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Numerical optimisation of anticancer therapeutics, especially chronotherapeutics, with toxicity constraints

I will firstly recall previous results on the optimisation of a chronotherapy delivered in the general circulation, with targets on two separate cell populations, healthy and tumour. In this representation, the proliferating cell populations under attack are modelled by simple ordinary differential equations (ODEs). The variables under control are numbers or densities of cells in homogeneous populations, healthy or tumour, the actual drug targets being cell death rates. A Lagrangian is designed from objective (killing cancer cells) and constraint (preserving healthy cells) functions. Its numerical maximization yields suboptimal solutions that can be implemented as continuous drug delivery schedules in programmable pumps that are in use in the clinic. Chronotherapeutics, a method used in the clinical treatment of cancers, takes advantage of circadian clock phase differences that exist between healthy and cancer cells to optimise drug delivery using such pumps. These differences are represented as differences between 24 h-periodic modulations of the drug effects in the cell population models.

Then I will develop more recent aspects of the same optimisation problem, where, instead of ODEs, physiologically structured partial differential equations (PDEs) representing the division cycle in proliferating cell populations are used here, with as variables cell population number or densities, healthy and tumour. The variables under control are however here not cell numbers, but growth rates (first eigenvalues of the linear PDE systems), yielding both the objective function (for tumour cells) and the constraint function (for healthy cells), from which a Lagrangian is also designed. The actual targets of control are in this representation cell cycle phase transition rates, which is much more realistic than cell death rates in the case of cytotoxic drugs, since their effects are not directly exerted by enhancing death rates, but rather by blocking cell cycle checkpoints. These checkpoints are both physiologically (by circadian clocks) and pharmacologically controlled. Differences between healthy and tumour cells are here modelled as different synchronisations between cell cycle phases, since healthy cell populations are assumed to be more synchronised, i.e., with steeper transition functions between cell cycle phases, than tumour cell populations.

Finally I will present a prospective view, adapted to personalised medicine, on therapeutic optimisation in oncology, which is based on physiological modelling throughout of the targets (cell populations in the whole body) and of the control means (fate of drugs, from their infusion in the general circulation until their molecular action at the cell and tissue level). To make these views more complete, I will also present extended principles of drug delivery optimisation, presently using only toxicity constraints on healthy cells, but also in the future, at a different time scale, simultaneously using drug resistance constraints on tumours with a cell Darwinian point of view.