From single-cell molecular to cell-populational phenotypically structured models to optimise cancer therapeutics

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The two major pitfalls of anticancer therapeutics are toxic side effects, i.e., unwanted damage done to healthy cell populations, and occurrence of drug-induced drug resistance in cancer cell populations. Leaving aside the patient-populational level, that is a matter of statistics applied to public health questions, I will focus on the individual-patient level, using dynamical models both at the single-cell and at the cell-populational level. At the single-cell level, molecular modelling, possibly using pharmacokinetic-pharmacodynamic representations and intracellular spatial reaction-diffusion models, may be used.

However, cell populations, particularly in cancer, are heterogeneous in numerous aspects, which limits the use of single-cell models to represent the asymptotic behaviour of growing cell populations. One of these heterogeneous aspects is the more or less asynchronous cell growth with respect to the division cycle in an age-structured cell population, which provides a first framework for drug delivery optimisation, aiming at minimising tumour growth under a constraint on limitation of unwanted toxicity in healthy cells.

To tackle the question of drug resistance in cancer, I will present an adaptive dynamic framework to represent the evolution in phenotype of cell populations, that allows to follow the instantaneous distribution and asymptotic behaviour of drug resistance phenotype(s) in the cell population. Such phenotypes evolve under drug pressure towards either established or transient, possibly reversible, drug tolerance, a behaviour taken into account by our models.

Optimal control strategies describing the combination of different categories of drugs on specified cell functional targets (thus far cytotoxics, that act on death terms, and cytostatics, that act on proliferation terms) are proposed, aiming at minimising a tumour cell population while limiting both unwanted toxic side effects on healthy cell populations and occurrence of drug resistance in cancer cell populations.

The models used for these representations, their asymptotic properties and their theoretical therapeutic control are ODE, integro-differential (non-local Lotka-Volterra-like) or PDE models (transport equations, reaction-diffusion models with or without advection). In the case of (linear) transport equations for the cell cycle, optimisation methods optimise or constrain eigenvalues of the growth processes, while in the other cases, healthy and tumour cell population densities will be the variables to be optimised or constrained.

Finally, I will present some transdisciplinary challenges of cancer modelling that concern mathematicians, cell biologists, evolutionary biologists and oncologists, aiming to go beyond the present state of the art in the treatments of cancer.

The lectures will be divided into five parts:

Part I Review of models of cancer growth with stress on age-structured cell-populational models of the cell division cycle

Part II Controlling cancer growth using chronotherapeutic time-scheduled drug delivery regimens

Part III An evolutionary perspective on cancer, with applications to modelling drug-induced drug resistance

Part IV Drug-induced drug resistance in cancer: perspectives in optimal therapeutic control

Part V Next steps: what mathematics should be developed to better understand, predict and control cancer evolution?

Bibliographical references can be found at the item Publications of my web page `https://who.rocq.inria.fr/Jean.Clairambault/`