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

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1. Introduction

Motivations

- Accounting for drug resistance in cancer requires considering the level of *cancer cell populations*
- Phenotype heterogeneity in cancer cell populations is likely the main cause of drug resistance
- Heterogeneity in cancer cell populations may be due to *fast backward evolution* (atavistic theory)
- We can assess it by biological and mathematical models of evolving heterogeneous cell populations
- Therapeutic strategies should rely on optimal control algorithms in such models of heterogeneity

Executive summary

BACKGROUND Drug-induced drug resistance in cancer has been attributed to diverse biological mechanisms at the individual cell or cell population scale, relying on stochastically or epigenetically varying expression of phenotypes at the single cell level, and on the adaptability of tumours at the cell population level.

SCOPE OF THIS REVIEW We focus on intra-tumour heterogeneity, namely between-cell variability within cancer cell populations, to account for drug resistance. To shed light on such heterogeneity, we review evolutionary mechanisms that encompass the great evolution that has designed multicellular organisms, as well as smaller windows of evolution on the time scale of human disease. We also present mathematical models used to predict drug resistance in cancer and optimal control methods that can circumvent it in combined therapeutic strategies.

MAJOR CONCLUSIONS Plasticity in cancer cells, i.e., partial reversal to a stem-like status in individual cells and resulting adaptability of cancer cell populations, may be viewed as backward evolution making cancer cell populations resistant to drug insult. This reversible plasticity is captured by mathematical models that incorporate between-cell heterogeneity through continuous phenotypic variables. Such models have the benefit of being compatible with optimal control methods for the design of optimised therapeutic protocols involving combinations of cytotoxic and cytostatic treatments with epigenetic drugs and immunotherapies.

GENERAL SIGNIFICANCE Gathering knowledge from cancer and evolutionary biology with physiologically based mathematical models of cell population dynamics should provide oncologists with a rationale to design optimised therapeutic strategies to circumvent drug resistance, that still remains a major pitfall of cancer therapeutics.

2. An evolutionary perspective

"Nothing in biology makes sense except in the light of evolution"
(Theodosius Dobzhansky)
... But what evolution? Have a look at the evolution of life on Earth:

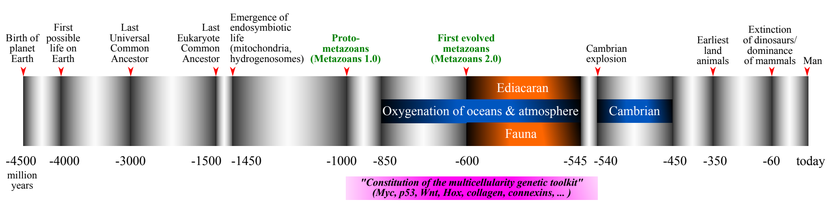

Figure 1: **Tentative reconstruction of the evolution of life on Earth (Ref. [1]).**

- The genes that have appeared in the process of development to multicellularity are precisely those that are altered in cancer.
- In what order in evolution, from 1) proliferation+apoptosis to 2) cell differentiation+division of work, and to 3) *epigenetic control* of differentiation and proliferation?
- Reconstituting the phylogeny of this 'multicellularity toolkit' should shed light on the robustness or fragility of genes that have been altered in cancer.
- Attacking cancer on proliferation is precisely attacking its robustness. It would be better to attack its weaknesses (e.g. absence of adaptive immune response).

Heterogeneity in cancer cell populations

- Conditions of oxygenation and of intercellular communications are quite poor in cancer cell populations, sending back tumours to very primitive forms of multicellularity (e.g., stochastic distribution of cellular functions without coordination)
- These two necessary conditions of multicellularity are closely related to one another, since intercellular communications, that rely in particular on gap junctions (appeared during the long oxygenation epoch of developing multicellular life and often altered in cancer), consume high quantities of energy
- High energy resources physiologically rely on the oxygen-dependent tricarboxylic acid (TCA, aka Krebs) cycle in mitochondria, power plants of the cell, that are altered in cancer: the Warburg effect describes the fact that cancer cells are hardly able to make their mitochondria work properly and depend on the poor energy-producing process of anaerobic glycolysis

The atavistic theory of cancer

- Why drug resistance in cancer, not in healthy, cell populations? We can find some answers in the *atavistic theory of cancer* (Davies and Lineweaver 2011).
- According to the atavistic theory, cancer is a 'backward evolution' from a sophisticated form of multicellularity (us), in which epigenetic processes control gene regulatory networks of transcription factors: differentiation factors, p53, etc., that physiologically control the basis of cellular life, i.e., proliferation.
- We bear in our genomes many attempts of species evolution since billions of years; dead-end tracks ('unused attractors' in S. Huang and S. Kauffman's version of the Waddington landscape) have been silenced (e.g., by epigenetic enzymes, resulting in evolutionary barriers in this landscape), but are still there.
- In cancer, global regulations are lost, differentiation is out of control, so that local proliferations without regulation overcome; sophisticated *adaptive epigenetic mechanisms are present, not controlling proliferation, but serving it*.
- Conditions of oxygenation and of intercellular communications are quite poor in cancer cell populations, sending back tumours to locally organised, very primitive forms of multicellularity (e.g., stochastic distribution of cellular functions without coordination), escaping external control.
- The basic cancer cell is also highly plastic and highly capable of adaptation to a hostile environment, as were its ancestors in a remote past of our planet (poor O_2, acidic environment, high UV radiations,...) *and likely presently even more*.

The Waddington landscape revisited

The classical 'metaphoric' Waddington landscape (1957)

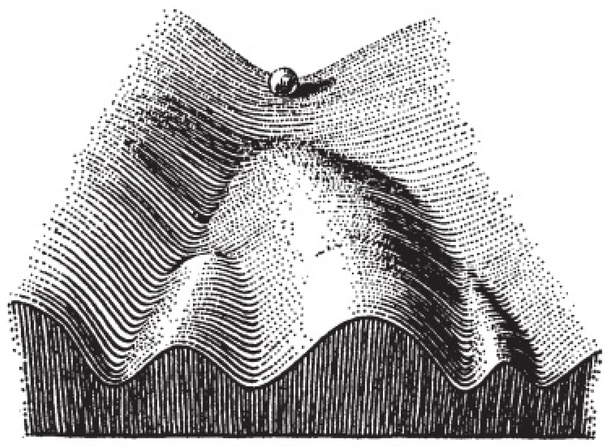

Figure 2: **Epigenetic cell differentiation in a given genome.**

Epigenetic drugs to target bifurcations in a plastic landscape?

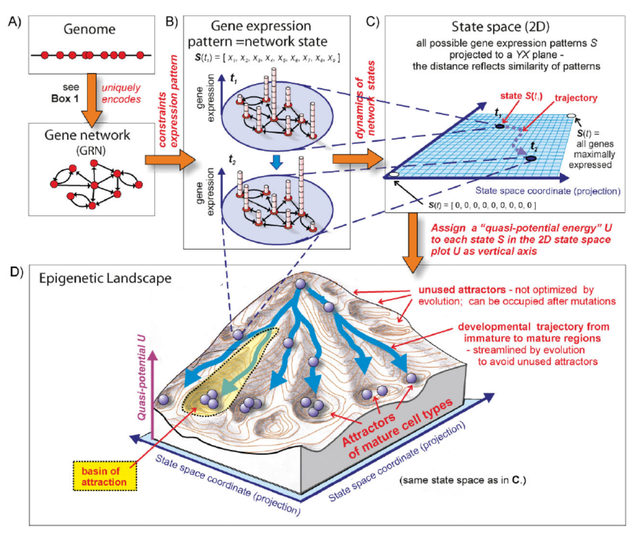

Figure 3: **A Waddington landscape revisited (Sui Huang, 2013).**

"Nothing in evolution makes sense except in the light of **systems** *biology"* (S. Huang, 2012)

3. Assessing drug resistance

Adaptive dynamics called to predict evolution of cell populations in the presence of drug pressure:

$$\frac{\partial}{\partial t}n_H(x,t) = \left[\frac{r_H(x)}{1+k_H u_2(t)} - d_H(x)I_H(t) - u_1(t)\mu_H(x)\right] n_H(x,t)$$
$$\frac{\partial}{\partial t}n_C(x,t) = \left[\frac{r_C(x)}{1+k_C u_2(t)} - d_C(x)I_C(t) - u_1(t)\mu_C(x)\right] n_C(x,t)$$

Environment variables (logistic terms):
$I_H(t) = a_{HH}.\rho_H(t) + a_{HC}.\rho_C(t)$, $I_C(t) = a_{CH}.\rho_H(t) + a_{CC}.\rho_C(t)$,
with $\rho_H(t) = \int_0^1 n_H(x,t)\,dx$, $\rho_C(t) = \int_0^1 n_C(x,t)\,dx$,
u_1 cytotoxic, u_2 cytostatic drugs.

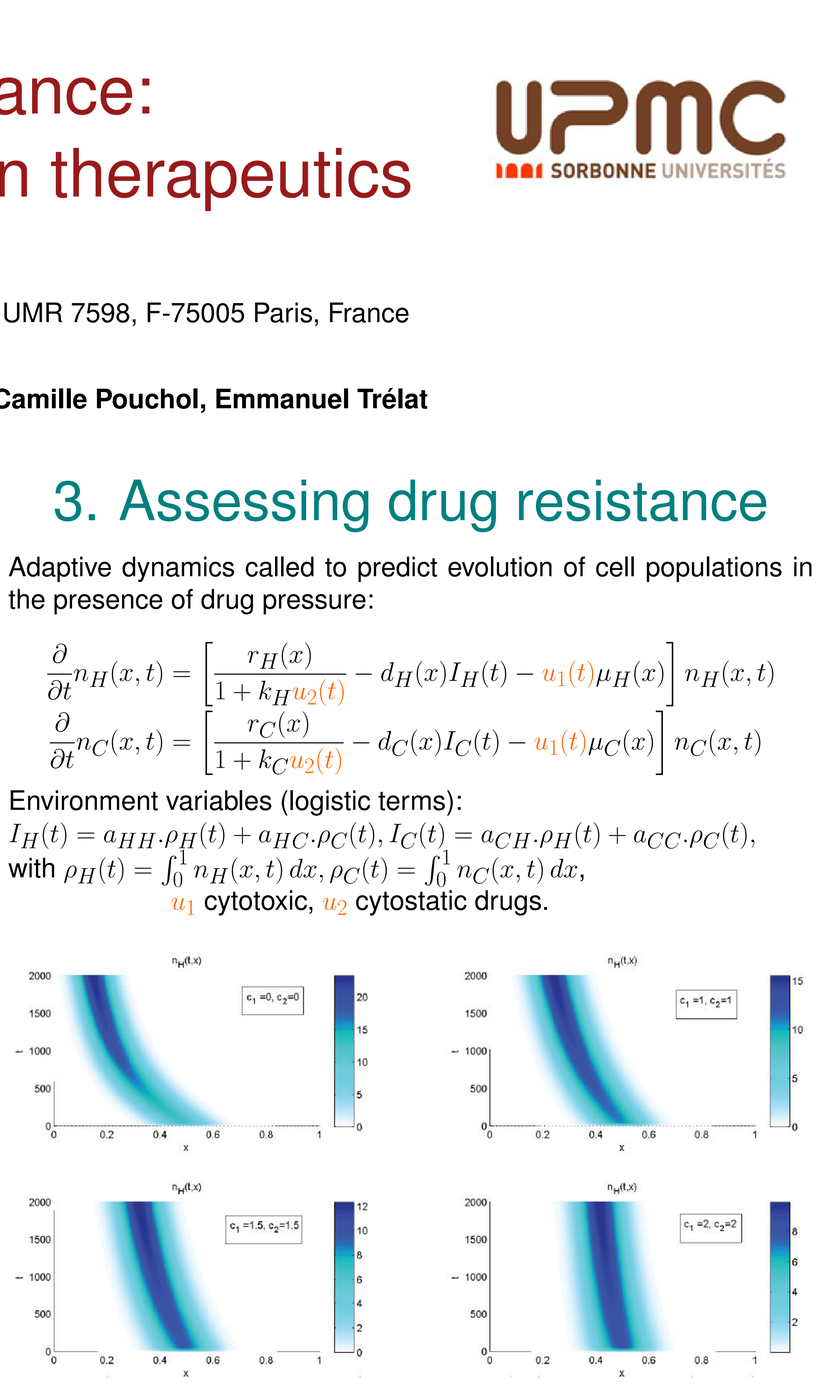

Figure 4: **Healthy cells: preserved (Ref. [2]).**

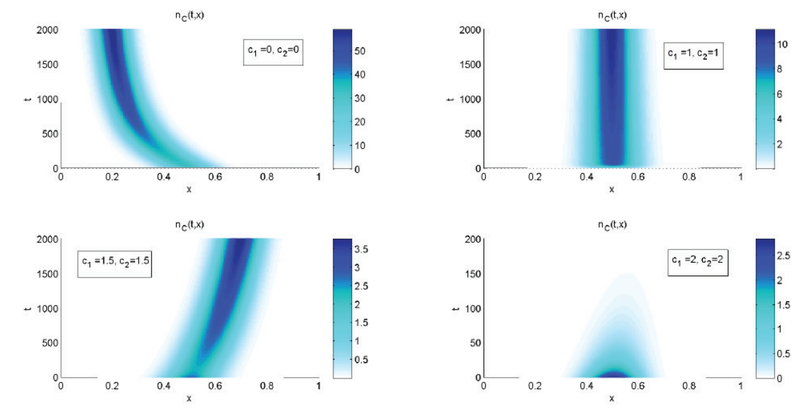

Figure 5: **Cancer cells: eventually extinct (Ref. [2]).**

4. Perspectives in therapeutics

- Systematically relating the phylogeny of multicellularity to the phylogeny of cancers (an *evo-devo-cancer viewpoint*, cf. **Ref. [1]**) should shed light on the responsible genes of cancer emergence and progression as possible druggable targets.
- Models of adaptive dynamics models for cell populations are relevant to represent their evolution under drug pressure, cf. **Ref. [2]**.
- Taking limitations in space and diffusion of drugs and nutrients is an option when some geometry of the tumour population is known, cf. **Ref. [3]**.
- Epigenetic control genes might offer such targets to stop the emergence of drug resistance (blocking the rise of *DTPs*, cf. **Ref. [4]**).
- Optimal control algorithms for anticancer drug infusion are being designed as proof of concept, aiming to block the emergence of drug resistance, cf. **Ref. [5]**. These should be developed in close collaboration with oncologists in the clinic in the forthcoming years.

5. References

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