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An evolutionary view of cancer with perspectives in therapeutics, taking drug resistance into account

Abstract: I will present an evolutionary viewpoint on cancer, seen as the two time scales of (large-time) evolution in the genomes and of (short-time) evolution in the epigenetic landscape of a constituted genome. These views, based on works by Lineweaver, Davies and Vincent, may serve as guidelines to propose a global conception of cancer, including towards possible innovating therapeutic strategies. Drug-induced drug resistance, the question I am tackling from a theoretical point of view, may be due to biological mechanisms of different natures, mere local regulation, epigenetic modifications (reversible, nevertheless heritable) or genetic mutations (irreversible), according to the extent to which the genome of the cells in the population is affected. In this respect, the modelling framework of adaptive dynamics I will present is more likely to correspond biologically to epigenetic modifications, although eventual induction of emergent resistant cell clones due to mutations under drug pressure is never to be excluded. The built-in targets for theoretical therapeutic control present in the phenotype-structured PDE models I advocate are not supposed to represent well-defined molecular effects of the drugs in use, but rather functional effects, i.e., related to cell death (cytotoxic drugs), or to cell proliferation (cytostatic drugs). I address this optimal control problem in the context of two populations, healthy and cancer, both endowed with phenotypes evolving with drug pressure, and competing for space and nutrients in a non-local Lotka-Volterra-like setting, taking into account a double constraint of limiting unwanted adverse effects and avoiding the emergence of drug resistance. I conclude by proposing a list of open challenging questions to modellers and mathematicians about the emergence and evolution of cancer.