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Cancer as a default of coherence between tissues in metazoans: what mathematical models should be developed to help prediction, prevention and treatment of cancer? Questions from a modeller

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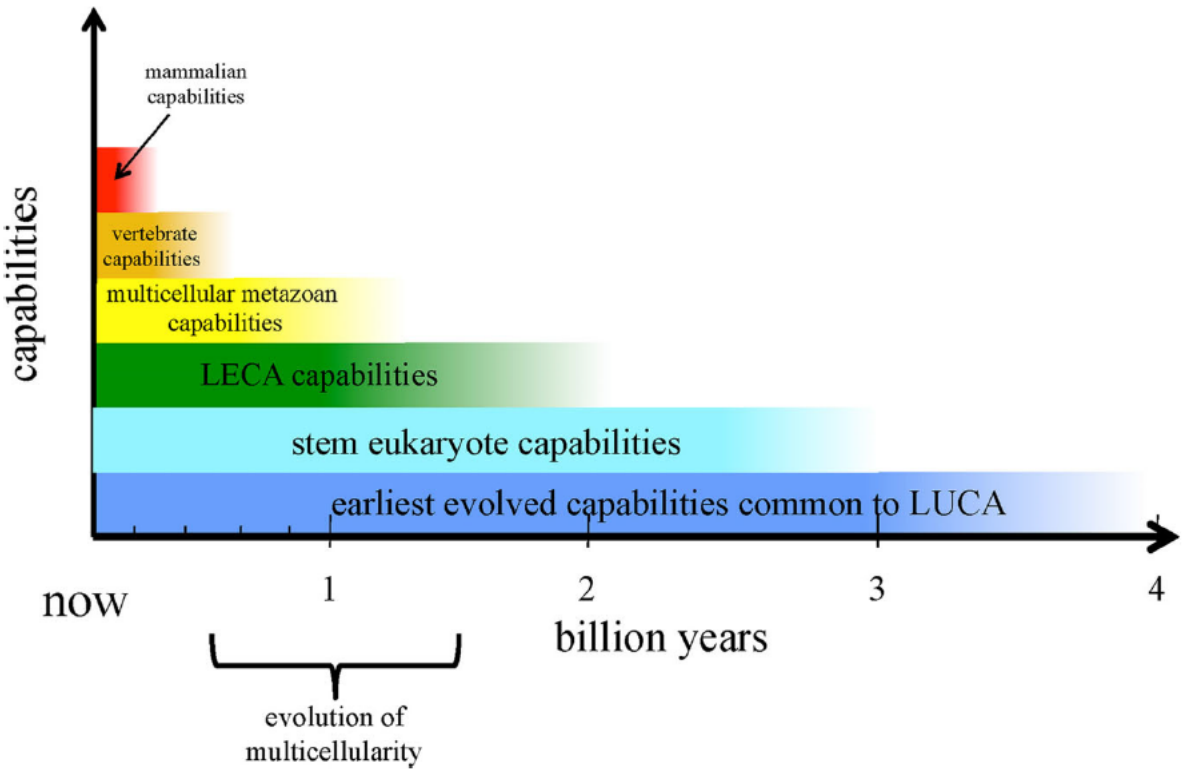
Motivation from and focus on drug resistance in cancer

- Intra-tumour heterogeneity, i.e., between-cell phenotypic variability within cancer *cell populations*, is a condition of evolution towards drug resistance in tumours.
- Slow genetic mechanisms of 'the great evolution' that has designed multicellular organisms, together with fast reverse evolution on smaller time windows, at the scale of a human disease, may explain transient or established drug resistance.
- Plasticity in cancer cells, i.e., epigenetic propension to reversal to a stem-like, de-differentiated status, and resulting adaptability of cancer cell populations, makes them amenable to resist abrupt drug insult as extreme stress response.
- Reversible plasticity is captured by mathematical models that incorporate between-cell heterogeneity by making use of continuous phenotypic variables.
- Such models have the advantage of being compatible with optimal control methods for the theoretical design of optimised therapeutic protocols involving combinations of cytotoxic and cytostatic (and possible epigenetic) treatments.

A possible evolutionary framework (*long-term view*): the atavistic hypothesis of cancer (1)

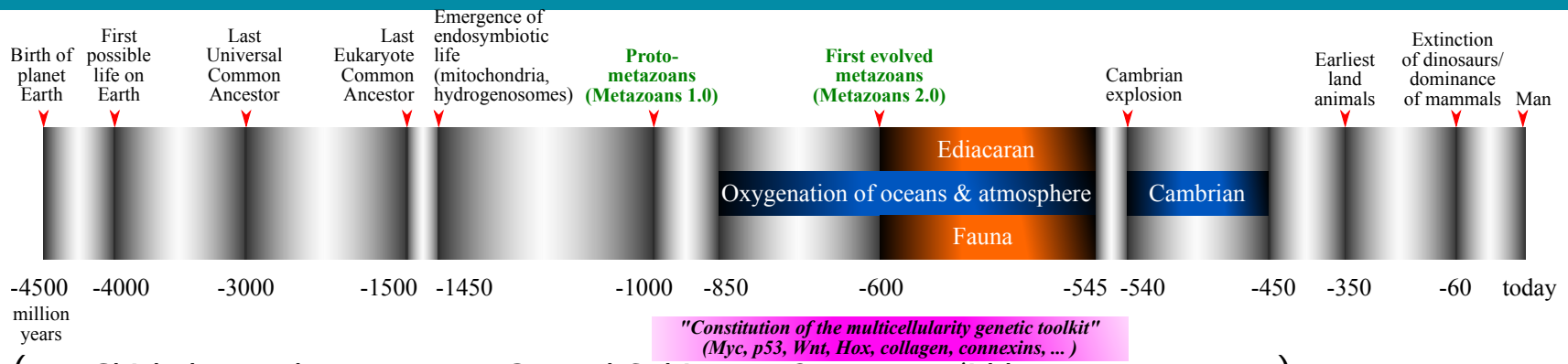
"Nothing in biology makes sense except in the light of evolution" (Th. Dobzhansky, 1973)



"Cancer: more archeoplasm than neoplasm" (Mark Vincent, 2011)

References: *Israel JTB 1996, Davies & Lineweaver Phys Biol 2011, Vincent Bioessays 2011, Lineweaver, Davies & Vincent Bioessays 2014, Chen et al. Nature Comm 2015*

A possible evolutionary framework (*long-term view*): the atavistic hypothesis of cancer (2)

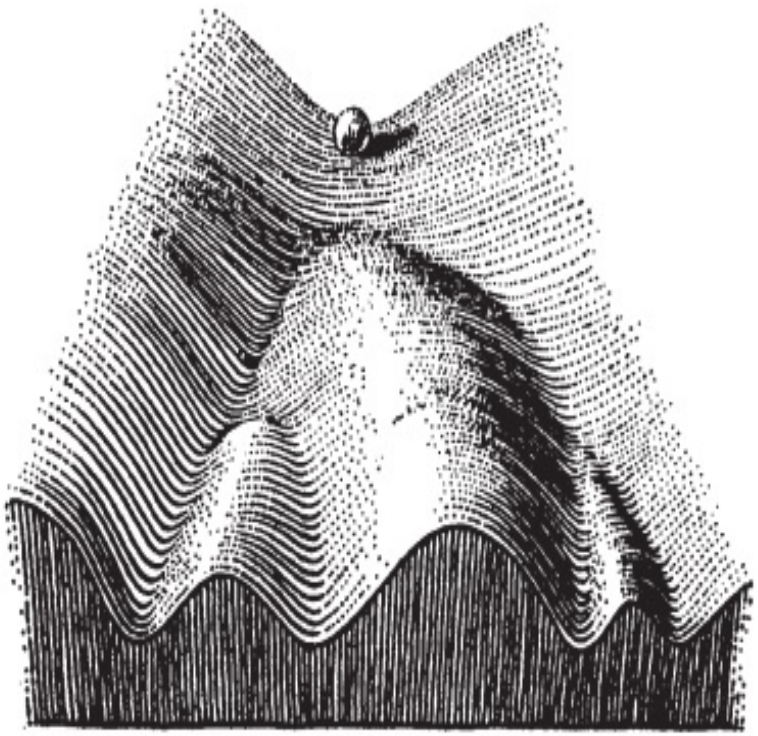


(*see Chisholm et al. 2016, BBA General Subjects DOI:10.1016/j.bbagen.2016.06.009*)

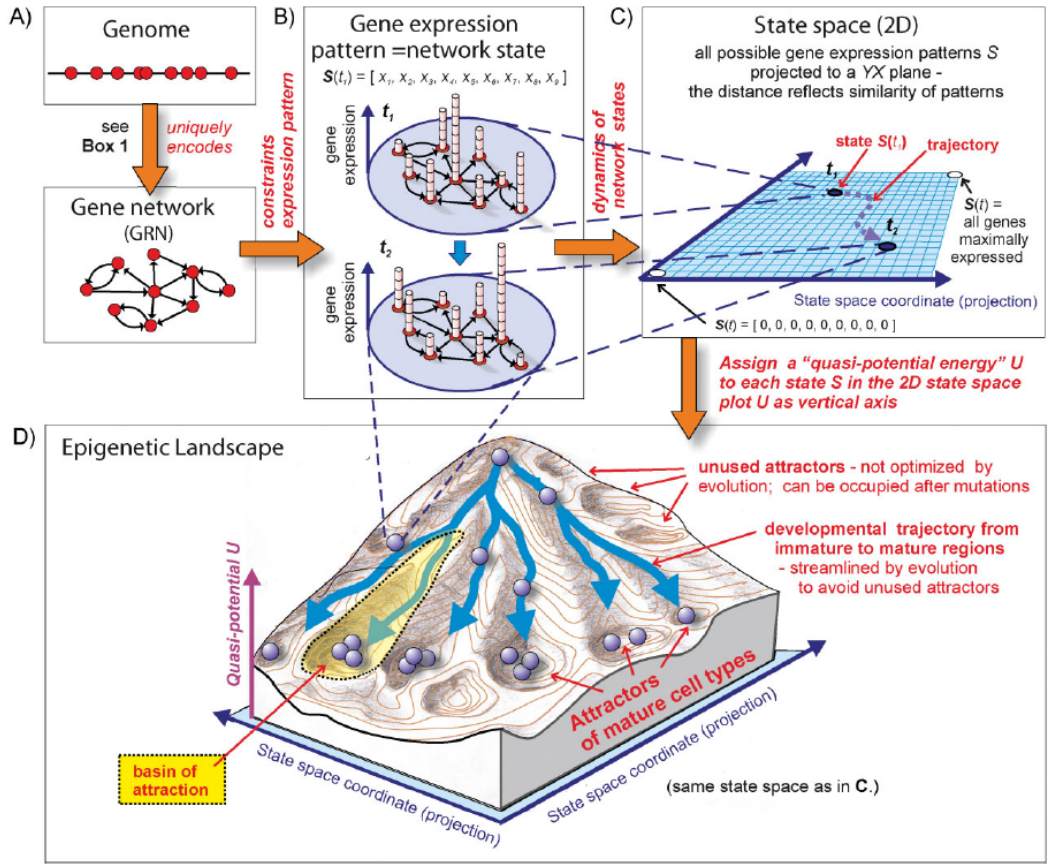
- The genes that have appeared in the process of development to multicellularity are those that are altered in cancer (Domazet-Lošo & Tautz)
- In what order in evolution, from 1) proliferation+apoptosis to 2) cell differentiation +division of work, and to 3) *epigenetic control* of differentiation and 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)

Another evolutionary framework (*life-term view*): revisiting the Waddington epigenetic landscape

The classic Waddington landscape (1957) for cell differentiation in a given organism (fixed genome)



Waddington landscape revisited by S. Huang (2011, 2012, 2013)



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

Why resistance in cancer, not in healthy, cell populations?

- According to the atavistic hypothesis, 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

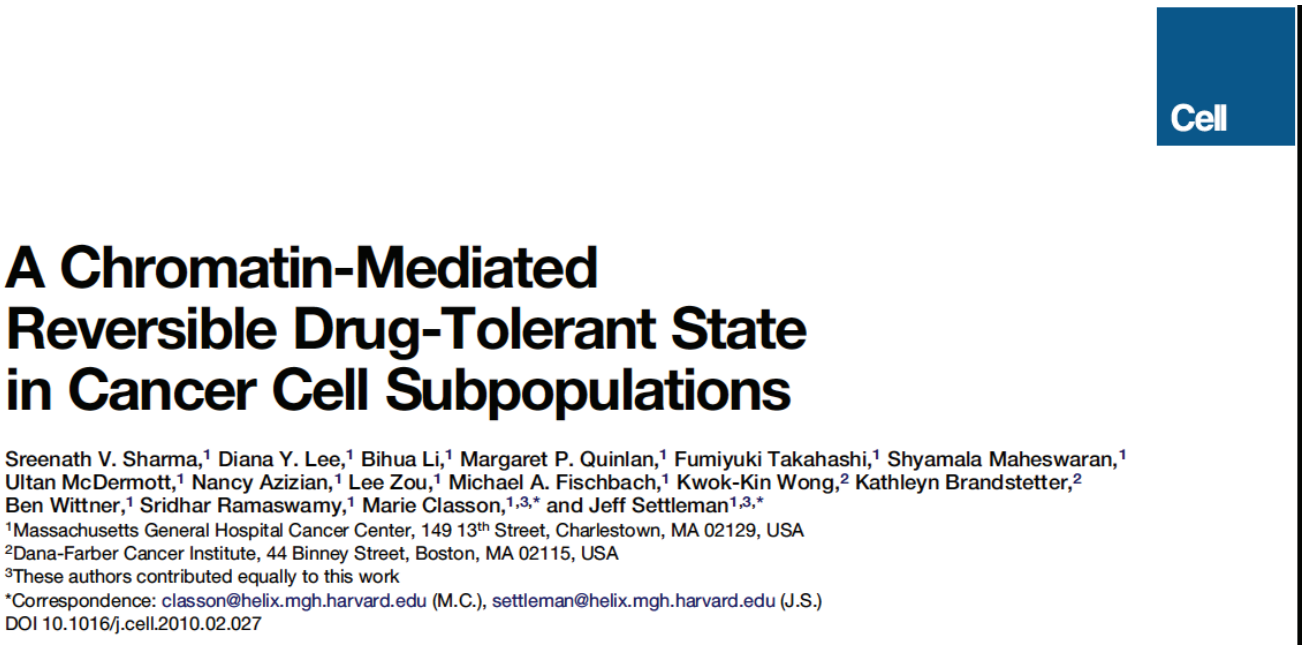
- We bear in our genomes many attempts of species evolution since billions of years; dead-end tracks ('unused attractors' in S. Huang and S. Kauffman's version of the Waddington landscape) have been silenced (e.g., by epigenetic enzymes, resulting in evolutionary barriers in this landscape), but are 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* (by stochastic expression of so-called *cold* genes? cf. Wu et al. PNAS 2015)... with subsequent *bet hedging* of resistance phenotypes?

- Primitive forms of cooperation between specialised cells in a locally organised multicellular collection (tumour), with plasticity between them, may be present, exhibiting coherent intratumoral heterogeneity, and escaping external control

- The basic cancer cell is 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*

Evolution towards resistance assessed experimentally: Reversible drug resistance of cancer cells in a Petri dish



Cell

A Chromatin-Mediated Reversible Drug-Tolerant State in Cancer Cell Subpopulations

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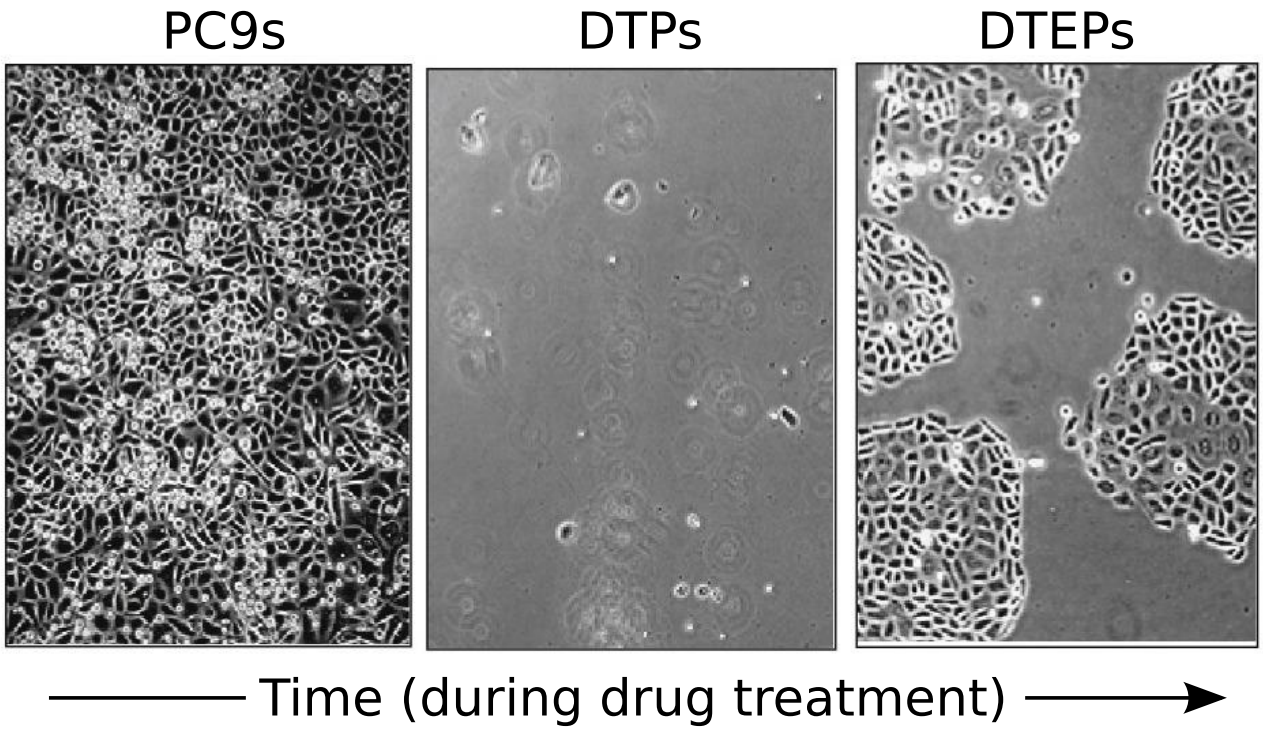
- Motivation for math: to account for biological observations of a reversible drug-resistant phenotype in cancer cell populations, *Sharma et al., Cell 2010*
- Underlying hypothesis: epigenetic modifications affect differently survival and proliferation potentials in cancer cell populations exposed to high drug doses
- Our model: 2 traits, x, stress survival potential ($\sim$ resistance to apoptosis) and y, proliferation potential ($\sim$ cell division cycle enhancement), both reversible
- A PDE model and an agent-based (AB) model both account for the observed behaviour of the cancer cell population exposed to the drug

(*Chisholm et al. Cancer Research 2015*)

Sum-up of the *Sharma et al. Cell 2010* paper

- Population of PC9 (NSCLC) cells under high doses of drugs (e.g., gefitinib)
- 99.7% cells die, .3% survive in this maintained hostile drug environment: DTPs
- In the same hostile environment, 20% of DTPs resume proliferation: DTEPs
- Total drug resensitisation is obtained by drug withdrawal after 9 doubling times for DTPs, and 30 to 90 doubling times, depending on the drug, for DTEPs
- Inhibition of epigenetic enzyme KDM5A blocks emergence of DTPs (*precisely: provokes rapid death of both DTPs and DTEPs, not affecting PC9s*)



(*Sharma et al., Cell 2010*)

2D continuous phenotype-structured PDE model

- Initial (PC9) cancer cell population structured by a 2D phenotype (x, y):
  $x \in [0,1]$: 'viability' = expression level of survival potential phenotype, and
  $y \in [0,1]$: 'fecundity' = expression level of proliferation potential phenotype
  (both biologically relying on, e.g., levels of methylation in DNA and histones)

- Population density of cells $n(x, y, t)$ with phenotypic expression (x, y) at time t satisfies

$$\frac{\partial n}{\partial t}(x,y,t) + \underbrace{\frac{\partial}{\partial y}\Big(v(x, c(t); \bar{v}).n(x,y,t)\Big)}_{\text{Stress-induced adaptation of the proliferation level}} =$$

$$\underbrace{\Big[p(x,y,\varrho(t)) - d(x,c(t))\Big]n(x,y,t)}_{\text{Non local Lotka-Volterra selection}} + \underbrace{\beta\Delta n(x,y,t).}_{\text{Non-genetic phenotype instability}}$$

- $\varrho(t) = \int_0^1 \int_0^1 n(x,y,t)\, dx\, dy$, $p(x,y,\varrho(t)) = (a_1 + a_2 y + a_3(1-x)).(1 - \varrho(t)/K)$ and $d(x, c(t)) = c(t).(b_1 + b_2(1-x)) + b_3$
- The drift term w.r.t. proliferation potential y represents possible (if $v \neq 0$) 'Lamarckian-like', epigenetic and reversible, adaptation from PC9s to DTPs
- $v(x, c(t); \bar{v}) = -\bar{v}c(t)H(x^* - x)$ where $t \mapsto c(t)$ is the drug infusion function
- No-flux boundary conditions

(Chisholm et al., Cancer Research 2015)

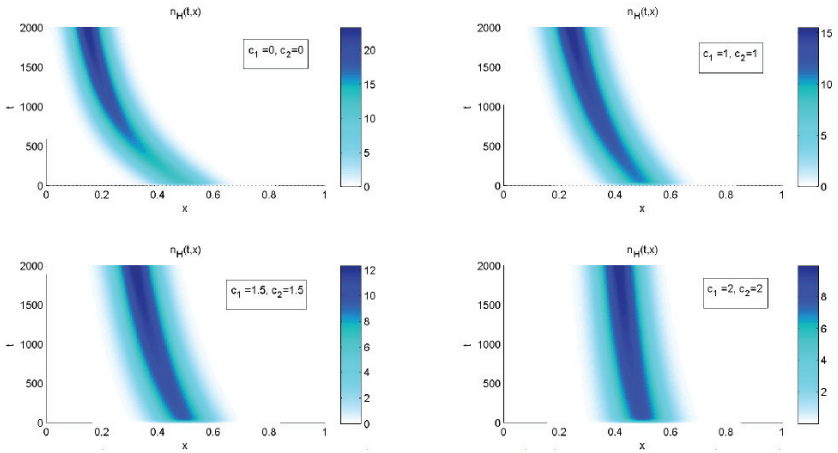
Non-local Lotka-Volterra 2D model (2 populations, H, C) with 2 different drugs and a resistance phenotype $x \in [0, 1]$

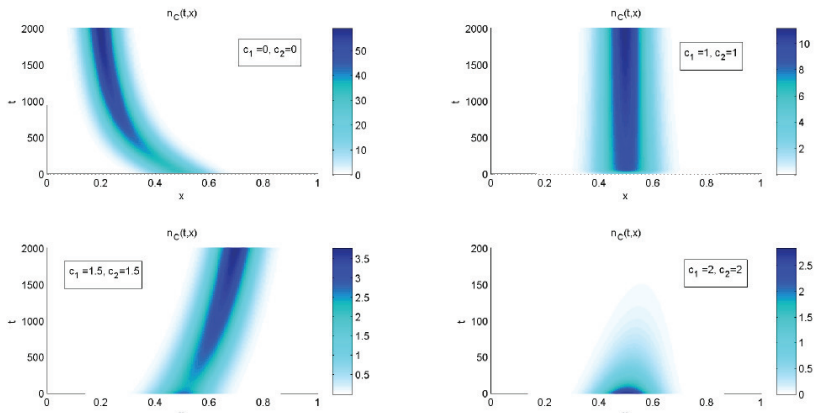
$$\frac{\partial}{\partial t} n_H(t,x) = \left[\frac{r_H(x)}{1 + k_H u_2(t)} - d_H(x) I_H(t) - u_1(t) \mu_H(x) \right] n_H(t,x)$$

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

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

Simultaneous combinations of the 2 drugs, with increasing equal constant doses





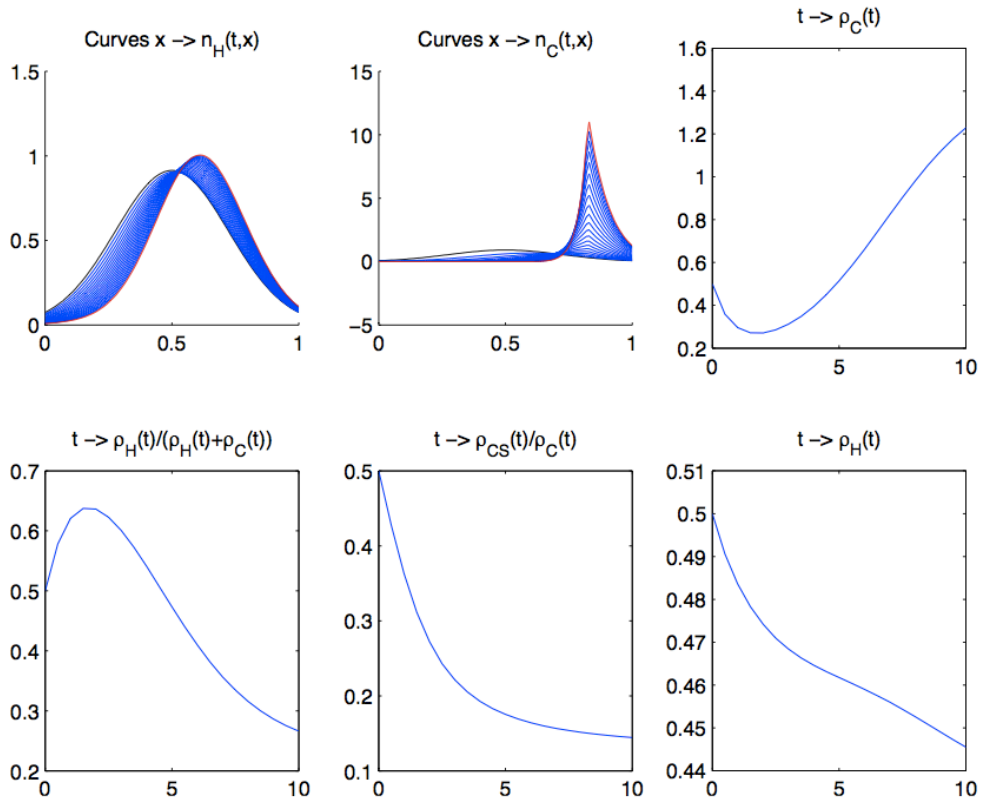
Healthy cells: preserved

Cancer cells: eventually extinct

Proof of concept, or here "Pedestrian's optimisation" *(Lorz et al. M2AN 2013)*

How to be deleterious by using constant doses of drugs

[We define the population of sensitive cancer cells by $\rho_{CS}(t) := \int_0^1 (1-x)\, n_C(t,x)\, dx$*]*
Simulation with $u_1(t) = \mathrm{Cst} = 3.5$ and $u_2(t) = \mathrm{Cst} = 2$, in time $T = 10$



- Quite small effect of the drug pressure on the phenotype of n_H
- n_C quickly concentrates around a resistant phenotype
- Catastrophic effects on ρ_H, ρ_C and ρ_{CS}.

(Pouchol et al., arXiv 2016; JMPA 2017)

Optimal control problem, phenotype-structured IDE model

Environment: $I_H(t) = a_{HH}.\rho_H(t) + a_{HC}.\rho_C(t), I_C(t) = a_{CH}.\rho_H(t) + a_{CC}.\rho_C(t)$, with $\rho_H(t) = \int_0^1 n_H(t,x)\,dx, \rho_C(t) = \int_0^1 n_C(t,x)\,dx$.

IDE model with evolution in phenotype x due to effects of cytotoxic drug $u_1(t)$

$$\frac{\partial}{\partial t} n_H(t,x) = \left(\frac{r_H(x)}{1+\alpha_H u_2(t)} - d_H(x) I_H(t) - u_1(t)\mu_H(x) \right) n_H(t,x)$$

$$\frac{\partial}{\partial t} n_C(t,x) = \left(\frac{r_C(x)}{1+\alpha_C u_2(t)} - d_C(x) I_C(t) - u_1(t)\mu_C(x) \right) n_C(t,x)$$

$$0 \le u_1(t) \le u_1^{\max}, \qquad 0 \le u_2(t) \le u_2^{\max}$$

Find controls (u_1, u_2) minimising

$$C_T(u_1, u_2) = \rho_C(T) = \int_0^1 n_C(T,x)\,dx$$

under the additional constraints

$$\frac{\rho_H(t)}{\rho_H(t)+\rho_C(t)} \ge \theta_{HC}, \qquad \rho_H(t) \ge \theta_H.\rho_H(0)$$

(the last constraint, with, e.g., $\theta_H = 0.6$, to limit damage to healthy cells)

Simulations (illustrating an underlying theorem)

Simulations with $T = 30$
(optimisation using AMPL-IPOPT)

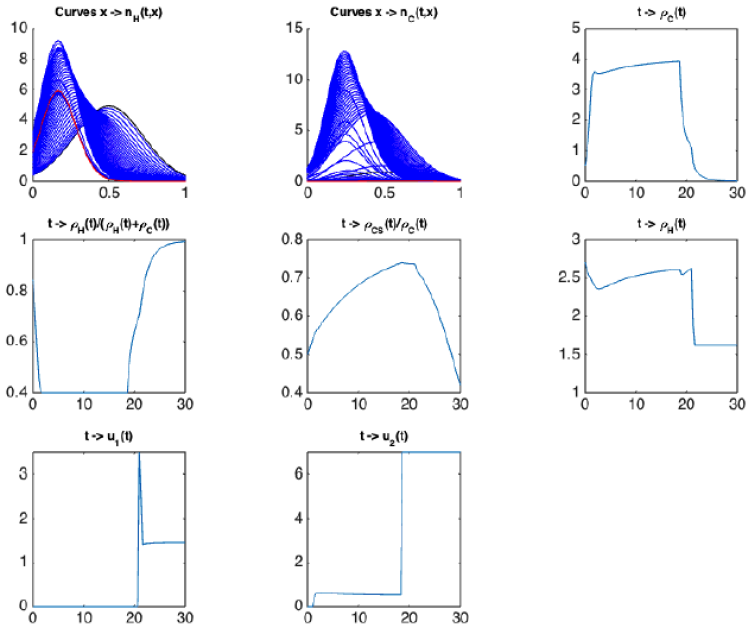


Figure 4: Simulation of (**OCP**) for $T = 30$.

Simulation with $T = 60$
(optimisation using AMPL-IPOPT)

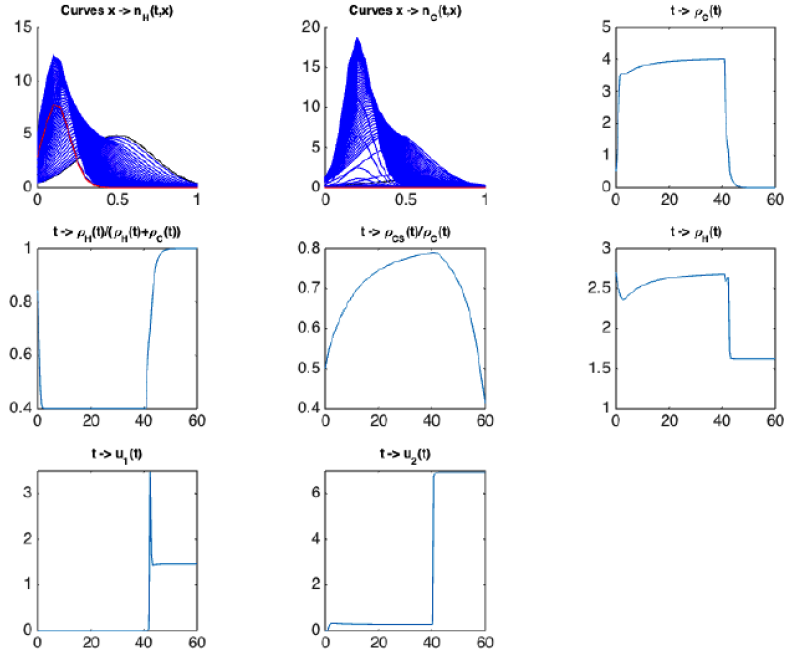


Figure 5: Simulation of (**OCP**) for $T = 60$.

Note that this *clinically oriented* strategy lets the cancer cell population ρ_C grow to a *sensitive* equilibrium level, while increasing the ratio $\dfrac{\rho_{CS}}{\rho_C}$ of drug-sensitive cancer cells, then shortly delivering $u_1 = u_1^{\max}$; only then indeed is the cytotoxic efficacy maximal.

Why is evolution important in cancer? Basic questions on *multicellularity and cancer*

- Cancer is a disease of multicellular organisms, that has been evidenced, including in fossils, in the whole animal kingdom
- Cancer *is* the failure of maintenance of a coherent (=founded on stable, nonconflicting, cellular differentiations) multicellularity, otherwise said:
- Cancer may be defined as a loss of cohesion of tissues and organs of a same organism following failures in differentiation
- Does there exist in the construction of multicellularity a qualitative succession of emergences of families of genes responsible for 1. proliferation and apoptosis; 2. differentiation (by transcription factors); 3. epigenetic control of differentiations ? Phylogenetic scenarios of evolution of mutations in AML go in the opposite direction with increasing malignancy (*Hirsch et al.* Nature Comm. 2016)
- Some gene mutations predispose subjects to well-identified organ cancers: do these genes play a role in the anatomic constitution of multicellularity?
- Evolution proceeds by *tinkering* (*François Jacob*, 'Evolution and tinkering', Science 1977), using every possible avaible material: what in such a succession of tinkerings makes a particular organism viable but fragile?
- The genes that are altered in cancers are the same that serve multicellularity design (*Domazet-Lošo & Tautz 2010, Davies & Lineweaver 2011*): can we methodically collect these genes?

Questions (continued)

- What defines *a same organism* ? A 'self' that would be conserved during the sequences of differentiations that in Man lead from the first embryonic cell to the "200 or so terminally differentiated cell types"?
- What holds together, normally without conflict, the cell types (the interferon pathways??), and what does the immune system recognise as non-self (foe rather than friend) in a cancer cell?
- Is there a relationship of such coherence with the major histocompatibility complex (MHC)? What is its primary function, if not to ensure organism cohesion (of tissues), and how does such coherence (of signals) operate?
- Can we parallel evolution of species and evolution of their immune system? Some enlightenment to collect genes active at multicellularity constitution? (paeloimmunology (?), paleogenomics... and the atavistic theory of cancer)
- Loss of control of differentiations: do all cancers have in their evolution an epigenetic origin or an epigenetic mandatory step?
- Some is known of mutations in genes that control epigenetics (e.g., DNMT3A, TET2) in early leukaemogenesis, and of genes of cell metabolism (IDH1, IDH2) in cancers (AML, glioblastoma): can we propose a standard scenario linking perturbations of metabolism / of epigenetic control of differentiations / cancers?

Questions (continued)

- Energetic metabolism of the cell, intercellular communications and cancer: appearance of gap junctions in multicellularity and perturbations of physiological gap junctions, essential to multicellularity, in solid tumours? (*James Trosko*)

- Glycolytic vs. mitochondrial respiratory phenotypes: do cancer cells shift easily from one to the other (in other words, does a tumour practice a form of metabolic *bet hedging*? *Gravenmier et al.* Bull. Math. Biol. 2017)

- What are the advantages and drawbacks of these 2 phenotypes? (efficiency of the TCA [=Krebs] cycle vs. rapidity of anaerobic glycolysis) When did appear the mitochondrial respiratory chain as a necessary condition for the physiological establishment of reliable intercellular communications?

Questions (continued)

- What is more relevant for stress response of a cell population (adaptable, as in the case of a tumour): maintain a subpopulation of all-stress resistant cells, or maintain a subpopulation of cells expressing 'cold genes' and able to launch different resistance mechanisms in different cells? (... stochastically chosen?)

- *Bet hedging* as a 'tumour strategy' to diversify its responses to deadly stress (as high doses of cytotoxic drugs) by launching different stress response mechanisms in different cells? (ABC transporters, detoxication enzymes, blocking influx, DNA repair)

- Stress response through derepression of *cold genes*? *Wu et al.* PNAS 2015: existence of very ancient genes, constituted in a remote past of our planet, able to put at work des survival programs in a state of emergency, with *bet hedging*, in a cancer cell population?

- Does *bet hedging* shuffle phenotypes, setting favorable bases for the emergence of innovative specialisation (*Michod et al.*) and cooperativity in tumours (*Tabassum & Polyak, Polyak & Marusyk*), making them viable?

- Bet hedging setting for $n(x, y, \theta, t)$, with x=fecundity, y=viability, θ=plasticity:

$$n_t + \nabla \cdot \{V(x, y, \theta, D)\, n\} = \alpha(\theta) n_{xx} + \beta(\theta) n_{yy} + n \left\{ r(x, y, \theta) - \frac{\rho(t)}{C(x, y)} - \mu(x, y, \theta, D) \right\}$$

Questions (continued)

- Phenotypic heterogeneity of cancer cell populations in a same tumour in the case of stress response: result of primary massive de-differentiation?

- "Maintenance of phenotypic heterogeneity within cell populations is an evolutionarily conserved mechanism that underlies population survival upon stressful exposures." (*Guler et al.* Cancer Cell 2017) Chromatin regulators as 'cold genes' aiming at maintaining a subpopopulation of resistant cells in case of extreme, life-threatening, stress?

- Role of transposable elements (repeat sequences) in the maintenance of such heterogeneity? "In the context of evolution, activation and propagation of transposable elements enables organisms to adapt to changing conditions by generating genomic diversity (...), but can also result in reduced fitness." (*Guler et al.* Cancer Cell 2017)

A few articles that open tracks and challenges

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A few articles that open tracks and challenges

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A few articles that open tracks and challenges

3. *Sui Huang: the Waddington epigenetic landscape revisited*

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A few articles that open tracks and challenges

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A few articles that open tracks and challenges

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A few articles that open tracks and challenges

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One may also consult a few personal articles

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