Stress gradients and the emergence of drug resistance in infection and cancer

Synopsis/Abstract
Cancer and antimicrobial resistance are among the greatest health threats of our time. Treatment failure in bacterial infection and cancer may result from the acquired resistance to drug therapy of the causative agents, namely bacterial or cancer cells. Both situations have interesting commonalities including the higher likelihood of progressive, sequential acquisition and accumulation of resistance mutations compared to the one-step appearance of high-level resistance; or the involvement of detoxification strategies in which cells cooperate to reduce local toxicity for the common good of the community.

Stress gradients are an additional common point of cancer and antimicrobial resistance. In solid tumors, stress gradients are found at increasing distances from blood vessels that supply both anticancer drugs and resources including oxygen. Similar gradients arise in tissue infections, with decreasing antimicrobial drug concentrations farther from the circulation, or biofilms in which drugs poorly penetrate deeper layers. Larger-scale stress gradients also encountered in the environment as bacteria migrate at the interface of drug-polluted and drug-free settings. Stress gradients have been demonstrated in microfluidic experiments to facilitate the fixation of resistance mutations both in bacterial populations under antimicrobial stress [Zhang 2011], and in cancer cell populations under anticancer stress [Baym 2016]. However, infection and cancer research are most often conducted separately and we lack a comprehensive understanding of the influence of stress gradients in the emergence and diffusion of stress resistance. We hypothesize that a systematic comparative study of antimicrobial and anticancer resistance emergence under stress gradient situations may benefit both fields.

Our objective is to construct a correspondence mapping between the phenomena involved in the evolution of solid tumor, tissue infection, and microbial communities in dynamic environments involving stress gradients. Based on this mapping, we will identify common points to develop a foundational model of stress gradient adaptation that may inform both microbial and cancer research. We will focus on key parameters that can apply to solid tumor, tissue infection and environmental adaptation: cell mobility, stress intensity, resource gradient and population diversity (both of bacteria and of cancer cells with varying phenotypes).

To conduct the comparison in a unified eco-evolutionary framework, we will rely on stochastic population modelling using *msevol*, a multiscale ecosystem modelling framework under continuous development at the Centre International de Recherche en Infectiologie (CIRI) of Lyon, France. The msevol framework implements a graph-based representation of the nested organization of resistance genes and cells structured in metapopulations (i.e. common environment with shared resources and stress) that are interconnected trough migration and submitted to spatio-temporal stress fluctuations. Biological entities (e.g. plasmids, cells, or patients) are graph nodes viewed as containers whose properties (e.g. basal growth for cells) are modulated by their content (e.g. resistance gene inducing a fitness cost) and their enclosing container (e.g. growth limited by the microhabitat occupancy and carrying capacity). Biological events are implemented as graph rewriting rules that modify node and edge multiplicities while avoiding redundancy of identical containers, that are represented as a single graph node with a multiplicity property. Compared with current ecosystem modelling paradigms such

as differential equations, agent-based, or membrane computing models, the msevol paradigm provides the required scalability and flexibility to examine complex multi-scale interactions in large populations.

The initial phase of the project will involve defining and implementing, utilizing the msevol formalism, a select number of pivotal biological events and parameters. These will be carefully chosen to capture the essential ecological phenomena driving the emergence and dissemination of resistance, while ensuring that the model remains manageable and tractable. Such rules (including logistic cell growth, natural and drug-induced cell death, plasmid transfer and loss, and patch-to-patch cell diffusion) have already been designed for the case of antimicrobial resistance. They will be adapted to model cancer cell dynamics as closely as possible to bacterial cells for comparison purposes.

Next, the effect of spatial structuring will be investigated using diverse patch organizations, varying in terms of migration intensity and stress. Base structures, such as linear 1-D or hexagonal-2D grid subject to stress gradients, could be used to calibrate the models based on published in vitro experiments in comparable systems [Zhang 2011, Baym 2016], then extended to more complex and natural organizations such as tissue, biofilms, or aquatic environments.

Finally, the msevol formalism will be extended to investigate the effect of spatial structuration on the sharing of public goods (e.g., beta-lactamase enzymes or diffusible growth factors), providing an alternative mechanism for a "cheating" cell to gain resistance without acquiring a costly trait. Incorporating evolutionary game theory, which is increasingly utilized in cancer modeling [Renton and Page, 2021], into msevol could complement the experimental studies aimed at understanding the detoxification process in biofilms or tissues [Amanatidou et al, 2019; Tai et al, 2022].

This research project is at the interface of ecology and medicine. The PhD candidate will have the opportunity to join a striving research environment at the Centre International de Recherche en Infectiologie of Lyon, tightly linked with the Lyon University Hospitals. Candidates with experience in mathematics, computer science or quantitative ecology will be considered favorably.

Supervisor(s) name(s), Affiliation(s), eMail address(es) for contact:
RASIGADE Jean-Philippe, University of Lyon, Centre International de Recherche en Infectiologie, jean-philippe.rasigade@univ-lyon1.fr

Proposed collaboration within ArchiFun network:
Randall Centre for Cell & Molecular Biophysics: cell motility, cancer biology

Proposed list of secondments:
Randall Centre for Cell & Molecular Biophysics: modelling of cancer cell motility and tissue structure based on cell imaging approaches

Main ArchiFun theme involved:

Mechanisms of bacterial resistance and cancer onsets;