Astronomy & Astrophysics*, 635, p. A136, 2020