Understanding and controlling microbial communities: optimal control of multiscale models

Context

For a number of applications of biomedical interest, one has to **understand** and **control** the behavior of **growing cell populations subjected to killing agents**. This is for example the case of pathogenic bacteria subjected to **antimicrobial treatments**, of tumor cells subjected to **anticancer treatments**, and of bacteria naturally **attacked by phage viruses**.

These systems are highly interesting dynamical systems. Firstly, the response of individual cells to treatments is non-trivial to capture. Because of their different past, **each cell is different from each other**, and because of molecular noise, cell responses are re **stochastic**. Secondly, these heterogeneous and stochastic "agents" are coupled to each other by the fact that they share and act on the same **environment**. Lastly, the number of interacting agents is evolving through time as a result of **birth** and **death, of cells** leading to complex **multiscale dynamics of the cell population.** Traditionally, problems of this type have been analyzed using mostly agent based simulation tools. Such tools can serve to forward analyze cell population behavior for given model parameters and in a given treatment scenario. For more complex tasks, such as inferring model parameters from experimental data or the optimization of treatments, agent based simulation is computationally too costly.

Problem and approach

Mathematically, cell fate decisions of individual cells exposed to killing agents can be represented as hitting time problems of a stochastic process (SDE or CTMC) representing biochemical reactions inside the cell to reach a certain set (e.g. an apoptotic protein reaching a level that is sufficiently high to kill the cell). The goal of this project is to develop a tractable multiscale modeling framework for cell populations subjected to killing agents by coupling these hitting time problems to models of growing cell populations: hitting times for individual cells then depend on the state of the environment and the cell population while reversely the environment and population growth are affected by the properties of the hitting times.

This mathematical framework will allow us to quickly fit models to experimental data and to evaluate, and optimize, the effect of different treatments on the cell population.

Regarding the applications mentioned above, the problems of interest include not only **predicting** systems behavior but also **optimizing** treatments and **fitting** parameters given data. To find more efficient solution to the latter problem, optimal experimental approaches could be employed.

In concrete terms, the first task amounts to propose appropriate **modeling frameworks** for these multiscale systems. One will consider first principle representations, in the form of stochastic individual based models, but also continuous approximations thereof, leading to Fokker-Planck equation models with continuous couplings. The inclusion of cell-to-cell heterogeneity in this framework is non-trivial. The second task is to specify **optimal control** problems and develop optimal control strategies for this class of systems, and more generally for parabolic partial differential equations. Lastly, one will investigate the possibility to use optimal control tools to design optimally-informative experiments for this class of systems and apply this framework in **active learning** contexts.

Application

These methodological developments will be motivated by experimental work we do on **antimicrobial resistance**. So far no model has been able to quantitatively capture the complex population dynamics presented by resistant clinical isolates treated multiple times with beta-lactams, a broad class of antibiotics. The optimality of treatment solutions will also be **tested experimentally** on these clinically-relevant resistant bacteria.

Scientific environment

The work will be carried out in the **Commands** team at Inria. This team, headed by Frédéric Bonnans, is part of the Centre de Mathématiques Appliquées of Ecole Polytechnique in Palaiseau (south of Paris). Its primary focus is on the development and application of optimal control methods.

The work will also be done in close collaboration with the **InBio** team hosted at Institut Pasteur. InBio is a mixed research group between Inria and Institut Pasteur doing interdisciplinary research with experimental and computational biology. Jakob Ruess and Gregory Batt will provide support with stochastic modeling of cell population systems and antimicrobial resistance mechanisms.

Duration of contract: 18 months. PhD obtained not before Sept. 1, 2017.

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References

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