J. Math. Study
doi: 10.4208/jms.v52n4.19.06

Vol. **52**, No. 4, pp. 470-496
December 2019

An Evolutionary Perspective on Cancer, with Applications to Anticancer Drug Resistance Modelling and Perspectives in Therapeutic Control

Jean Clairambault*

Sorbonne Université, CNRS, Université de Paris, Laboratoire Jacques-Louis Lions (LJLL), & Inria Mamba team, Paris, France.

Received January 24, 2019; Accepted May 28, 2019

Abstract. The question of a mathematical representation and theoretical overcoming by optimised therapeutic strategies of drug-induced drug resistance in cancer cell populations is tackled here from the point of view of adaptive dynamics and optimal population growth control, using integro-differential equations. Combined impacts of external continuous-time functions, standing for drug actions, on targets in a *plastic* (i.e., able to quickly change its phenotype in deadly environmental conditions) cell population model, represent a therapeutical control to be optimised. A justification for the introduction of the adaptive dynamics setting, retaining such plasticity for cancer cell populations, is firstly presented in light of the evolution of multicellular species and disruptions in multicellularity coherence that are characteristics of cancer and of its progression. Finally, open general questions on cancer and evolution in the Darwinian sense are listed, that may open innovative tracks in modelling and treating cancer by circumventing drug resistance. This study sums up results that were presented at the international NUMACH workshop, Mulhouse, France, in July 2018.

AMS subject classifications: 35B40, 35Q92, 35R09, 45J05, 49J20, 92C50, 92D15, 92D25, 93D20

Key words: Integro-differential equations, asymptotic analysis, optimal control, mathematical oncology.

1 Introduction

This study presents 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, which led to the proposal of mathematical models elaborated within the Jacques-Louis Lions laboratory of Sorbonne Université, Paris. These

*Corresponding author. *Email address:* jean.clairambault@inria.fr (J. Clairambault)

views, inspired by works of Lineweaver, Davies and Vincent (cancer as anatomically located backward evolution in multicellular organisms, aka atavistic theory of cancer) and of 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 in cancer, 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 presented here is likely to biologically correspond to epigenetic modifications, although eventual induction of emergent resistant cell clones due to mutations under drug pressure is not 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). I 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 under drug pressure acting as an environmental constraint, and reciprocally inhibiting the proliferation of the other population in a non-local Lotka-Volterra model. Our objective is thus to minimise the proliferation of a cancer cell population while limiting the emergence of drug resistance in it, and taking into account the constraint of limiting toxicity to a population of healthy cells, that are also targets of unwanted adverse effects of the cytotoxic drug.

To conclude, I present an informal list of open questions on cancer and its treatments that may be considered as challenges to mathematicians (and others).

2 Biological background on evolution and cancer

2.1 Motivation from, and focus on, drug resistance in cancer

Intra-tumour heterogeneity with respect to drug resistance potential, modelling between-cell phenotypic variability within cancer cell populations, is a convenient setting to represent continuous evolution towards drug resistance in tumours [6]. Going beyond the