Tumour growth and drug resistance: an evolutionary view with perspectives in therapeutics

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I will present an evolutionary viewpoint on cancer, seen as the 2 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 (cancer as anatomically located backward evolution in multicellular organisms, aka atavistic theory of cancer) and by Sui Huang and collaborators (revisited Waddington epigenetic landscape), respectively, may serve as guidelines to propose a global conception of cancer, including towards possible innovating therapeutic strategies.

Drug-induced drug resistance, the biological and medical question we are 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 we 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. From the biologist's point of view, we study phenotypically heterogeneous, but genetically homogeneous, cancer cell populations under stress by drugs.

The built-in targets for theoretical therapeutic control present in the phenotype-structured PDE models we 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 proliferation in the sense of slowing down the cell division cycle without killing cells (cytostatic drugs). We propose that cell life-threatening drugs (cytotoxics) induce by far more resistance in the highly plastic cancer cell populations than drugs that only limit their growth (cytostatics), and that a rational combination of

the two classes of drugs - and possibly others, adding relevant targets to the model - may be optimised to propose therapeutic control strategies to avoid the emergence of drug resistance in tumours.

We 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 way, taking thus into account a constraint of limiting unwanted adverse effects.