2018-00634 - PDE Modelling for Chronic Myeloid Leukemia.[PHD campaign]

Niveau de diplôme exigé : Bac + 5 ou équivalent
Fonction : Doctorant

A propos du centre ou de la direction fonctionnelle
Grenoble Rhône-Alpes Research Center groups together a few less than 800 people in 35 research teams and 9 research support departments.

Staff is localized on 5 campuses in Grenoble and Lyon, in close collaboration with labs, research and higher education institutions in Grenoble and Lyon, but also with the economic players in these areas.

Present in the fields of software, high-performance computing, Internet of things, image and data, but also simulation in oceanography and biology, it participates at the best level of international scientific achievements and collaborations in both Europe and the rest of the world.

Contexte et atouts du poste

The project will be supervised by Thomas Lepoutre (Junior researcher Inria Rhône-Alpes, HDR), member of the Institut Camille Jordan and the Inria Dracula project-team in Lyon. It is a project of applied mathematics (structured EDP) related to clinical issues. The candidate will be hosted by the Inria DRACULA team (led by Mostafa Adimy) joint team with the Camille Jordan Institute.

We will collaborate for this work with Franck-Emmanuel Nicolini, hematologist at the Léon Bérard center in Lyon and in charge of a phase 3 clinical trial (200 patients) to which we will have access.

The thesis project is part of a collaboration with Doron Levy of the University of Maryland and funded until 2018 by an Associate team Inria (fund funding missions Lyon-Maryland) and the student will be brought to travel to the University of Maryland to collaborate with Doron Levy.

Mission confiée

The project primarily concerns the study of problems in cell population dynamics, with application to the effects of treatments for chronic myeloid leukemia and in particular the question of the cessation of treatments. Chronic myelogenous leukemia (CML) is a cancer of the blood cells and can be fatal if it turns into acute form. The introduction of tyrosine kinase inhibitors (TKIs) in the early 2000s revolutionized the treatment of CML. By targeting tumor cells almost exclusively, ITK treatments have turned deadly disease CML into a chronic condition. However, ITKs alone do not seem to be able to cure cancer, which implies a treatment for life. In recent years, treatment cessation experiments have shown that some patients manage to control (perhaps even eradicate) residual disease. An important part of the project will focus on understanding the control mechanisms involved in this so-called Treatment-Free-Remission.

The immune system plays an important role in the prevention and control of tumor growth, and is possibly a crucial element for the eradication of tumors. We have introduced in [3] a model of interaction between the immune system and leukemia that has been compared to the data and to propose new interpretations. The results from the Apollos Besse [1, 2] thesis on a simplified version of the model interpret the success of treatment discontinuation as stabilization around a steady state. But it turns out in the context of discontinuation experiments that some patients manage to control (perhaps even eradicate) residual disease. An important part of the project will focus on understanding the control mechanisms involved in this so-called Treatment-Free-Remission.

The immune system plays an important role in the prevention and control of tumor growth, and is possibly a crucial element for the eradication of tumors. We have introduced in [3] a model of interaction between the immune system and leukemia that has been compared to the data and to propose new interpretations. The results from the Apollos Besse [1, 2] thesis on a simplified version of the model interpret the success of treatment discontinuation as stabilization around a steady state with a low leukemic load. It is now necessary to complexify the model while continuing the theoretical analysis. One of the axes that we wish to explore is that of a continuous maturation variable x (we will first base ourselves on models inspired by [4] representing the stem cells and more mature. Firstly, we will have to ask ourselves the question of avoiding to describe separately the most mature compartment (this separation is used in the original model to bring a feedback of the mature towards the others which will not be our intention) even to envisage of everything described by density (the strain is then also more diffuse). In this context the stem cells would simply correspond to x small and the mature to large X. It will be necessary to couple with more advanced models of autologous immune response.

Principales activités

Several questions arise:

- Can we manage through structured PDEs to a model better representative of the reality of the distribution of maturities of circulating cells and move from a compartmental model to a model where maturity is described continuously?

- Can we do this by keeping a reasonably parameterizable model and allowing not only to reproduce but also to predict and interpret data? In particular, it will be interesting to represent the effect of maturity-dependent ITKs by a parameterizable function.

- How to propose a better representation of the immune system and its interaction with treatments based on more recent results [5]? This is not linked to the continuous maturation structuration but will be the object of important investigation.

Compétences

Theoretical and numerical knowledge of partial differential equations. Interest for applications (the candidate will need to interact with clinicians). Skills in parameter estimation will be an additional asset.

Avantages sociaux

Restaurant on site
Financial participation for public transport
Social security
Social and sporting activities
Arranging working time
French courses