ATAC 2022: Seminar on the atavistic theory of cancer

From mathematical modelling by structured cell population dynamics for cancer plasticity to philosophy of cancer: role of the atavistic theory

*Jean Clairambault**

Mamba INRIA team, Laboratoire Jacques-Louis Lions, Sorbonne Université, Paris

Grenoble University, June 8-9, 2022

Joint work at LJLL with Frank E Alvarez Borges, José Antonio Carrillo, Rebecca Chisholm, Tommaso Lorenzi, Alexander Lorz, Camille Pouchol and Emmanuel Trélat

* *http : //who.rocq.inria.fr/Jean.Clairambault/Jean_Clairambault_en.html*

SORBONNE UNIVERSITÉ Inria Mamba MODELLING AND ANALYSIS FOR MEDICAL AND BIOLOGICAL APPLICATIONS JJL cnrs Université Paris Cité

Cancer puzzle: beyond intracellular signalling pathways

- Cancer is a disease of multicellular organisms: save for known molecular events (CML, APL, Ewing sarcoma), there are no *determinants* of cancer in a single cell
- Cancer is a localised *loss of cohesion* between cells and tissues in a multicellular organism: loss of control on differentiations, prior to uncontrolled proliferation
- What is coherence/cohesion within/between cells and tissues made of in a multicellular organism? Why and how is it disrupted in cancer?
- Disrupted expression of genes in cancer hits genes of multicellularity (Domazet-Lošo & Tautz 2008, 2010, Trigos et al. 2017, 2018, 2019)
- The atavistic hypothesis of cancer by Davies, Lineweaver and Vincent (2011) sets a *reverse* evolutionary origin for the emergence of cancer cell populations

Plan of the talk

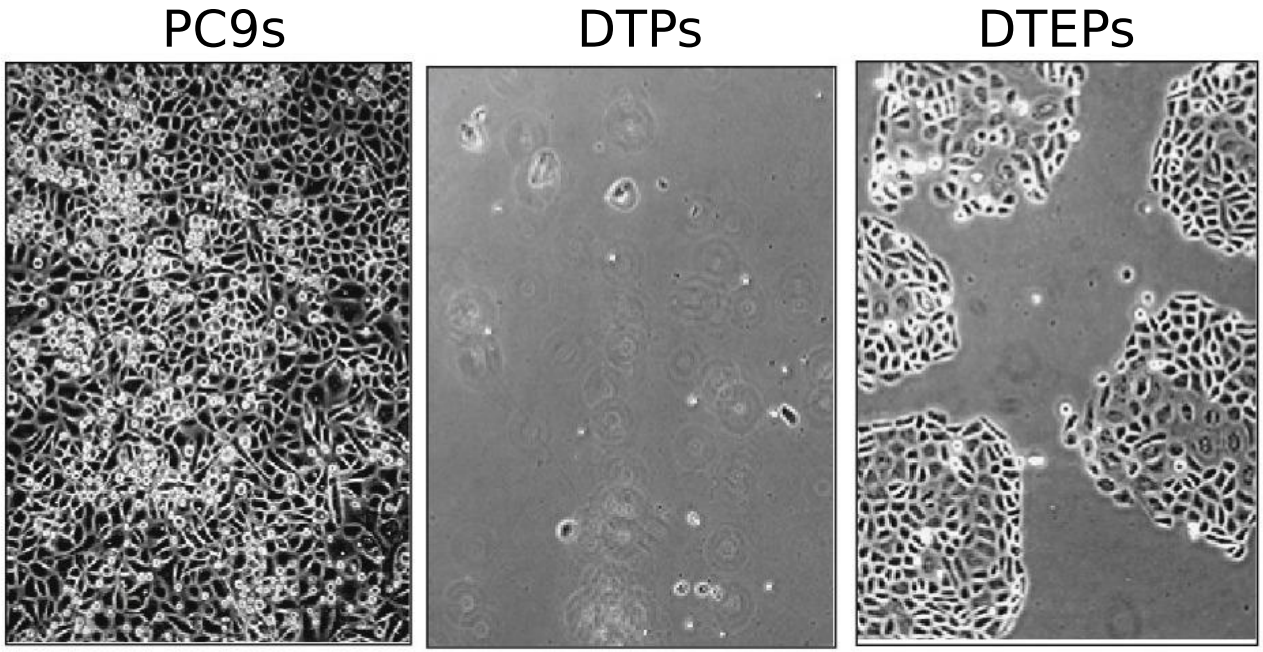
1. Cell plasticity in development and in cancer
2. Modelling cell population plasticity by structured equations
3. Theoretical therapeutics
4. Multicellularity and atavism

1. Cell plasticity in development and in cancer

- Non-genetic mechanisms of plasticity in cancer
- Plasticity *is* relaxation or loss of control on differentiations
- The Waddington landscape and beyond
- Another metaphor for the tree of differentiations

Evidence of cell plasticity in cancer: non-genetic mechanisms

- 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:
  Drug Tolerant Persisters, DTPs
- In the same hostile environment, 20% of DTPs resume proliferation:
  Drug Tolerant Expanded Persisters, DTEPs
- Total reversibility to drug sensitivity is obtained by drug withdrawal, occurring after 9 doubling times for DTPs, and 90 doubling times for DTEPs
- Inhibition of epigenetic enzyme KDM5A blocks emergence of DTPs



(Sharma et al. Cell 2010, modelled in Chisholm et al. Cancer Research 2015)

Genetic mutations or phenotypic switches?

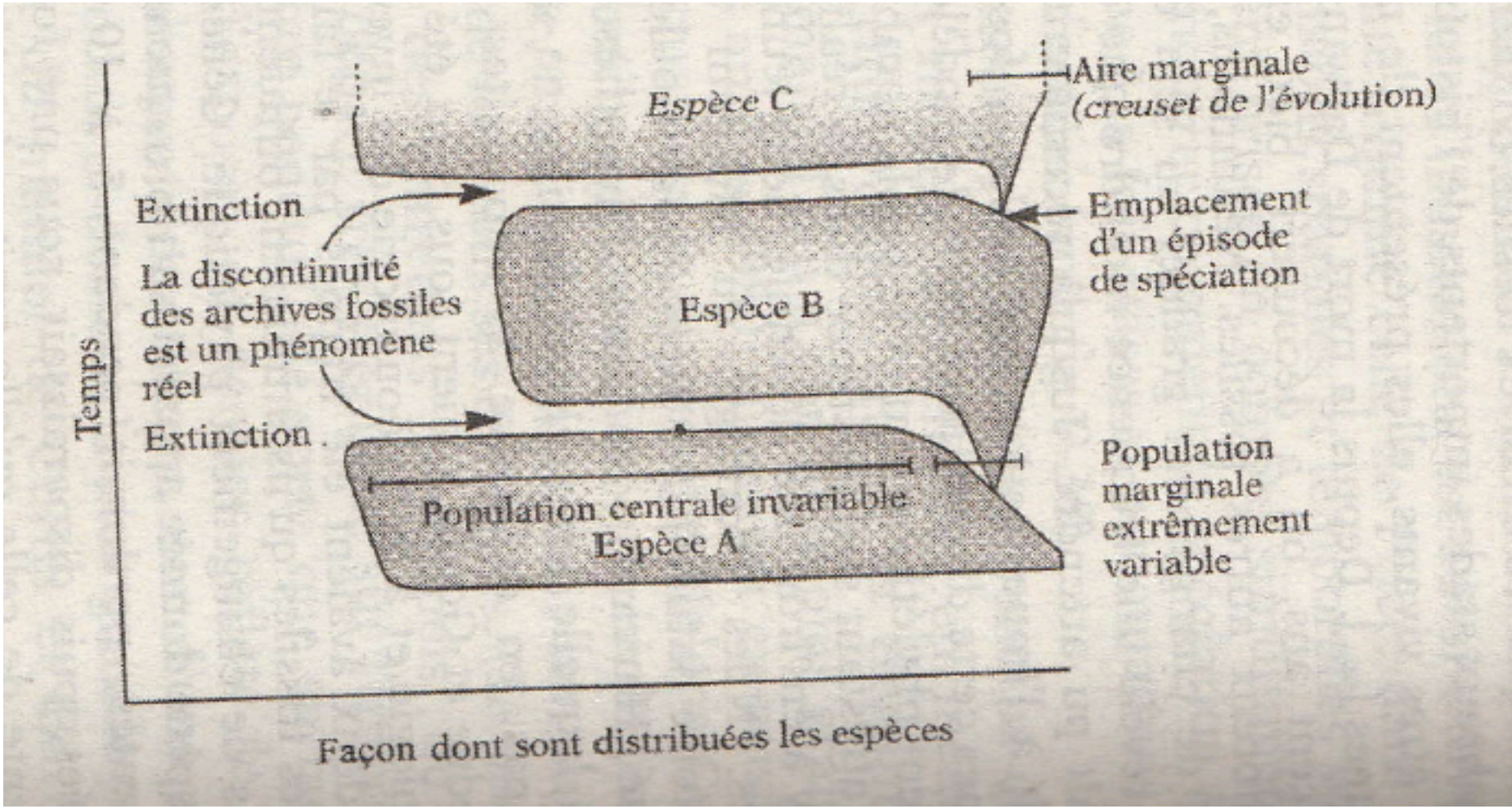
- EMT/MET and *drug persistence* (if a *prolonged* drug-insensitive subpopulation can be identified), or *drug tolerance* (if the whole population is concerned by *transient* treatment escape), are non-genetic adaptive, *reversible* mechanisms that rely on environment-induced phenotypic switches...

- ... Whereas the expression *drug resistance* today most frequently assumes established, *irreversible*, genetic mutations. However, I will use in the sequel resistance as a generic term for persistence, tolerance or resistance.

- Anyhow, cannot *prolonged tolerance* induce generalised *stable persistence*, that itself may promote (by selection on genetically instable cells) irreversible drug resistance by mutations? (Think of SJ Gould's punctuated equilibria)

- Indeed, it has been reported that epigenetic silencing by methylation makes single nucleotide C to T mutations on the DNMT3A locus highly probable, entraining in turn more epigenetic alterations *(You & Jones Cancer Cell 2012)*.

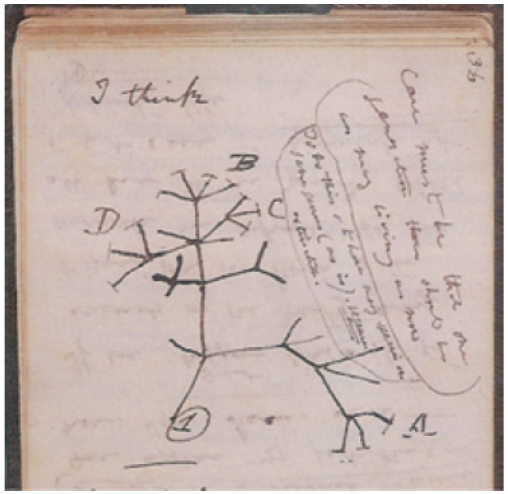
Punctuated equilibria in evolution: evolutionary rescue



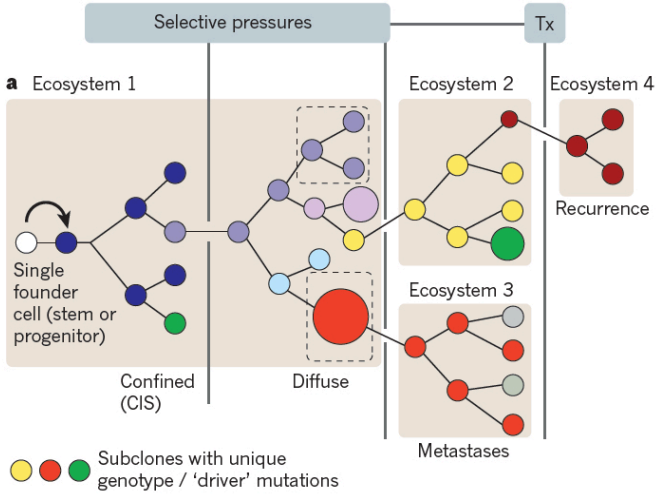
(SJ Gould 'Punctuated equilibrium' 2007, citing PW Price 'Biological evolution' 1996)

Mutations and evolutionary branching in solid tumours

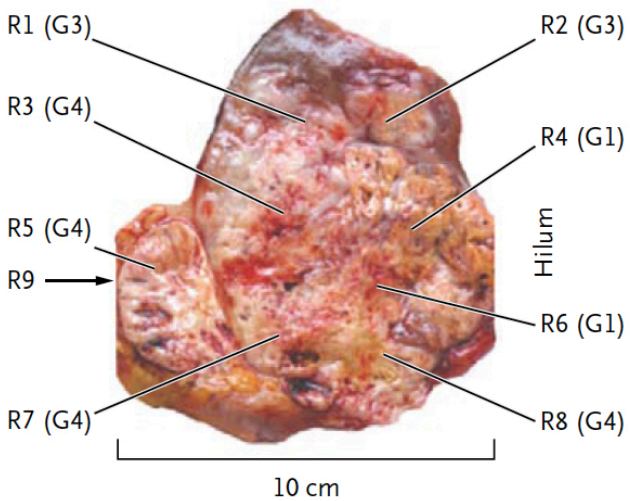
... A vision completely compatible with further spatially localised genetic heterogeneity

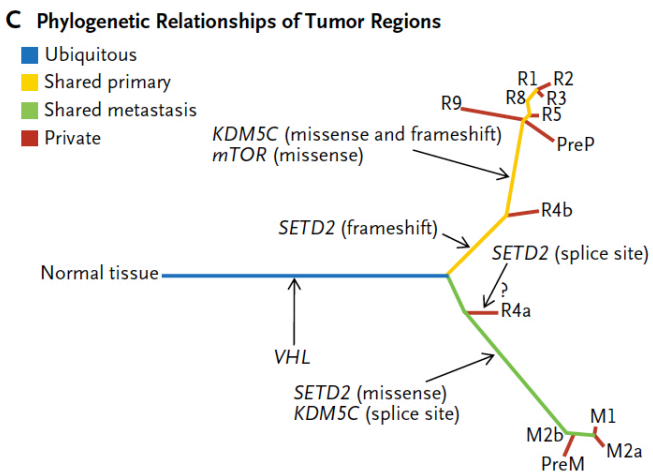


Darwin's notebook 1837



Maley & Greaves Nature 2012





Gerlinger et al. NEJM 2012

Physiological framework: development and tissue repair

- In development (in particular in embryogenesis), physiological cell populations are initially functionally indeterminate and very plastic; they depend for their differentiation on the genetic programme they bear in their genome and on close interactions (contact, delta/notch, connexons?) between neighbouring cells.

- Such plasticity is epigenetically determined (differentiation is obviously of epigenetic nature), transient during development, but can be reactivated under physiological circumstances such as tissue repair. In particular some vertebrate species (e.g., axolotl) are able to regenerate a missing limb.

- The possibility of de-differentiation, although normally repressed, is thus naturally present in the genome of all cells in multicellular organisms, and can easily be exploited by plastic cancer cells - *and not by healthy cells* - to adapt their phenotypes to a hostile environment (e.g., drug insult), or to the cancer invasion process through EMT, recovering normally lost motility in epithelia.

Plasticity in cancer *is* loss of control on differentiations

- Blockade of differentiation of the myeloid lineage leads to immature (myeloblast) cell proliferation in acute myeloid leukaemia (AML).
- Uncontrolled differentiation leads to immature cell proliferation in unclear histological zones: Barrett's oesophagus, ductal carcinoma in situ (DCIS).
- Transdifferentiation from interfollicular epidermis (IFE) cells to bulge cells, favours basal cell carcinoma (BCC) upon activation of the Hedgehog oncogenic pathway, and vice versa from BCC to an IFE/isthmus mixed cell state upon inhibition of Hedgehog (reviewed in Shen & *JC*, *F1000 Research* 2020).
- In castration-resistant prostate cancer, transdifferentiation of epithelial cells may lead to a neuroendocrine cellular type.
- Epithelial to mesenchymal transition (EMT) and its reverse (MET): normally differentiated epithelial cells are unable to move, a capacity mainly left to immune or mesenchymal cells (fibroblasts). De-differentiation of transformed epithelial cells into a mesenchymal state endows them with the mandatory motility to invade remote tissues where they re-acquire an epithelial state and proliferate, making metastases.

Cancer stem cells? Not always needed

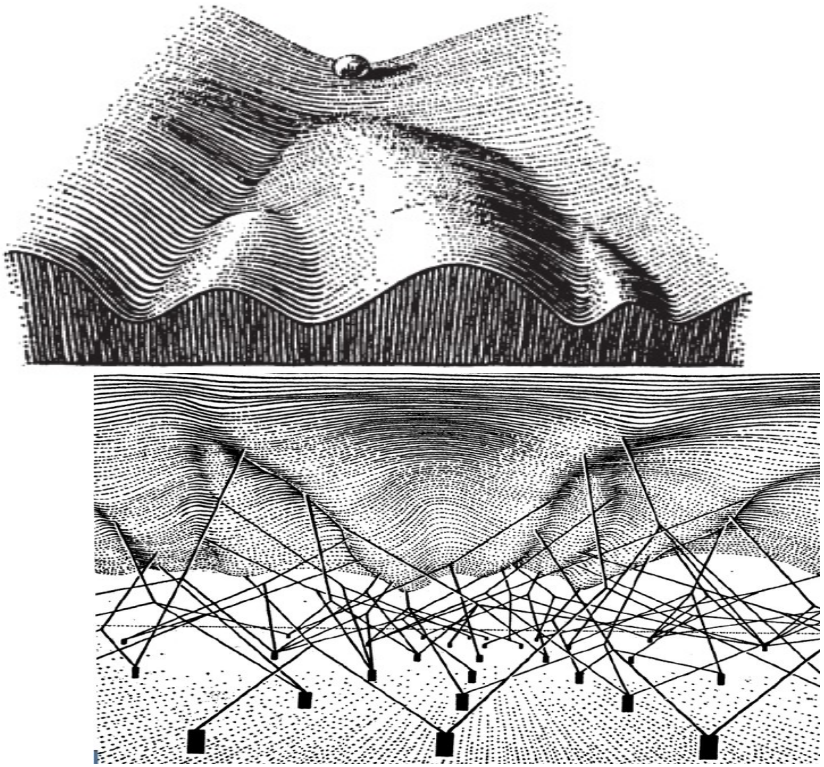
- Cancer stem cells have been proposed to be at the origin of cancers. This may be so for a number of cancers, however not for all of them.

- In particular, cancer may occur at intermediate stages of differentiation, as in the case of acute myeloid leukaemia, AML3 in the old French-American-British (FAB) classification. For instance, reestablishing impaired differentiation by ATRA at the promyelocytic stage (AML3, aka APL) of myeloid differentiation cures the disease.

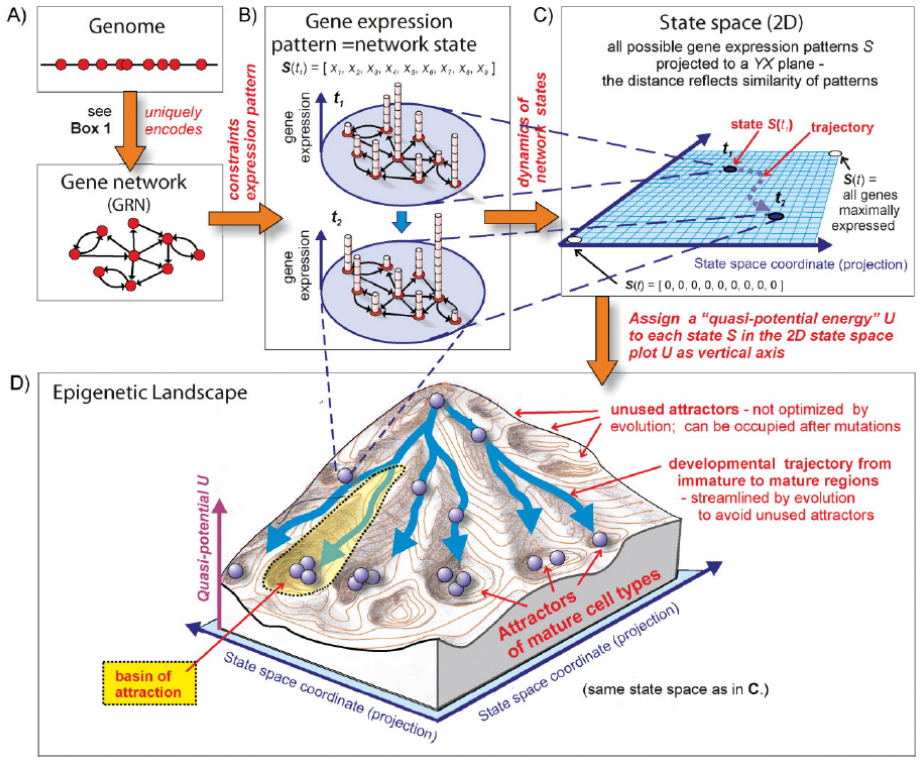
- Differentiation control may thus be altered at any differentiation stage, stem cell state and many others downstream the cell differentiation flows without mandatorily involving stem cells.

A classic evolutionary framework (*life-term view*) revisited: the Waddington epigenetic landscape with systems biology

The classic Waddington landscape ("The strategy of genes", 1957): differentiation of cells *within a given organism*

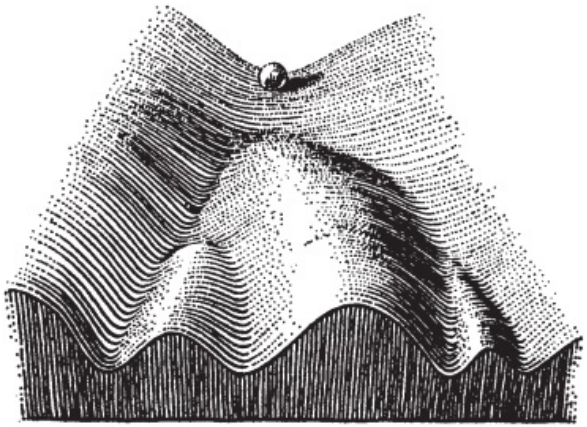


Waddington landscape revisited by S. Huang (2011, 2012, 2013)

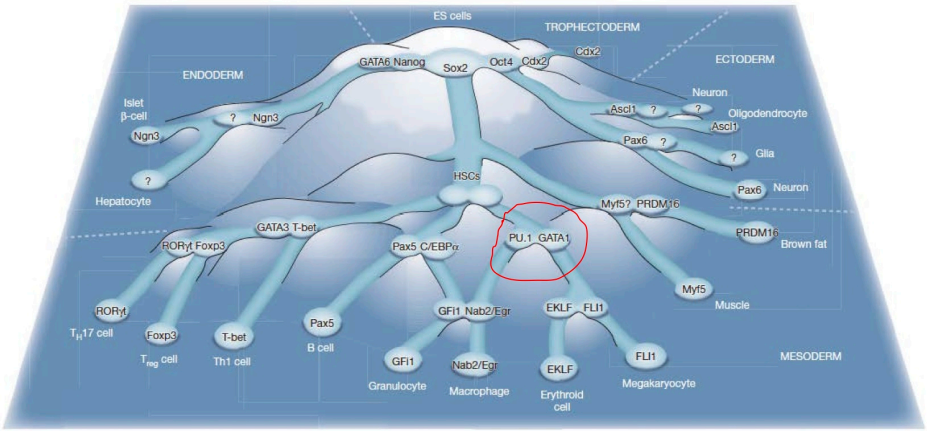


"Nothing in evolution makes sense except in the light of *systems* biology" (S. Huang 2012)

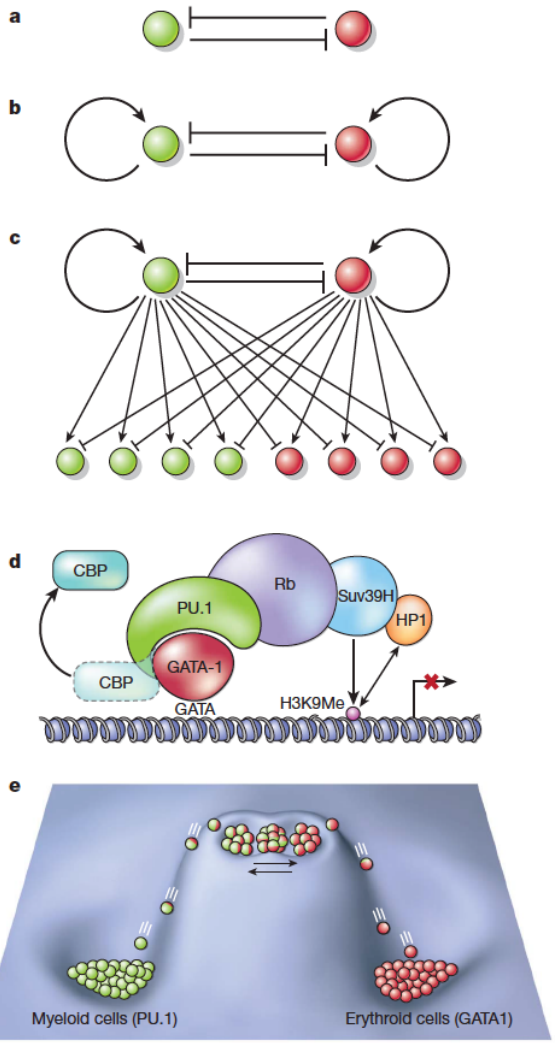
Milestones to reconstruct the global differentiation landscape



[Classic Waddington landscape]



Stem cell fate: modern version by Tariq Enver *(ASH meeting 2011)*



Zoom on the PU.1/GATA1 node (for equations and bifurcations, see Huang, Guo, May & Enver *Devel Biol 2007*)

Sketch of the first stages of multicellularity in evolution

- Emergence of multicellularity appeared several times in evolution, with possible species extinction, and there are cases in which it may be considered as optional, e.g., in Volvocine green algae (*Volvox carteri*), which have evolved from colonies of unicellular *Chlamydomonas rheinhardti*, with many known intermediate states.

- Primitive multicellular organisms, such as the sponges *Porifera* (closest existing descendants of the *"Urmetazoa"*, according to *Müller et al. 2001*), have been extensively studied. Although endowed with about only 20 cell types (200 to 400 in Humans), they share fundamental characteristics at the molecular stage: cell-cell and cell-matrix adhesion molecules, morphogens, transcription factors, tight-junction proteins, which make them able to separate their organised colonies of cells in a cohesive individual from the extracellular environment.

- Furthermore, although they have not proper organs, sponge cells have the ability to differentiate, they are endowed with an apoptotic machinery, and, most of all, they have an immune system, an essential capability to distinguish friend and foe, and thus to define a coherent individual.

- The existence of tumours has not been documented thus far in *Porifera*, but it has been evidenced in *Hydra* (*Ćetković 2018*), a rather primitive non-bilaterian Metazoan, which may hint to the expected fact that all multicellular organisms may be prone to develop cancer. On the contrary, it makes little sense to try and characterise cancer in unicellular organisms.

What makes an individual in the animal kingdom

- Although sexual reproduction may be bypassed in a variety of animals under particular circumstances, it is the rule in Metazoa, and the zygote (fecundated egg by the union of male and female gamete, *Wolpert & Szathmáry 2002*) is the primitive cell containing coded in its genome the *Bauplan* (or body plan), i.e., the design program mandatory to build a coherent isogenic multicellular organism (*Müller et al. 2004*). It has no other existence than the one of a program of instructions written in genetic code.

- The production of cellular matter by successive divisions from the zygote, conserving in each new cell the *Bauplan*, transmitting and updating *positional information* (*Wolpert 2011*) to the descendants, and on the other hand obeying physical laws of fluid dynamics (*Collinet & Lecuit 2020*), is the basis of embryological development, which by successive differentiations yields in evolved animals the different terminal cell types, basis of the anatomic organs that support the great physiological functions.

- To ensure compatibility between tissues and cooperativity between organs and functions, which is arguably from a teleological viewpoint what multicellularity is made for, i.e., division of work (as it is at higher levels of evolution, in anthropology and in sociology), molecular mechanisms of cohesion between tissues and of coherence between signals must exist all along the process of development and organism maintenance, i.e., such molecular mechanisms must also be coded by instructions in the *Bauplan*.

A generalisation of the immune system to maintain cohesion

- The immune response, humoral and cellular, is a manifestation by armed force (a police) of the maintenance of such coherence, which is (the common law tables) made of an ensemble of intercellular gene regulatory networks (GRNs, *Davidson, Erkenbrack, Peter 1995,... 2017*) that guides embryological construction by controlling epigenetic mechanisms of differentiation, and maintenance of this coherence in the terminally developed individual. These law tables, to which the immune response elements are plain servants, may be seen as a natural extension of the immune system as the coherence framework of the organism.

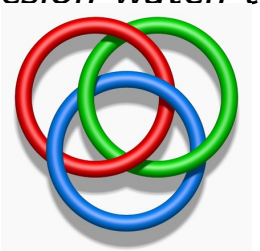
- When cell differentiation is (locally) out of control, immature cells endowed with a high proliferation potential may accumulate, de-differentiate or transdifferentiate, also escaping mechanisms of proliferation control, and thus reverting to their fundamental program, which is by default proliferation (*Soto & Sonnenschein 2004*, cited in particular by Marta Bertolaso, *Philosophy of cancer 2012*, about TOFT as opposed to SMT), secondarily escaping all the control mechanisms that make the law of coherence of a multicellular organism.

- Cancer may thus be seen as a *deunification of the individual* (*Pradeu 2019*), usually starting from a precisely located anatomical tissue, on which differentiation mechanisms of control are impaired. Note that for Pradeu, such coherence is ensured by the "good immunitary glue", which is completely true from the point of view of the effector mechanisms, nevertheless masking the real (hidden and widely unknown) coherence system of intercellular GRNs in charge.

Differentiation control to make a multicellular organism coherent: yet another metaphor, the wickerwork basket

A fibre bundle (base, the Bauplan; fibres, the cell differentiation trees; at the rim of tips, terminally differentiated cells). Intertwining the trees that stem from the Bauplan are between-fibre connections (e.g., intercellular metabolic networks) that *control the coherence (in compatibility/cooperativity) of differentiations* (part of a proposed extended vision of the immune system, that makes the unity of the organism), making the *cohesion watch*, which is disrupted in cancer. These 3 elements: (1) Bauplan, (2) differentiation trees and (3) *cohesion watch* together make a Borromean knot.

JC Frontiers in Genetics 2020



Bauplan, differentiation fibres/trees and the cohesion watch

- The *Bauplan* is the program of construction, written in genetic code, contained in all nucleated cells, beginning with the fecundated egg, or zygote (we deal with animals). It contains a variable, namely positional information (Wolpert), that will give the organism its extent (size) and its anatomy (distribution of organs and functions). Its only materiality is the material with which it is written.

- The *fibres* are material trees of differentiation, made of differentiating cells, that instantiate the functions, together with their allocated organs, which make the building bricks of the organism. Biophysical fluxes of cellular matter in the cellular mass that they constitute together govern the processes by which organs and functions are created during early development.

- The *cohesion watch* is a (non-cellular, i.e., molecular, or nervous) system of communication, between cells and tissues and between cells within a given tissue, which ensures friend-or-foe recognition, compatibility and cooperativity leading division of work within the organism. It may be thought of as a set of law articles, that the immune cells have mission to make respect by all cells.

- The *cohesion watch* may thus be seen as part of an extended version of the immune system considered as both the law and the police, in which the immune *response*, humoral and cellular, is the 'immune cell police', maintaining organism cohesion by enforcing the 'common law', which is defined by the cohesion watch, imposed to all cooperator cells to ensure homeostasis of the organism.

Another illustration by a wickerwork of intertwined branches

Urban landscape in Singapore

What sort of disruptions may elicit cancer?

- Fibres may be fragile and break. For instance, in the case of acute myeloid leukaemia (AML), differentiation in the haemopoietic tree is blocked at different possible stages.Then immature cells accumulate at these stages and invade surrounding structures (bone marrow, then blood).

- This illustrates the fact that cancer is primarily loss of control on differentiations, here in the most abrupt way: blockade, by differentiation fibre break, a rough pathology of the vertical *cohesion watch* (along fibres).

- More commonly, loss of control on differentiations may be due to impaired connections between fibres. When neighbouring differentiation trees are not clearly determined (as in the case of histological poor separation between oesophagus and stomach epithelia, or duct and endometrium epithelia), then immature cells may develop and proliferate, uncontrolled.

- This illustrates again the fact that cancer is primarily loss of control on differentiations, but in a less abrupt way than by sheer blockade: poor intercellular communication control, a pathology of the transversal *cohesion watch* (between fibres).

Future therapeutic prospect: reformatting the *cohesion watch*? (i.e., reinforcing concord between stromal cells towards serving the health of the whole organism?)

- If we admit the necessary existence, within the immune system seen as *what sticks cells together* in a multicellular organism, of a *cohesion watch*, firstly virtual as principles of coherence within the genetic developmental program launched by fecundation, then material as a set of cohesive intercellular connections within the constituted organism, it remains for us to identify it (e.g., a system of molecular communications between metabolic networks?).

- This should lead us to investigate intercellular connections during development, i.e., during the first stages of embryogenesis that follow the Bauplan, and later during the following steps in which functionally defined trees (the great physiological functions of the organism) stem from the Bauplan. These connections should be conserved in some way in the adult multicellular organism to ensure its cohesion. Understanding them as generic elements of a global unifying system, part of the immune system, might be a help to recognise them.

- Then finding ways to enhance these connections, possibly but not necessarily by molecular therapies, would be the next step to design non-cell killing anticancer therapies, a goal that is still far ahead of us, but not unreachable.

2. Modelling cell populations by structured equations

- Modelling cell plasticity and drug resistance
- Adaptive dynamics: structured cell population models
- Emergence of multicellularity and bet hedging in cancer
- Optimal control and therapeutic strategies in oncology

Modelling cell plasticity and drug resistance in cancer

- 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.

- Intra-tumour heterogeneity, here meant as between-cell phenotypic variability within cancer *cell populations*, is a relevant setting to represent continuous evolution towards drug resistance in tumours.

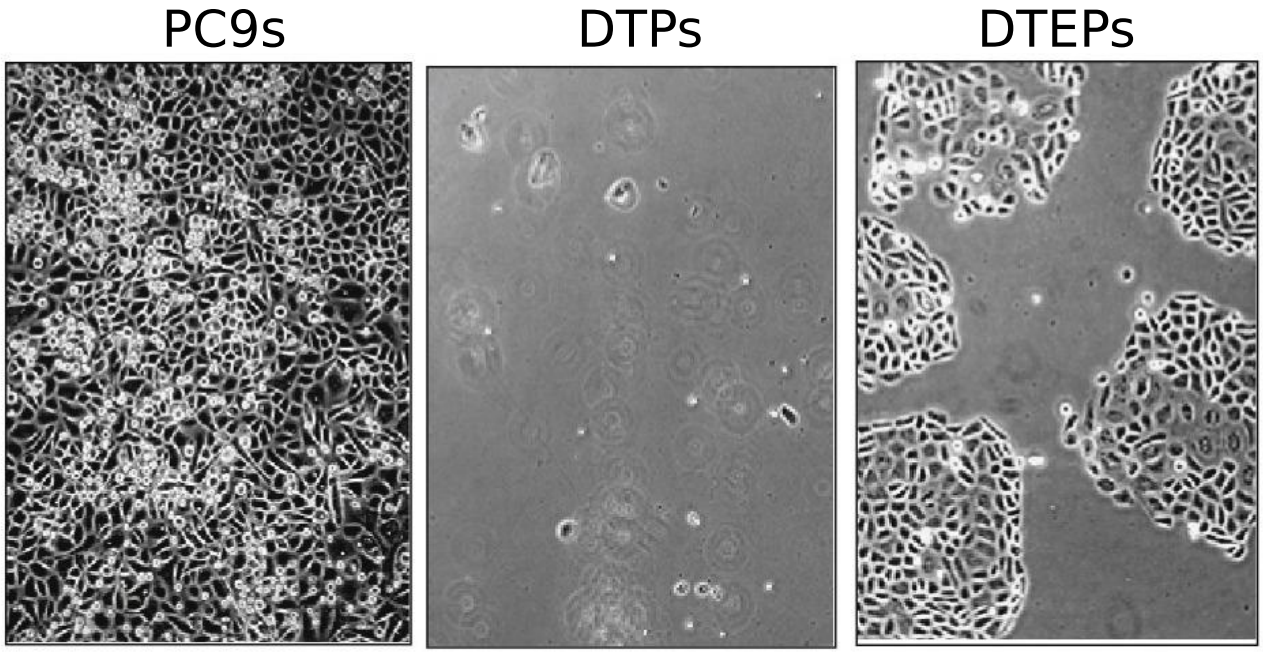
- *Plasticity* in cancer cells, i.e., propension of epigenetic nature to reversal to a de-differentiated status, and resulting adaptability of cancer cell populations, makes them able to *reversibly* resist abrupt drug insult as sharp stress response.

- Such *reversible* plasticity is captured by mathematical models (PDEs) that incorporate between-cell population heterogeneity by making use of structuring *continuous phenotypic variables*.

- These models are compatible with *optimal control* methods for the design of therapeutic strategies involving combinations of cytotoxic and cytostatic drugs, expression of drug resistance being such a continuous phenotypic variable.

Evidence of cell plasticity in cancer: non-genetic mechanisms

- 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:
  Drug Tolerant Persisters, DTPs
- In the same hostile environment, 20% of DTPs resume proliferation:
  Drug Tolerant Expanded Persisters, DTEPs
- Total reversibility to drug sensitivity is obtained by drug withdrawal, occurring after 9 doubling times for DTPs, and 90 doubling times for DTEPs
- Inhibition of epigenetic enzyme KDM5A blocks emergence of DTPs



(Sharma et al. Cell 2010, modelled in Chisholm et al. Cancer Research 2015)

2D continuous phenotype-structured PDE model

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

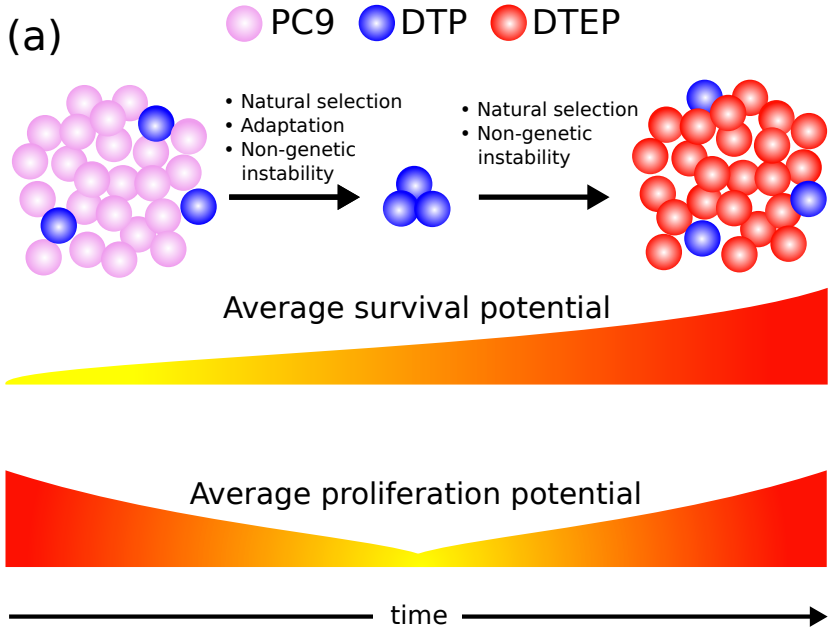
- Population density of cells $n(x, y, t)$ with phenotypic expression (x, y) at time t satisfies

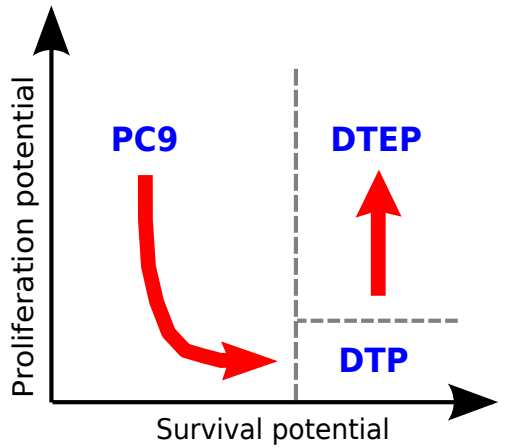
$$\frac{\partial n}{\partial t}(x,y,t) + \underbrace{\frac{\partial}{\partial y}\Big(v(x,c(t);\bar{v})n(x,y,t)\Big)}_{\text{Stress-induced adaptation of the proliferation level}} = \underbrace{\Big[p(x,y,\varrho(t)) - d(x,c(t))\Big]n(x,y,t)}_{\text{Non local Lotka-Volterra selection}} + \underbrace{\beta\Delta n(x,y,t).}_{\text{Non-genetic phenotype instability}}$$

- $\varrho(t) = \int_0^1 \int_0^1 n(x,y,t)\,dx\,dy$, $p(x,y,\varrho(t)) = (a_1 + a_2 y + a_3(1-x))(1-\varrho(t)/K)$ and $d(x,c) = c(b_1 + b_2(1-x)) + b_3$
- 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

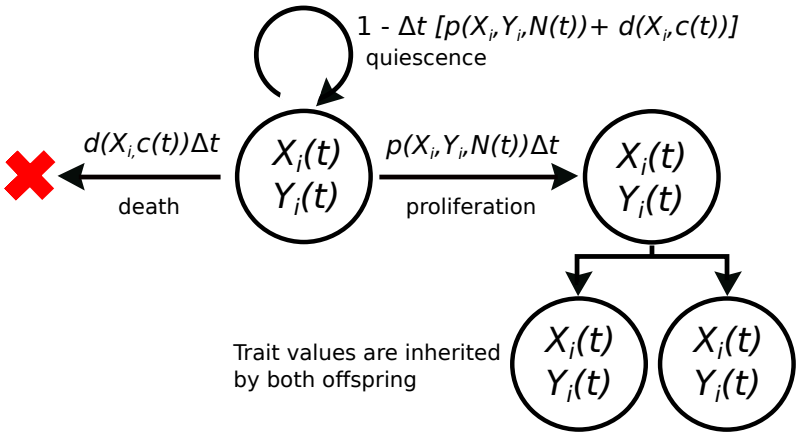
(Chisholm et al., Cancer Research 2015)

Agent-based model (ABM)





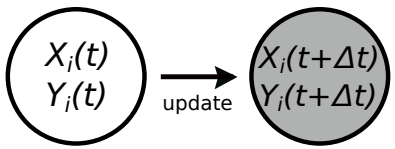
(a) Each cell i undergoes either proliferation, death or remains quiescent:



(b) Each cell i updates its trait values according to the discretised SDEs:

$$X_i(t+\Delta t) = X_i(t) + D\sqrt{\Delta t}\, W_i^1$$

$$Y_i(t+\Delta t) = Y_i(t) + D\sqrt{\Delta t}\, W_i^2 + \Delta t\, v(X_i, c(t))$$



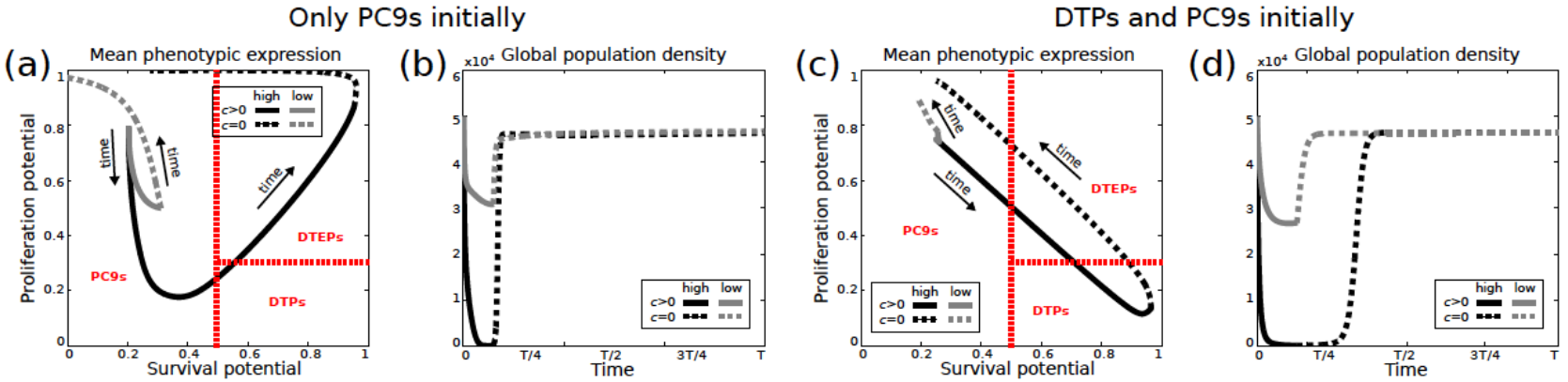
(Chisholm et al., Cancer Research 2015)

AB and PDE models recover the same phenotype dynamics

During drug exposure and after drug withdrawal: total recovery of drug sensitivity (either high or low drug dose)

2 scenarios studied:

(A) Initially no drug-tolerant cells (Lamarckian instruction)
(B) Initially a few drug-tolerant cells (Darwinian selection)



(a), (b) Only PC9s initially, adaptation on $v \neq 0$: *'Lamarckian adaptive' scenario* (A)

(c), (d) PC9s and DTPs initially, no adaptation $v = 0$: *'strict Darwinian' scenario* (B)

(Chisholm et al., Cancer Research 2015)

Use PDE model to address 3 questions

Q1. Is non-genetic instability (Laplacian term) crucial for the emergence of DTEPs?

Q2. What can we expect if the drug dose is low?

Q3. Could genetic mutations, i.e., an integral term involving a kernel with small support, to replace both adapted drift (advection) and non-genetic instability (diffusion), generate similar dynamics?

Consider $c(\cdot) = constant$ and two scenarios:

(i) (*'Darwinian' scenario (B)*: the dogma) PC9s and few DTPs initially, no adaptation ($v = 0$)

(ii) (*'Lamarckian' scenario (A)*: the outlaw) Only PC9s initially, adaptation present ($v \neq 0$)

To make a long story short, (simulations not shown)

Q1. Always yes! Whatever the scenario

Q2. Low drug doses result in DTEPs, but no DTPs

Q3. Never! Whatever the scenario

(Chisholm et al. Cancer Research 2015)

Summary of simulation results on the *Sharma et al.* paper

- Both mathematical models (ABM, PDE) reproduce the main experimental observations

- To see the transient appearance of the DTPs during high-dose drug therapy:

  - If there are **some DTPs** present initially, model explanation requires only
    - non-genetic instability
    - selection
  - If **no DTPs** are present initially, model explanation requires interplay between
    - stress-induced adaptation
    - non-genetic instability
    - selection

- Therapeutic consequences? Not clear yet. Epigenetic drugs? Not many of them exist (in particular no KDM5A inhibitor). Acting on epigenetics by modifying metabolism? Combining cytotoxic (inducing drug resistance) drugs and cytostatic drugs at low doses (in principle not inducing drug resistance)? Might be assessed using this model, not done yet.

Asymptotics of structured equations for heterogeneous populations

- Description of an evolving population *at time t and relevant phenotype (trait) x*
- 'Structure variable' x: trait chosen as bearing the biological variability at stake
- Variable : $n(t,x)$ population density of individuals bearing trait x at time t
- (1) Evolution in numbers of individuals constituting the population

$$t \mapsto \rho(t) = \int_0^1 n(t,x)\, dx \qquad \text{(if, e.g., } x \in [0,1]\text{)}$$

- (2) Asymptotics of distribution of the trait in the population

$$x \mapsto lim_{t\to+\infty} \frac{n(t,x)}{\rho(t)}$$

- Cancer cell populations: (1) tumour growth; (2) asymptotic distribution of trait

Adaptive dynamics: cell population asymptotic behaviour

Questions: what is the asymptotic behaviour ($t \to +\infty$) of

- the total population $\rho(t)$?
- the phenotypes in the population (*i.e.*, possible limits for $\dfrac{n(t,\cdot)}{\rho(t)}$ in $M^1(0,1)$)?

Nonlocal Lotka-Volterra integrodifferential model: $n(t,x)$ density of cells of phenotype (trait) $x \in [0,1]$:

$$\frac{\partial n}{\partial t}(t,x) = \big(r(x) - d(x)\rho(t)\big)n(t,x),$$

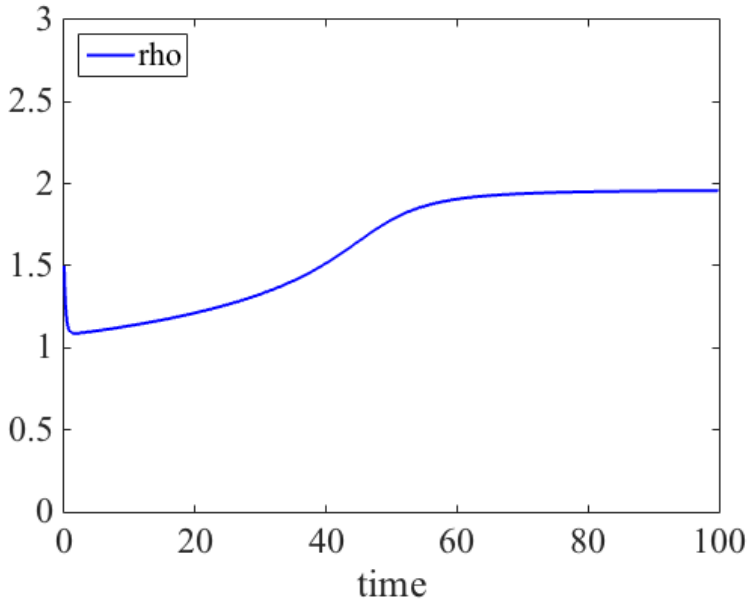
with

$$\rho(t) := \int_0^1 n(t,x)\,dx \quad \text{and} \quad n(0,x) = n^0(x).$$

We assume reasonable (C^1) hypotheses on r and d, and $n^0 \in L^1([0,1])$

Non-local Lotka-Volterra 1D model: time convergence in ρ

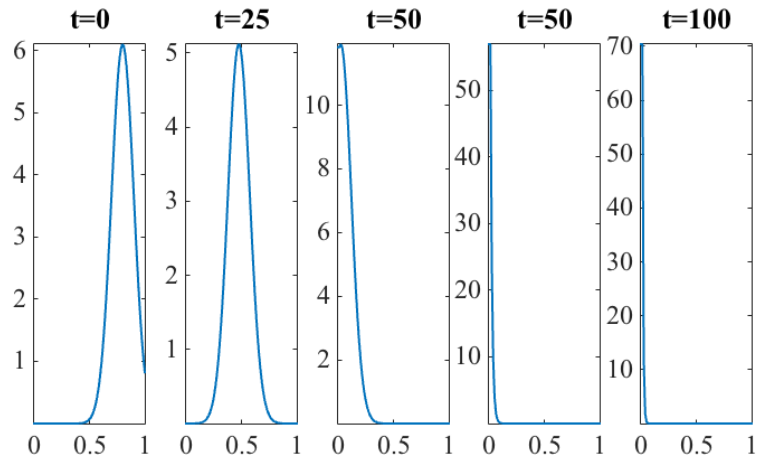
Convergence (one-population case): plot of $t \mapsto \rho(t) := \int_0^1 n(t,x)\,dx$



Firstly, it can be shown that: ρ converges to $\rho^\infty = \max_{[0,1]} \frac{r}{d}$, i.e., to the smallest value ρ such that $r(x) - d(x)\rho \leq 0$ on $[0,1]$.

Non-local Lotka-Volterra 1D model: concentration in x

Concentration (one population): Plot of $x \mapsto n(t,x)$ for different times t



Theorem

- *ρ converges to ρ^∞, the smallest value ρ such that $r(x) - d(x)\rho \leq 0$ on $[0,1]$.*
- *$n(t,\cdot)$ concentrates on the set $\{x \in [0,1],\ r(x) - d(x)\rho^\infty = 0\}$.*
- *Furthermore, if this set is reduced to a singleton x^∞, then*

$$n(t,\cdot) \rightharpoonup \rho^\infty \delta_{x^\infty} \ \text{ in } M^1(0,1).$$

The same result (time convergence in ρ and concentration in trait x) can be shown with two or more variables, see for two *Pouchol et al. J Maths Pures Appl 2018*, and for more *Pouchol & Trélat J Biol Dynamics 2018*

Non-local Lotka-Volterra 1D model: convergence (in ρ) and concentration (in trait x) using a Lyapunov functional

Although in the 1D case a direct proof of convergence based on a BV hypothesis may be obtained, from which concentration easily follows, it is interesting to note, *as this argument can be used in the case of 2 populations*, that a global proof based on the design of a Lyapunov function gives at the same time convergence and concentration: choosing any measure n^∞ on $[0,1]$ such that $\int_0^1 n^\infty(x)\,dx = \rho^\infty = \max_{[0,1]} \frac{r}{d}$, and for an appropriate weight $w(x)$ $(= \frac{1}{d(x)}$, P.-E. Jabin & G. Raoul, *J Math Biol 2011*), setting

$$V(t) = \int_0^1 w(x)\left\{n(t,x) - n^\infty(x) - n^\infty(x)\ln n(t,x)\right\}\,dx,$$

one can show that

$$\frac{dV}{dt} = -(\rho(t) - \rho^\infty)^2 + \int_0^1 w(x)\left\{r(x) - d(x)\rho^\infty\right\} n(t,x)\,dx,$$

which is always nonpositive, tends to zero for $t \to \infty$, thus making V a Lyapunov functional, and showing at the same time convergence and concentration. Indeed, in this expression, the two terms are nonpositive and their sum tends to zero; the zero limit of the first one accounts for convergence of $\rho(t)$, and the zero limit of the second one accounts for concentration in x (on a zero-measure set) of $\lim_{t\to+\infty} n(t,x)$.

[See Pouchol et al., *J Maths Pures Appl* 2018]

Another Lotka-Volterra model with advection and diffusion to represent *bet hedging* using a 3D phenotype structuring

Bet hedging as a 'tumour strategy' to diversify its phenotypes in response to deadly stress (cytotoxic drugs) Let $D = \Omega \times [0,1]$, where $\Omega := \{C(x,y) \leqslant K\}$ (a constraint between traits x and y). The evolution of a plastic cell population $n(z,t)$ structured in a 3D phenotype z =(x,y,θ), where x=viability, y=fecundity, θ=plasticity is given by

$$\partial_t n + \nabla \cdot \Big(Vn - A(\theta)\nabla n \Big) = (r(z) - d(z)\rho(t))n,$$

with (Vn-A(θ)$\nabla n\Big) \cdot \mathbf{n} = 0$ for all $z \in \partial D$; $n(0,z) = n_0(z)$ for all $z \in D$, where $\Omega = \{(x,y) \in [0,1]^2 : (x-1)^2 + (y-1)^2 > 1\}$, and the diffusion matrix

$A(\theta) = \begin{pmatrix} a_{11}(\theta) & 0 & 0 \\ 0 & a_{22}(\theta) & 0 \\ 0 & 0 & a_{33} \end{pmatrix}$, with a_{11} and a_{22} non decreasing functions of θ, gives the speed at which non-genetic epimutations occur, otherwise said, it is a representation of how the internal plasticity trait θ affects the non-genetic instability of traits x and y, by tuning the diffusion term $\nabla.\{A(\theta)\nabla n\}$; the advection term

$$\nabla.\{V(t,z)n\} = \nabla.\{(V_1(t,z), V_2(t,z), V_3(t,z))n\}$$

represents the force of external evolutionary pressure on the population, i.e., changes in the environment; and $\rho(t) = \int_D n(t,z)dz$ stands for the total amount of individuals in the population at time t.

(FE Alvarez Borges, JA Carrillo, JC, in revision)

Bet hedging as phenotypic divergence: numerics

The existence and unicity of solutions may be obtained by numerical methods showing convergence of the algorithms used to discretise the model. Illustrations may be obtained with instances of the functions used in the equations. For instance, to obtain phenotypic divergence (which we take as the basis of both bet hedging in cancer and of emergence of multicellularity in evolution) , we consider over the domain $D = \Omega \times [0, 1]$ an initial density given by the expression

$$n_0(z) = a 1_{\{f(z)<1\}} e^{-\frac{1}{1-f(z)}},$$

with $f(z) = \frac{\|z-z_0\|^2}{(0.025)^2}$, where $z_0 = (0.25, 0.25, 0.5)$ and $\|\cdot\|$ is the euclidean norm. We choose the value of a in such a way that $\rho_0 = \int_D n_0(z) = 1$.
We set the growth rate and the death rate as

$$r(x, y, \theta) = 1_{\{y>x\}} e^{-(0.1-x)^2-(0.9-y)^2} + 1_{\{x\geqslant y\}} e^{-(0.1-y)^2-(0.9-x)^2},$$

$$d(x, y, \theta) = \frac{1}{2}.$$

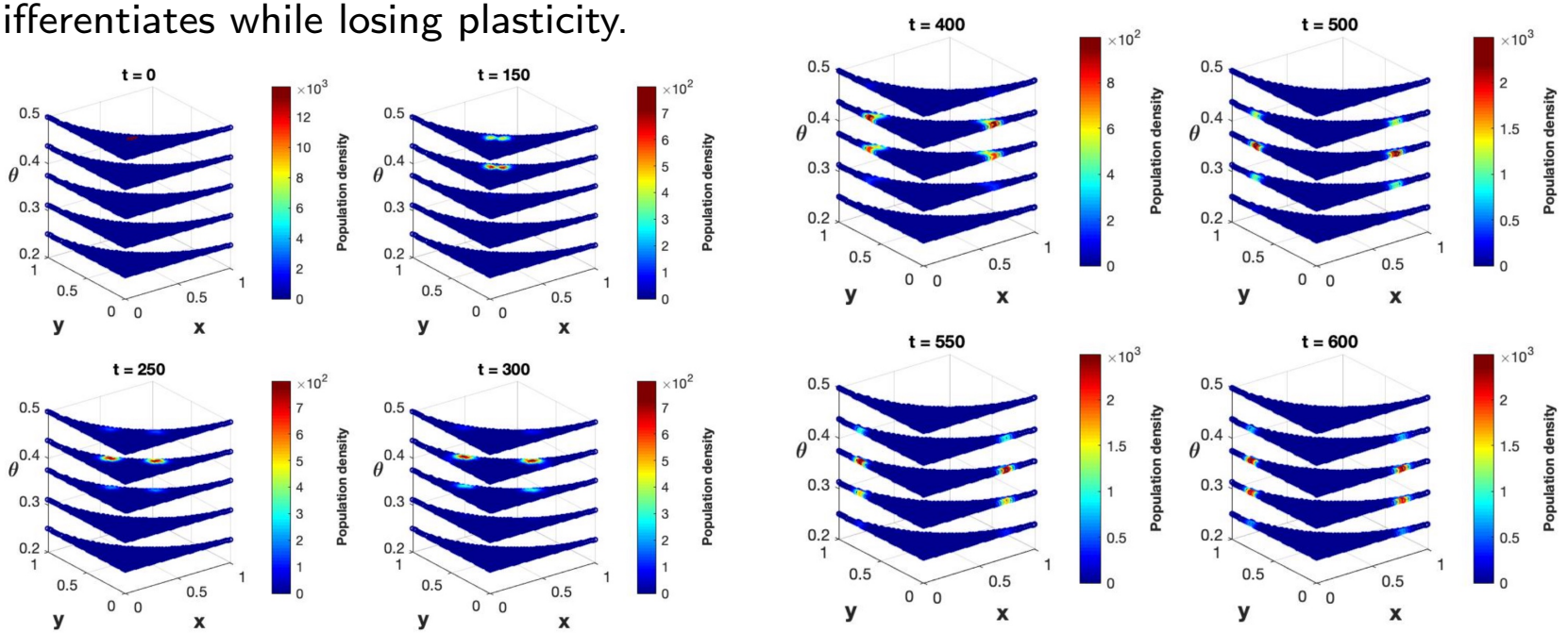
We choose the diffusion matrix

$$A(\theta) = \begin{pmatrix} (\theta+1)10^{-6} & 0 & 0 \\ 0 & (\theta+1)10^{-6} & 0 \\ 0 & 0 & 10^{-6} \end{pmatrix},$$

and the advection term $V(t, z) = 10^{-3}\theta(-y, -x, -(x + y))$

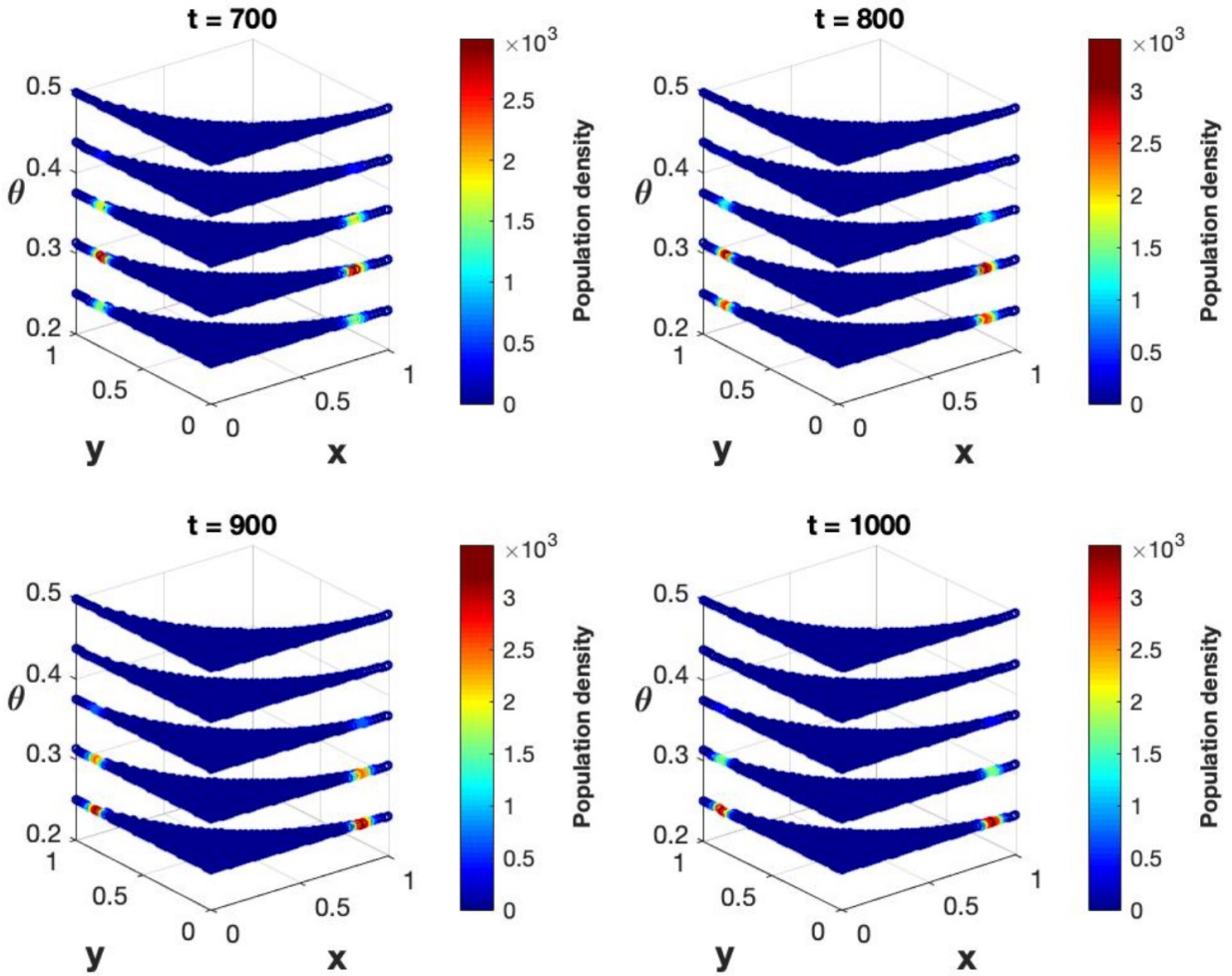
Phenotypic divergence: illustration (first stages)

The "push" towards specialisation imposed by V is inversely proportional to the current set of traits (individuals with traits (x, y) are specialising with a rate proportional to $(-y, -x)$). We see on the illustration below that initially the population is concentrated around the phenotype $z_0 = (0.25, 0.25, 0.5)$, and gradually differentiates while losing plasticity.



Initial stages of the population density for different values of θ: the differentiation process starts. At around $t = 250$ (bottom left) most of the population has already concentrated around the plasticity level $\theta = 0.4375$ and around $t = 300$ (bottom right) we observe that the migration towards a less plastic state continues. Around $t = 500$ most of the population has reached $\theta = 0.375$ and at subsequent times the migration continues.

Phenotypic divergence: illustration (final stages)



Final stages of the population density for different values of θ (end): around $t = 900$ (bottom left) the differentiation process is over and most of the population has reached the plasticity level $\theta = 0.25$. At $t = 1000$ (bottom right) we observe that the population concentrated around any other level of plasticity is almost extinct, and only the one around $\theta = 0.25$ survives.

FE Alvarez Borges, JA Carrillo, JC, in revision 2022

3. Theoretical therapeutics to circumvent drug resistance

- An integro-differential model for healthy and cancer cells
- Optimal control by combination of drugs
- Theoretical therapeutic strategies: illustrations

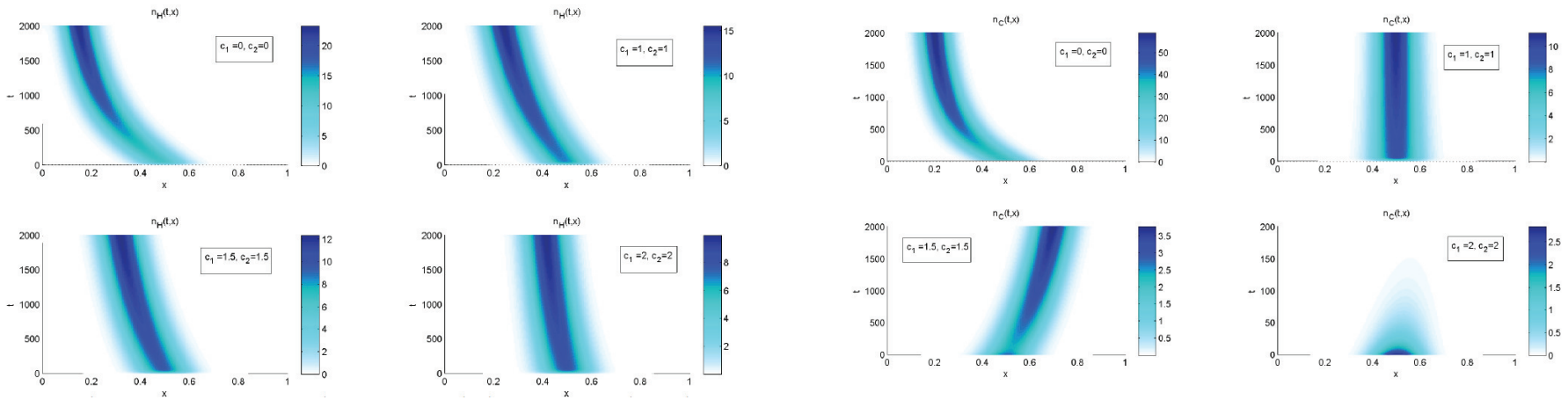
Non-local Lotka-Volterra model of treatment for 2 cell populations, 2 different drugs and a resistance phenotype x

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

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

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

[A kernel integral has been added for epimutations]

Cancer cells: eventually extinct

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

Asymptotic behaviour with constant controls

Following an argument by P.-E. Jabin & G. Raoul (*J Math Biol 2011*) we prove at the same time convergence and concentration by using a Lyapunov functional of the form

$$\int w(x)\left\{n(t,x) - n^\infty(x) - n^\infty(x)\ln n(t,x)\right\}\ dx$$

Theorem

(Asymptotic behaviour theorem, generalising to 2 populations the 1D case)
Assume that u_1 *and* u_2 *are constant:* $u_1 \equiv \bar{u}_1$, *and* $u_2 \equiv \bar{u}_2$. *Then, for any positive initial population of healthy and of tumour cells,* $(\rho_H(t), \rho_C(t))$ *converges to the equilibrium point* $(\rho_H^\infty, \rho_C^\infty)$, *which can be exactly computed as follows.*
Let $a_1 \geq 0$ *and* $a_2 \geq 0$ *be the smallest nonnegative real numbers such that*

$$\frac{r_H(x)}{1+\alpha_H \bar{u}_2} - \bar{u}_1 \mu_H(x) \leq d_H(x) a_1 \quad \text{and} \quad \frac{r_C(x)}{1+\alpha_C \bar{u}_2} - \bar{u}_1 \mu_C(x) \leq d_C(x) a_2.$$

Then $(\rho_H^\infty, \rho_C^\infty)$ *is the unique solution of the invertible* $(a_{HH}.a_{CC} >> a_{CH}.a_{HC})$ *system*

$$I_H^\infty = a_{HH}\rho_H^\infty + a_{HC}\rho_C^\infty = a_1,$$
$$I_C^\infty = a_{CH}\rho_H^\infty + a_{CC}\rho_C^\infty = a_2.$$

Let $A_H \subset [0,1]$ *(resp.,* $A_C \subset [0,1]$*) be the set of all points* $x \in [0,1]$ *such that equality hold in one of the inequalities above. Then the supports of the probability measures*

$$\nu_H(t) = \frac{n_H(t,x)}{\rho_H(t)}\,dx \quad \text{and} \quad \nu_C(t) = \frac{n_C(t,x)}{\rho_C(t)}\,dx$$

converge respectively to A_H *and* A_C *as* t *tends to* $+\infty$.

Cell-killing strategy preserving healthy cells: optimal control problem using this 1D phenotype-structured 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 $\rho_H(t) = \int_0^1 n_H(t,x)\,dx, \rho_C(t) = \int_0^1 n_C(t,x)\,dx$.

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

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

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

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

Optimal control problem: find controls (u_1, u_2) minimising in fixed horizon T

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

under the additional constraints

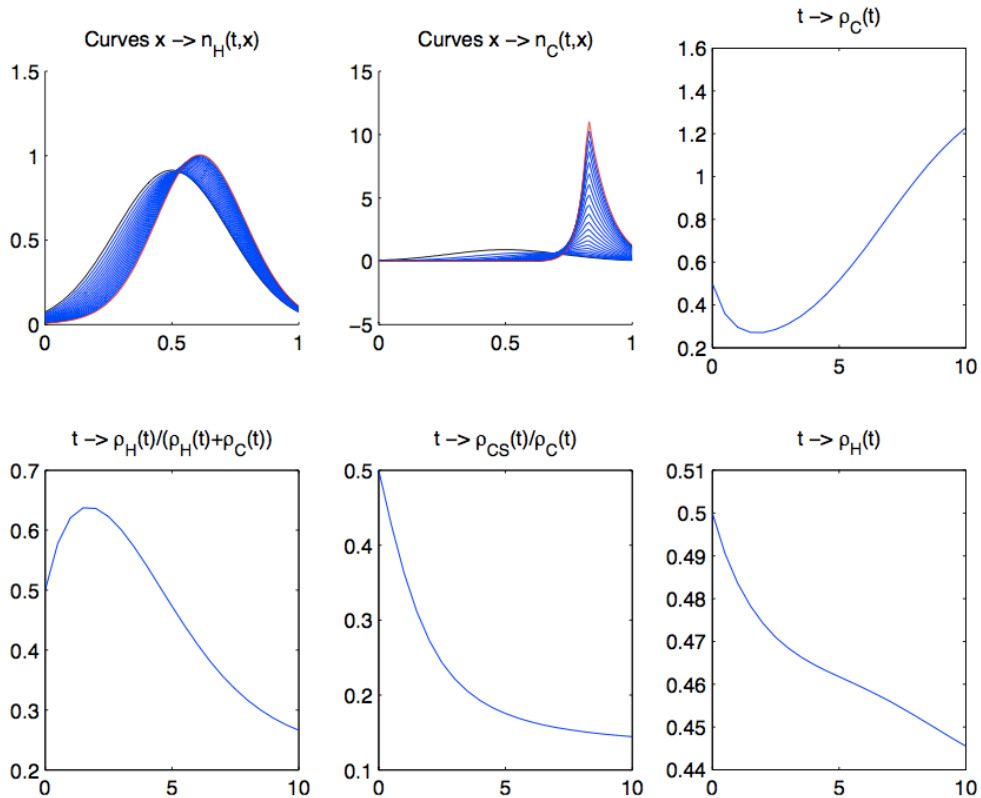
$$\frac{\rho_H(t)}{\rho_H(t)+\rho_C(t)} \ge \theta_{HC}, \qquad \rho_H(t) \ge \theta_H.\rho_H(0)$$

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

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 $T = 10$ yields a seemingly 'pessimal' solution:



- 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}.

Optimal control problem: theoretical results

Theorem
(Optimal control theorem)

The optimal therapeutic trajectory (u_1, u_2) in large time $T > 0$ consists of 2 parts: v

- a long-time part, with constant controls on $[0, T_1]$, at the end of which populations have almost concentrated in phenotype (for T_1 large);
- a short-time part on $[T_1, T]$ consisting of at most three arcs, for $T - T_1$ small:
  1. a boundary arc, along the constraint $\dfrac{\rho_H(t)}{\rho_H(t) + \rho_C(t)} = \theta_{HC}$,
  2. a free arc (no constraint saturating) with controls $u_1 = u_1^{\max}$ and $u_2 = u_2^{\max}$,
  3. a boundary arc along the constraint $\rho_H(t) \geq \theta_H . \rho_H(0)$ with $u_2 = u_2^{\max}$;
- the proof (C. Pouchol and E. Trélat) uses the Pontryagin maximum principle.

Simulations illustrating this theorem

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

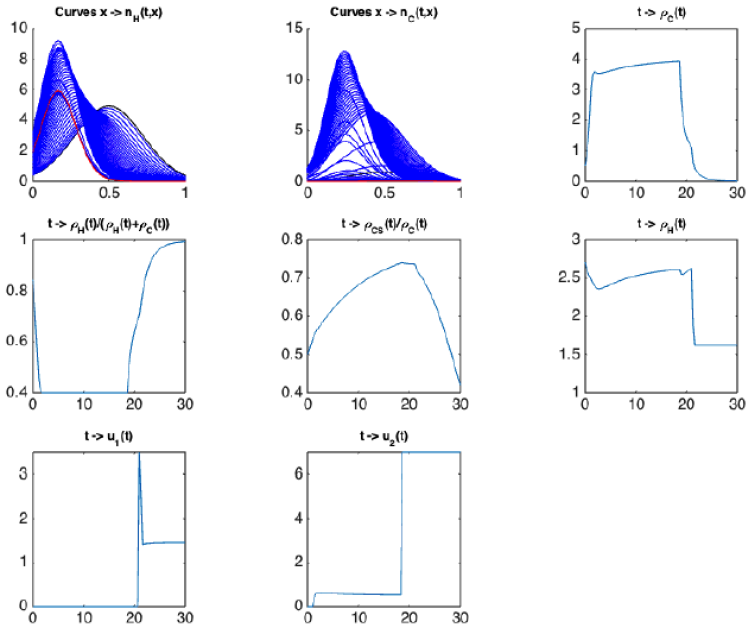


Figure 4: Simulation of (**OCP**) for $T = 30$.

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

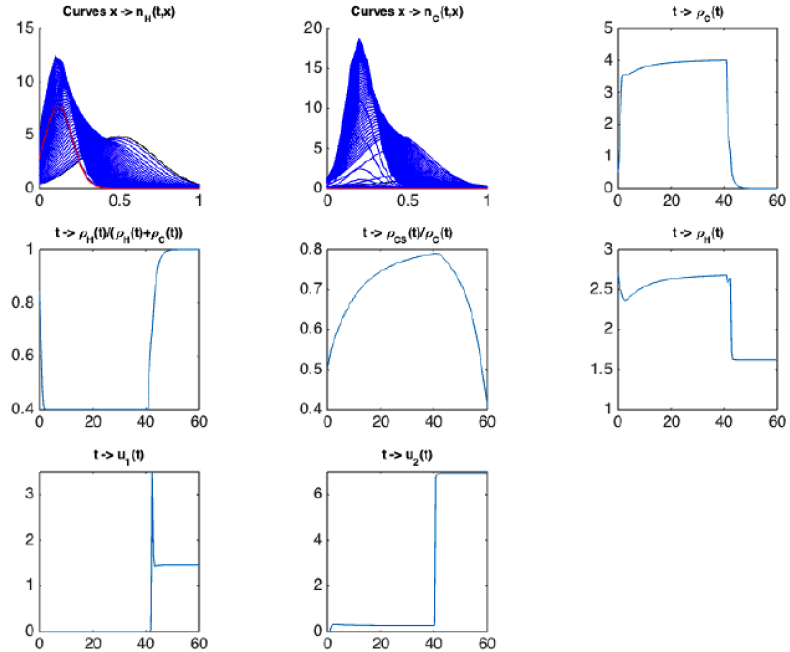


Figure 5: Simulation of (**OCP**) for $T = 60$.

Note that this strategy (drug holiday) lets the cancer cell population ρ_C grow initially to an equilibrium level, while increasing the ratio $\dfrac{\rho_{CS}}{\rho_C}$ of drug-sensitive cancer cells, before delivering $u_1 = u_1^{\max}$; only then is the cytotoxic efficacy maximal.

Comparison with "almost periodic" therapeutic strategies

1) Mimicking the clinic; 2) the same with saturation of the constraint $\rho_H = \theta_H.\rho_H(0)$

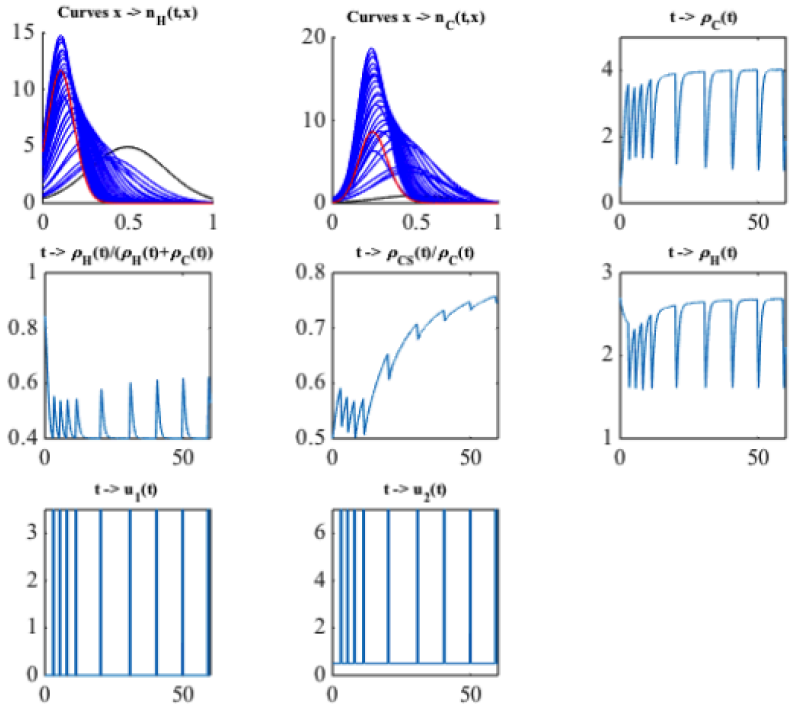


Figure 6: Quasi-periodic strategy, for $T = 60$.

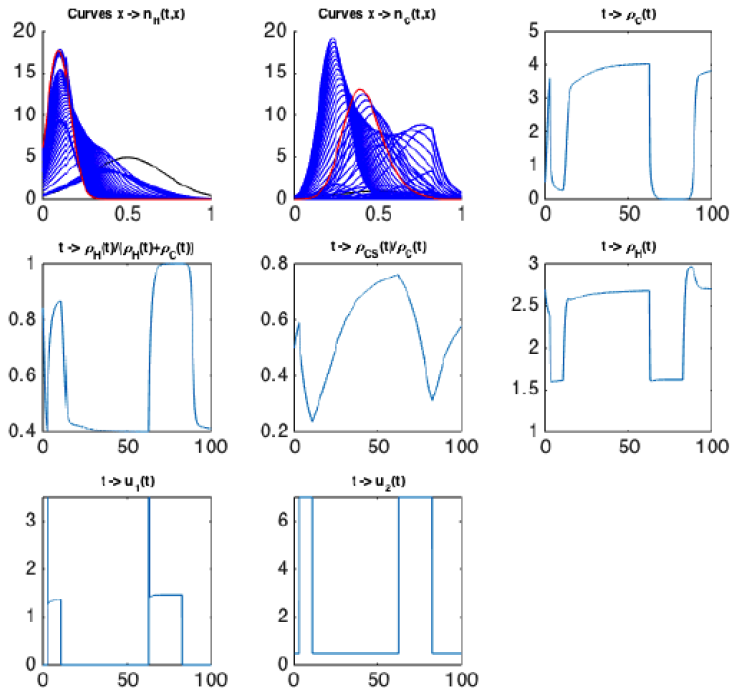


Figure 7: Second quasi-periodic strategy, for $T = 100$.

1) Left: (unsatisfying) periodic strategy: stabilisation of ρ_C only. 2) Right: second strategy, same, but *with added arc following the constraint* $\rho_H = \theta_H.\rho_H(0)$, with $u_2 = u_2^{max}$, and control u_1 obtained from the equality $\frac{d\rho_H}{dt} = 0$ (saturation of the constraint) and back to the drug holiday strategy $u_1 = 0$ as ρ_C starts increasing again: we see that ρ_C can be brought arbitrarily close to 0 (tumour eradication?).

4. Multicellularity and atavism

- Cellular stress to launch loss of control on differentiations
- The atavistic theory in a nutshell
- Atavism, mathematics and 'Philosophy of cancer'

Cellular stress-launched de-differentiation signals?

- Cellular stress is a cell state in which a cell threatened by a deadly environmental insult (drugs, UV radiations, hypoxia, etc.) launches a variety of response signals, with internal or external destination (*Nedelcu & Michod 2020*).

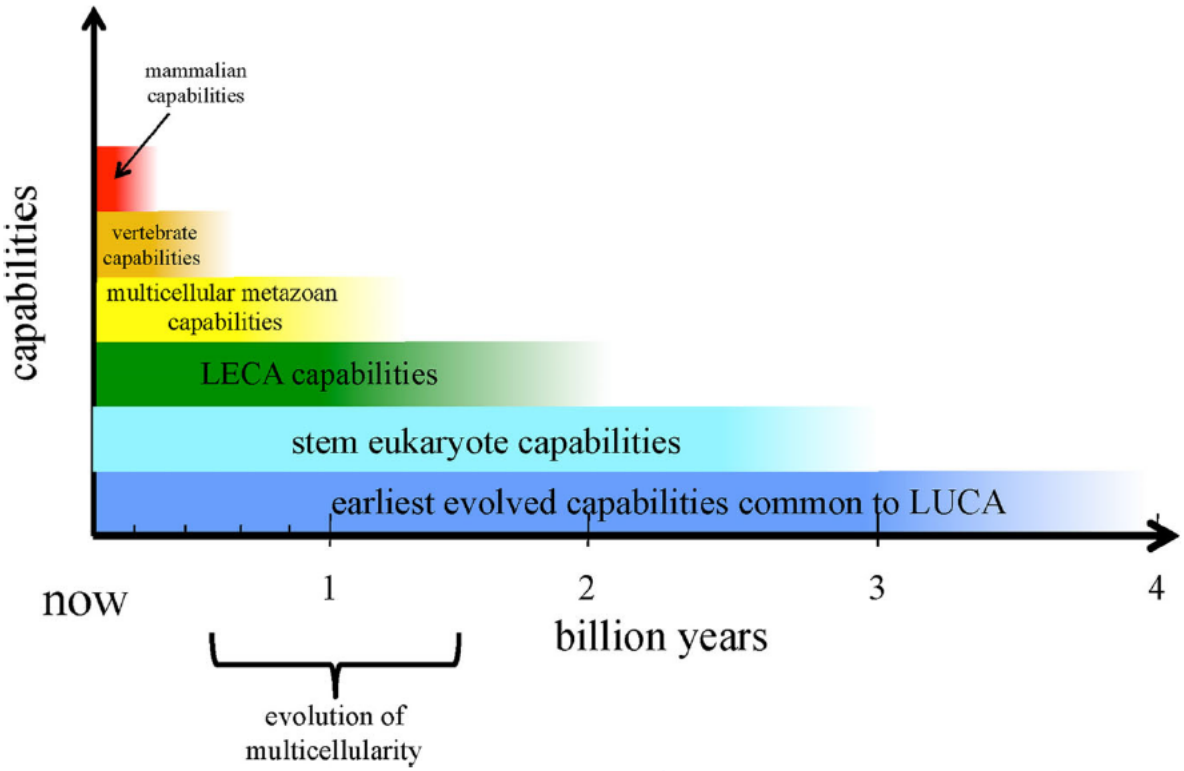
- It has been proposed that under extreme stress (Multiple Myeloma exposed to doxorubicin, *A. Wu et al. PNAS 2015*), cancer cells overexpress so-called 'cold genes', i.e., (very ancient) genes that are never substituted, thus being possible testimonies of 'a form of life adapted to high fitness under extreme stress', as the expression of these genes coincides with the rapid emergence of a subpopulation of MM cells resistant to doxorubicin.

- Could the expression of these 'cold genes', launched by a de-differentiation stress signal sent to the chromatin, be, or secondarily result in unmasking, thanks to the plasticity of cancer cells, the expression of diverse (with *bet hedging, Nichol 2016*) ancient genes, dating back to unicellular ancestors that were able to resist extreme stress conditions on our planet?

- This speculation refers to the so-called 'atavistic theory of cancer' (*Davies, Lineweaver and Vincent 2011*), according to which cancer is a very primitive state of multicellularity, unable to lead to a cohesive multicellular organism by lack of a coherent development program, and nevertheless trying to put at work the bases of multicellularity (division of work, i.e., cooperativity between cells on different tasks, motility, plasticity in developmental stages) for its own benefit.

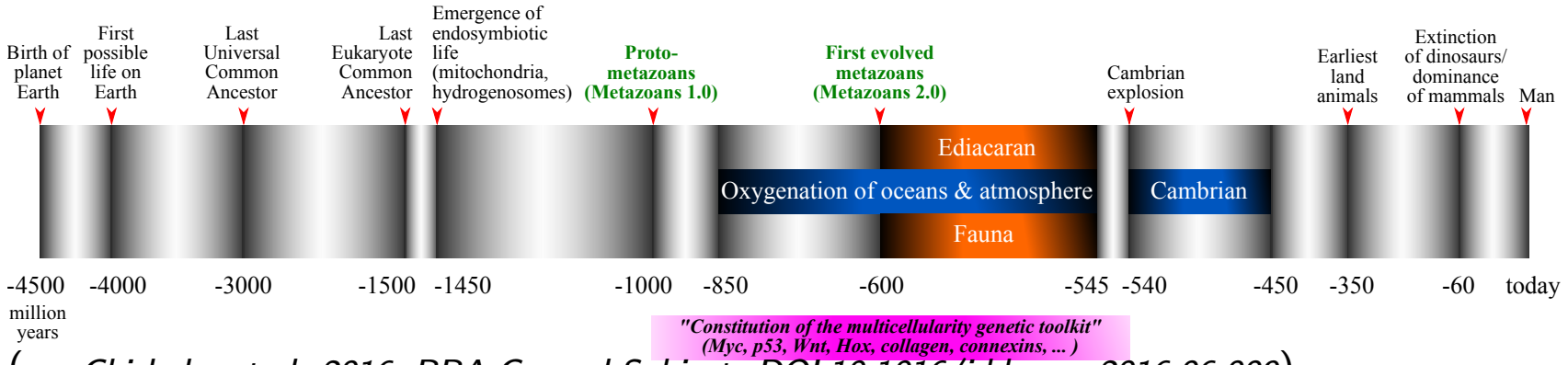
Reverse evolutionary framework (*billion year-term view* for multicellular organisms): the atavistic theory of cancer (1)

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



"Cancer: more archeoplasm than neoplasm" (Mark Vincent, 2011) More references: *Boveri: 'Zur Frage der Entstehung der maligner Tumoren' 1914, Israel JTB 1996, Davies & Lineweaver Phys Biol 2011, Vincent Bioessays 2011, Lineweaver, Davies & Vincent Bioessays 2014, Chen et al. Nature Comm 2015, Bussey et al. PNAS 2017, Cisneros et al. PLoS One 2017, Trigos et al. PNAS 2017, Trigos et al. BJC 2018, Trigos et al. eLife 2019*

Reverse evolutionary framework (*billion year-term view* for multicellular organisms): the atavistic theory 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 development of multicellularity are those that are altered in cancer (as shown in phylostratigraphic analyses by Domazet-Lošo & Tautz 2010; investigated by Trigos *et al.* 2017, 2018, 2019)
- In order, in evolution, from 1) proliferation + contact inhibition to 2) cell differentiation + division of work, and to 3) *epigenetic control* on differentiation and proliferation? (reverse mutation order w.r.t. *Hirsch Nature Comm. 2016*)
- Reconstituting the phylogeny of this 'multicellularity genetic 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)

Functional arguments in favour of the atavistic theory

- Physiologically in wound healing, and in cancer cells as a way to gain motility or viability (EMT, persister cells), changes of phenotypes appear as a *temporary* reversal to more adapted ones to challenging situations: wound, cancer invasion, resistance to life-threatening treatments.

- However, such changes of phenotypes do not revert cells to a complete unicellularity state, and furthermore these changes are themselves reversible: the physiological wound healing program is abandoned when the healing is complete (*the axololotl*), in epithelial cancers EMT is reverted to MET in metastatic niches, and persister cells in Petri dishes apparently disappear, reverting the cancer cell population to their initial (main) phenotype when a life-threatening drug is withdrawn (*Sharma et al. Cell 2010*).

- Which naturally leads to consider, in particular by analogy with the physiological wound healing case, that plasticity of cancer cell populations is not all of the scenery, but an essential component of it, which must be completed by the possibility of a *primitive state of control of cohesion* within cancer cell populations, making them amenable to very coarse homeostasis principles, likely by minimisation of global energy costs.

- Such coarse homeostasis principles might be constitutive of the primitive state of multicellularity *Metazoa 1.0*, in the terminology of Davies and Lineweaver.

What role for the atavistic theory in mathematical models of cell population dynamics under treatment?

- Although the atavistic theory is not needed to introduce plasticity as a structure variable to describe heterogeneity in cell populations, healthy and cancerous, it provides fundamentals for characterising these two different, well identified types of cell populations when taking into account unwanted toxic side effects.

- Indeed, cancer cell populations are not just disorganised colonies of cells. They are in particular able to show organised at the population level, successful reactions to treatments by the emergence of thriving persister cells (*Sharma et al. Cell 2010*, modelled in *Chisholm et al. Cancer Research 2015*).

- The atavistic theory gives a clear rationale for such emergence: choosing, by necessity to resist deadly changes coming from the environment, in the genome of Metazoa 1.0 the available genes, usually silenced, to be expressed to develop enough viability (yielding new or hitherto masked cell types, possibly by bet hedging of phenotypes) for tolerance of the population to treatments.

- Similarly, the existence of coarse cooperativity in cancer cell populations (e.g., *Marusyik et al. Nature 2014, Tabassum & Korneliak Nature Rev. Cancer 2015*), another testimony of rough multicellular organisation in cancer, supported by the atavistic theory, is a further challenge to design mathematical models, not only of cheating between defectors and cooperators, but also of cooperation within organised cancer cell populations.

The atavistic theory and 'philosophy of cancer'

- Do 'philosophers of cancer' need the atavistic theory? Apparently not, as no mainstream publications refer to it, whereas the opposition between the dominating somatic mutation theory (SMT) and the less accepted tissue organisational field theory (TOFT, *Soto & Sonnenschein*) is often reported (e.g., by *Marta Bertolaso*, for whom cancer is a disruption of control on both differentiations and proliferation), while the atavistic theory usually is not.

- However, did seismologists need the hypothesis of continental drift, proposed by Alfred Wegener in 1912 to predict seisms? Apparently, they were reluctant to admit it, until it gave rise to plate tectonics, which is now accepted since the late sixties and is an essential theory in seismology.

- Although direct observations are more feasible on our planet than on ancient genomes, observations by *Domazet-Lošo & Tautz 2008, 2010* on comparison by stratigraphic analyses of genomes, and by a team in Australia by *Trigos et al. 2017, 2018, 201*) on the allocation of unicellularity and multicellularity characteristics to genes constituting modern genomes, may represent new tracks in compared evolution and in genetics to assess the atavistic theory.

- Can we expect in the forthcoming years from new developments in the atavistic theory a better understanding of the emergence of cancer and improved ways to fight it? We may be on the verge of discovering hidden ways of organisation in cancer cell populations, which might lead to new therapeutic developments.

What mathematics for an emerging mathematical oncology?

- By investigating mechanisms of the emergence of multicellularity and of possible phenotype bet hedging in cancer *and by designing mathematical models based on already well-established methods of structured equations for cell population dynamics*, taking both space and phenotypes into account, we may contribute to shed light on the dynamics of cancer and propose new methods of control.

- In parallel, can we develop a 'geometrical theory of the wickerwork basket' (Bauplan, fibres-trees and cohesion connections between fibres) to better understand normal development and maintenance of multicellular organisms and of how they are disrupted in cancer?

- Can we make more precise by mathematical models (e.g., piecewise deterministic Markov processes, PDMPs) possible transitions between reversible epimutations and irreversible fixations as genetic mutations forced by the environment to represent mixed ways towards such disruptions?

- Are there ways of convergence between these different perspectives? The atavistic theory at least may help by hinting to a finite number of disrupted mechanisms to be searched for in our 'archeogenome', with functional phenotype categories from theoretical ecology such as fecundity, viability, motility, plasticity.

By way of conclusion

- To find new therapeutic tracks for fighting the cancer disease, one can make use of existing (cell-killing) therapies, however one has to optimise their use by designing mathematical models of heterogeneous cell populations with built-in therapeutic targets and optimal control for the therapeutic means of action.

- Immunotherapies are no exception to this proposition, as they are also cell-killing therapies. They may be optimally combined with chemotherapies and targeted therapies, provided that their pitfalls are well enough identified to design optimal combinations... which does not seem to be the case so far (and to the best of my knowledge, we still have not understood the reasons of the successes and failures of William Coley's founding experiments in cancer immunotherapy, more than a century ago).

- This situation invites us to better understand what a multicellular organism is (limiting ourselves to the metazoan, i.e., animal case), what its cohesion consists of, how it is altered in cancer, and how such cohesion could be reinforced by enhancing intercellular connection means. Mere speculations? Not necessarily only so. At least having such prospects in mind might help us to give sense to upcoming new observations and possibly reinterpret old ones.

References

- Alvarez Borges, FE, Carrillo, JA, *JC*. Evolution of a structured cell population endowed with plasticity of traits under constraints on and between the traits. *In revision*, May 2022
- Kuznetsov, M., *JC*, Volpert, V. Improving cancer treatments via dynamical biophysical models. *Physics of Life Reviews*, 39:1-48, October 2021
- *JC*. Plasticity in cancer cell populations: biology, mathematics and philosophy of cancer, https://link.springer.com/chapter/10.1007/978-3-030-64511-3_1, December 2020 (author's proof: https://who.rocq.inria.fr/Jean.Clairambault/JC4ISMCOfinal2020.pdf)
- *JC*. Stepping from modelling cancer cell plasticity to philosophy of cancer. *Frontiers in genetics*, November 2020 https://who.rocq.inria.fr/Jean.Clairambault/JC4FrontiersGenetics2020R3.pdf
- Shen, S., *JC*. Plasticity in cancer cell populations. *F1000 Research*, 15 pages, Online June 2020.
- *JC*, Pouchol, C. A survey of adaptive cell population dynamics models of emergence of drug resistance in cancer, and open questions about evolution and cancer. *BIOMATH*, vol. 8, issue 1, 23 pages, Online May 2019.
- Pouchol, C., Trélat, E, Lorz, A, *JC*. Asymptotic analysis and optimal control of an integro-differential system modelling healthy and cancer cells exposed to chemotherapy. *J Maths Pures Appl*, 116:268-308, 2018.
- Goldman, A., Kohandel, M., *JC*. Integrating Biological and Mathematical Models to Explain and Overcome Drug Resistance in Cancer. *Curr Stem Cell Rep*, 3:253-268, Online August 2017.
- Chisholm, RH, Lorenzi, T., *JC*. Cell population heterogeneity and evolution towards drug resistance in cancer: biological and mathematical assessment, theoretical treatment optimisation. *BBA General Subjects*, 1860(11):2627-2645, 2016.
- Chisholm, RH, Lorenzi, T, Lorz, A, Larsen, AK, Almeida, L, Escargueil, A, *JC*. Emergence of drug tolerance in cancer cell populations: an evolutionary outcome of selection, non-genetic instability and stress-induced adaptation. *Cancer Research*, 75(6):930-939, 2015.
- Lorz, A, Lorenzi, T, *JC*, Escargueil, A, Perthame, B. Effects of space structure and combination therapies on phenotypic heterogeneity and drug resistance in solid tumors. *Bull Math Biol*, 77(1):1-22, 2015.

An announcement about *Frontiers in Mathematical Biology*

(Section of *Frontiers in Applied Mathematics and Statistics*)

I edit a research topic in *Frontiers in mathematical biology* on

Eco-evolutionary models of cancer,
cell plasticity, adaptive dynamics of cancer cell populations

Interested contributors may go to the website

`https://www.frontiersin.org/research-topics/30069/`
`eco-evolutionary-models-of-cancer-cell-plasticity-adaptive-dynamics-of-cancer-`
`utm_source=LOP&utm_medium=Profile&utm_campaign=editorialRolesBrick_`
`FrontiersRTSubmissions_OpenSubmit`

Publication fees exist, but are not expensive (between 400 and 1000 euros, pending on the type of article: 400 opinion, 700 mini-review, 1000 research).

Also note the Summer school and workshop on mathematical biology MBMC 2022 in Heraklion, Crete, Aug. 29 - Sep. 6: `https://mbmc22.iacm.forth.gr/`