Modelling Complexity in Mechanics and Applied Mathematics: Theory, Experiments, and Simulations

Cancer as localised disorganisation of the body plan: partial failure of tissue specialisation and cooperation

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Sum-up of principles that will be developed in this talk (1)

- Multicellularity is a mandatory framework to be considered when trying to understand and explain cancer.
- Multicellularity is a daring construction that needs permanent strict control of cohesion of its cell constituents.
- Plasticity is a mandatory cellular trait in such construction (i.e., in embryogenesis), which cannot be kept in cells of an achieved multicellular organism (with a few exceptions: repair, wound healing), lest the cohesion of the organism be in permanent danger of dissolving. Acquired cellular plasticity is central in cancer, and it is due to such loss of control.
- Cancer is impairment of control on local differentiations and, secondarily only, on proliferation.
- Physiological differentiation makes sense within cell lineages, starting from the zygote, with the purpose a) to develop cell specialisations and b) to develop compatibility and cooperativity between specialised cells (division of labour). It is absolutely opposed to plasticity, that is physiologically more and more lost in successive differentiations.

Sum-up of principles that will be developed in this talk (2)

- Loss of control on differentiations in cancer is histologically evidenced in plastic de-differentiations (cells swimming upstream a lineage towards a stem cell-like status) and transdifferentiations (such as the very plastic EMT/MET).
- Physiological control on differentiations and on proliferation must be ensured by a coherent ensemble of intercellular gene regulatory networks (GRNs, that may be seen as taking care of compatibilities and cooperativities between cells and organs), an ensemble that we call the *cohesion watch*.
- *The body plan is the completely deterministic program that is carried out in physiological development by the making of cohesive cellular matter which is achieved in the stable construction which is a multicellular animal. It is unique to a given species and it *is* the basic evolutionary unit in the Darwinian evolution of species.*
- The cohesion watch mentioned above is an essential part of the body plan, the unfolding of which results in the making of cohesive multicellular organisms, in their development and maintenance. In cancer, the cohesion watch is impaired, initially locally, in anatomy and physiology.
- Proliferation is the default state of all cells. All multicellular animals (except eutelic ones, since cancer implies loss of control on proliferations, that are absent in eutely) from Hydra to sponges and humans may be subject to cancer.

Plan of the talk

1. Isogenic multicellularity, the body plan and cancer
2. Modelling phenotype divergence with reaction-diffusion-advection equations
3. Modelling cooperation with the prisoner's dilemma and with PDEs
4. Conclusion and future prospects

Physiological isogenic multicellularity and cancer

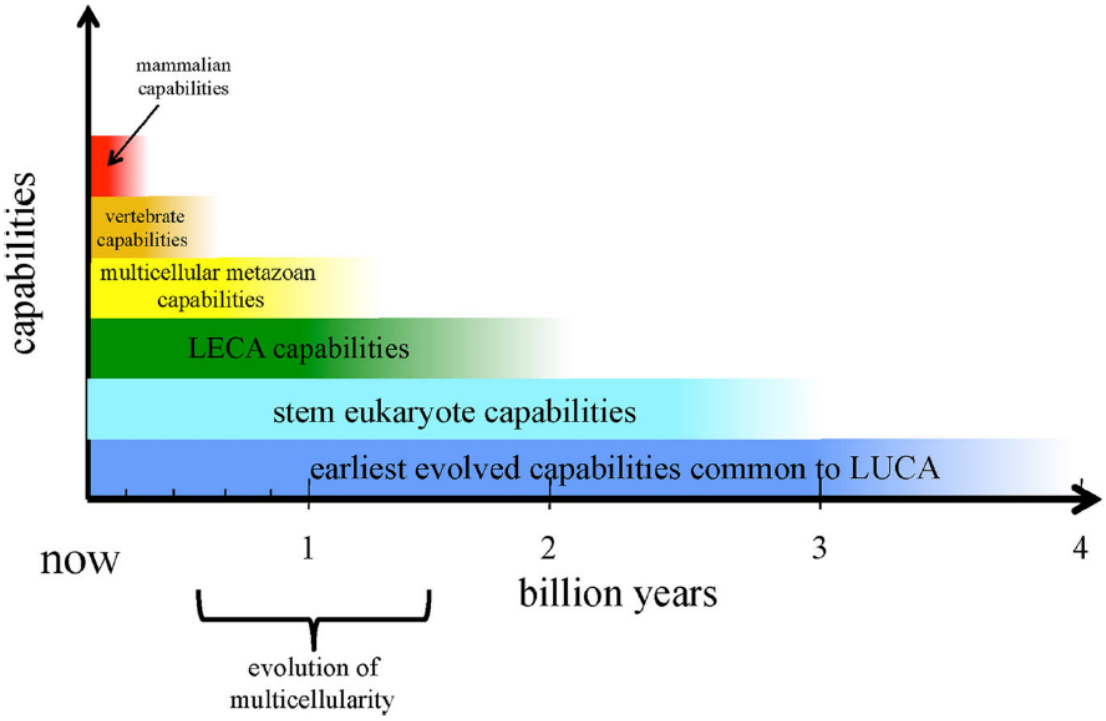
- Multicellularity is a mandatory framework to consider when trying to understand and fight cancer, a disease of multicellular animals only. Multicellularity is a daring physiological construction from the zygote, based on the *body plan* of each species, needing for its maintenance a *strict control of cohesion* of its isogenic cell constituents, which is lost in cancer.
- *Physiological phenotype cell plasticity*, potential of dynamic and reversible phenotype change in cells according to both the deterministic developmental program of the *body plan*, and random adaptations of the same body plan program to changing microenvironments, is a *transient, of epigenetic nature*, cellular trait which cannot be kept as such in cells of an achieved multicellular organism, lest the organism be in permanent *danger of losing its cohesion*.
- Cancer and its uncontrolled cell plasticity is primarily loss of the normal local *epigenetic* control mechanisms on differentiations, work of a coherent set of *gene regulatory networks* contained in the species *body plan*, i.e., the deterministic 'program of making an animal' in a given species, and maintaining its cohesion. Secondarily only, cancer is also loss of control on proliferations.
- Cell differentiations in embryogenesis occur within cell lineages from the zygote, following the *body plan*, with the purpose to develop a) *cell specialisations* and b) *compatibility and cooperativity* between specialised cells (*division of labour*). In the unfolding of the body plan, cell plasticity is normally progressively lost in successive physiological differentiations, until terminally differentiated cell types.

The two settings: Darwinian evolution and development, or: *a story of how ontogeny recapitulates phylogeny*

- In the billion-year perspective of Darwinian evolution of animal species, i.e., of their *body plans*, phenotype divergence, leading to cell type branchings, was likely imposed by environmental constraints, as different ways to optimally solve existential problems due to new conditions of living. When adaptation of the *body plan* gave way to such divergent specialisations in the same changing conditions for one given species, the divergent choices made were *likely random, firstly reversible*, later irreversible, due to *fixation by mutations*.
- On the contrary, in multicellular development from the egg in a given animal species according to its *body plan*, *epigenetic phenotype divergence* and resulting successful cooperations are *completely deterministic*, written in the program of the body plan of each species. The body plan, borne in each cell of the organism, is the evolutionary unit with which Darwinian evolution of species proceeds in individuals. This is how may be understood Haeckel's ansatz that physiologically (deterministic) *'ontogeny recapitulates'* (random) *'phylogeny'*.
- *Cancer alters the maintenance* of the anatomically and physiologically unfolded body plan by the ensemble of gene regulatory networks that make its cohesion. However, tumour cells keep in their genome facilities, relics of their body plan program, to *develop specialisations* (possibly *with bet hedging*) *and cooperations* inherited from their evolutionary past, that can easily be recruited to face environmental changes, as they have acquired *uncontrolled phenotype plasticity*.

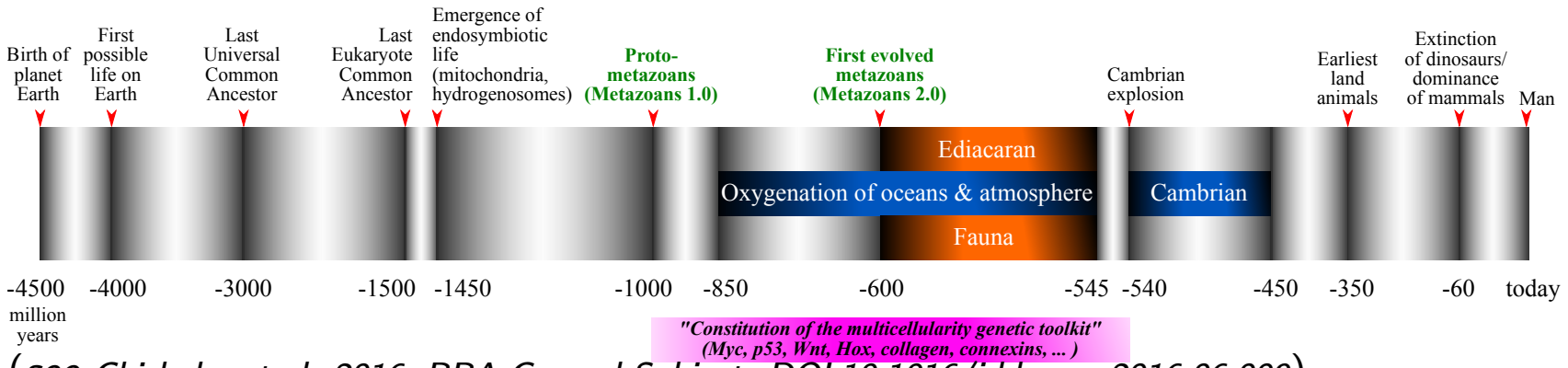
A billion-year evolutionary framework: *the atavistic theory of cancer* provides a vision of cancer as a regression towards a coarse, unachieved, incoherent form of multicellularity

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



"Cancer: more archeoplasm than neoplasm" (Mark Vincent, 2011) More references: *Israel JTB 1996, Davies & Lineweaver Phys Biol 2011, Vincent Bioessays 2011, Lineweaver, Davies & Vincent Bioessays 2014, Lineweaver et al. 2020, 2021, Trigos et al. PNAS 2017, BJC 2018, eLife 2019, bioRxiv 2023.*

A billion-year evolutionary framework: *the atavistic theory of cancer* provides a vision of cancer as a regression towards a coarse, unachieved, incoherent form of multicellularity



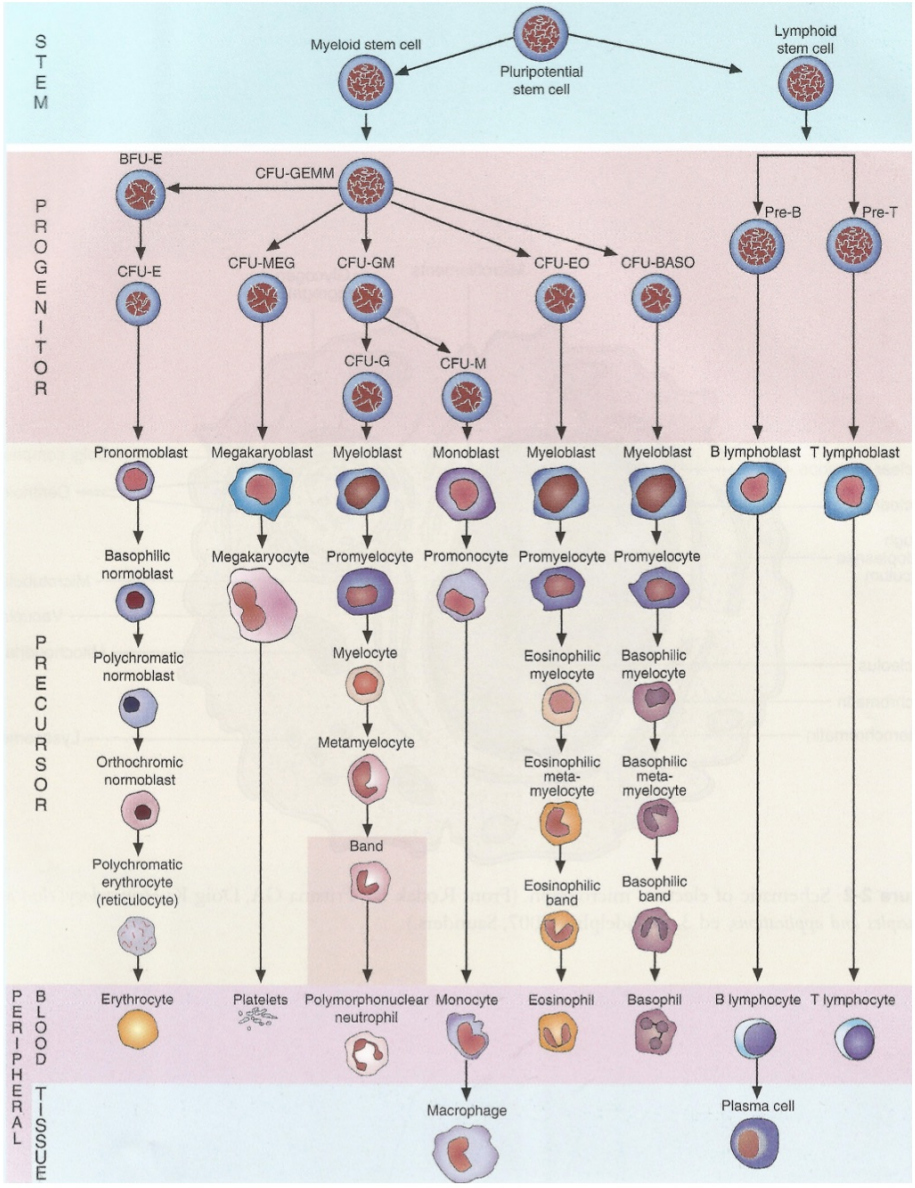
(*see Chisholm et al. 2016, BBA General Subjects DOI:10.1016/j.bbagen.2016.06.009*)

- The genes that have appeared in the development of multicellularity are those that are altered in cancer: phylostratigraphic analyses by *Domazet-Lošo & Tautz 2010*; multicellularity vs. unicellularity gene investigations by *Trigos et al. 2017, 2018, 2019, 2023* show overexpression of unicellularity genes and underexpression of multicellularity genes in cancer.
- Evolution order: 1) proliferation + contact inhibition to 2) cell differentiation + division of work, and to 3) achieved *epigenetic control* on differentiation and proliferation (reverse mutation order in AML, *Hirsch et al. Nature Com. 2016*).
- Attacking cancer on proliferation is precisely attacking its robustness. It is better to attack its weaknesses: absence of protecting immune system in tumours.

The *body plan* unfolds in normal development according to branchings by successive phenotype divergences in all cell lineages from the egg to terminally differentiated cell types

A personal metaphor: the wickerwork basket. A fibre bundle (base, the *body plan* in the zygote, i.e., the initial egg); fibres, the cell differentiation trees; at the rim of tips, terminally differentiated cells. Intertwining the trees that stem, unfolding from the body plan, are *between-fibre connections* (intercellular gene regulatory networks of epigenetic nature) that *control the coherence (in compatibility/cooperativity) of differentiations*, making their coherent ensemble a *cohesion watch*, maintenance mechanism in the *body plan*, primarily disrupted in cancer by altered differentiations.

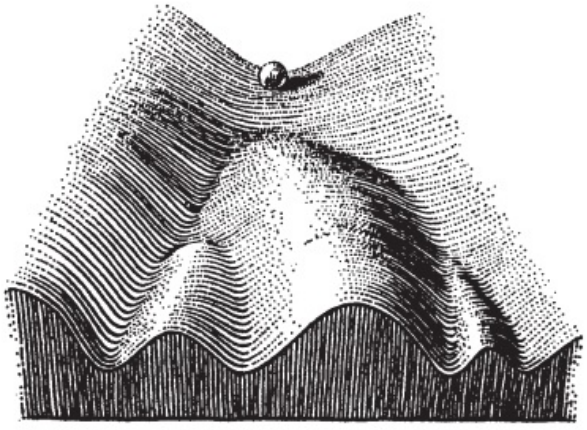
The best known case in development: haematopoiesis



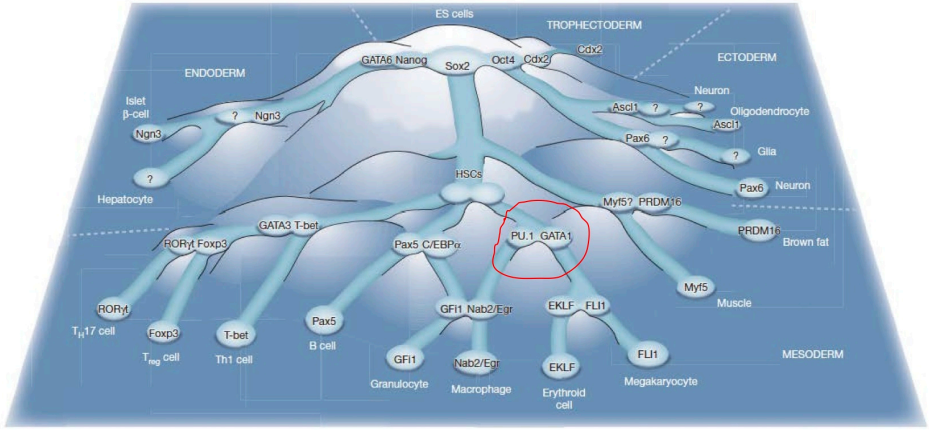
Haematopoiesis, after *Carr & Rodack, Clinical hematology atlas*, 2012.

Succession of phenotype divergences, i.e., cell specialisations, followed by *successive within-lineage differentiations*, from the pluripotent haematopoietic stem cell (top) until the terminally differentiated formed cells in tissues, here mainly blood (bottom).

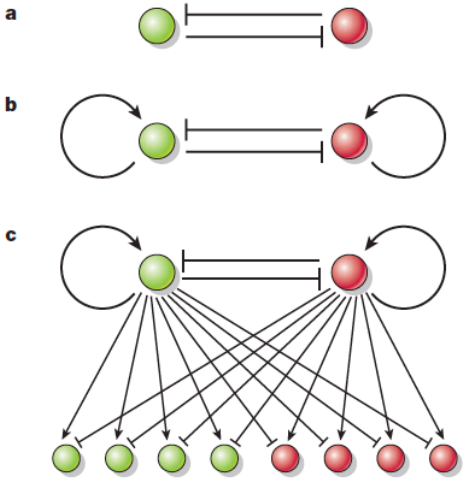
Milestones to reconstruct the global differentiation landscape

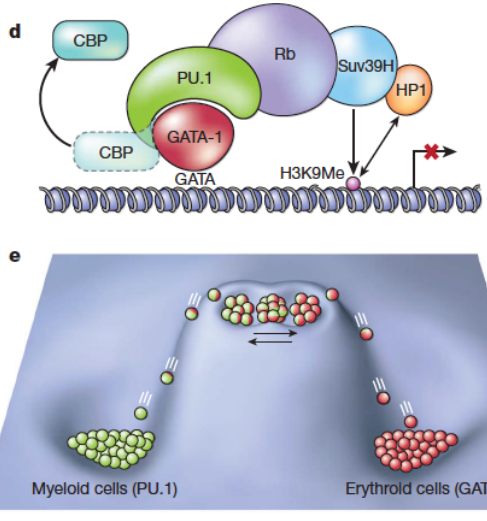


A classic metaphor *(Waddington 1940)*: the Waddington epigenetic landscape



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*)

Cell population model with trade-offs between phenotypes to represent divergences in the unfolding of the body plan

[And also: bet hedging as a 'tumour strategy' to diversify its phenotypes in response to deadly stress (e.g., cytotoxic drugs): glutathione, ABC transporters, DNA repair..)]
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 $z = (x, y, \theta)$, where, e.g., x=viability, y=fecundity, and 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 $\left(\text{Vn-A}(\theta)\nabla n\right) \cdot \mathbf{n} = 0$ 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, influences 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 cellular stress exerted by external evolutionary pressure on the population, i.e., by changes in the environment; and $\rho(t) = \int_D n(t,z)dz$ is the total mass of individual cells in the population at time t.

FEA, JA Carrillo, JC, J. Math. Biol. 2022

Phenotype divergence: numerics

The existence and uniqueness of solutions may be obtained *in finite horizon* 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

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

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 (two maxima at $(0.1, 0.9)$ and $(0.9, 0.1)$) and the death rate as

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

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

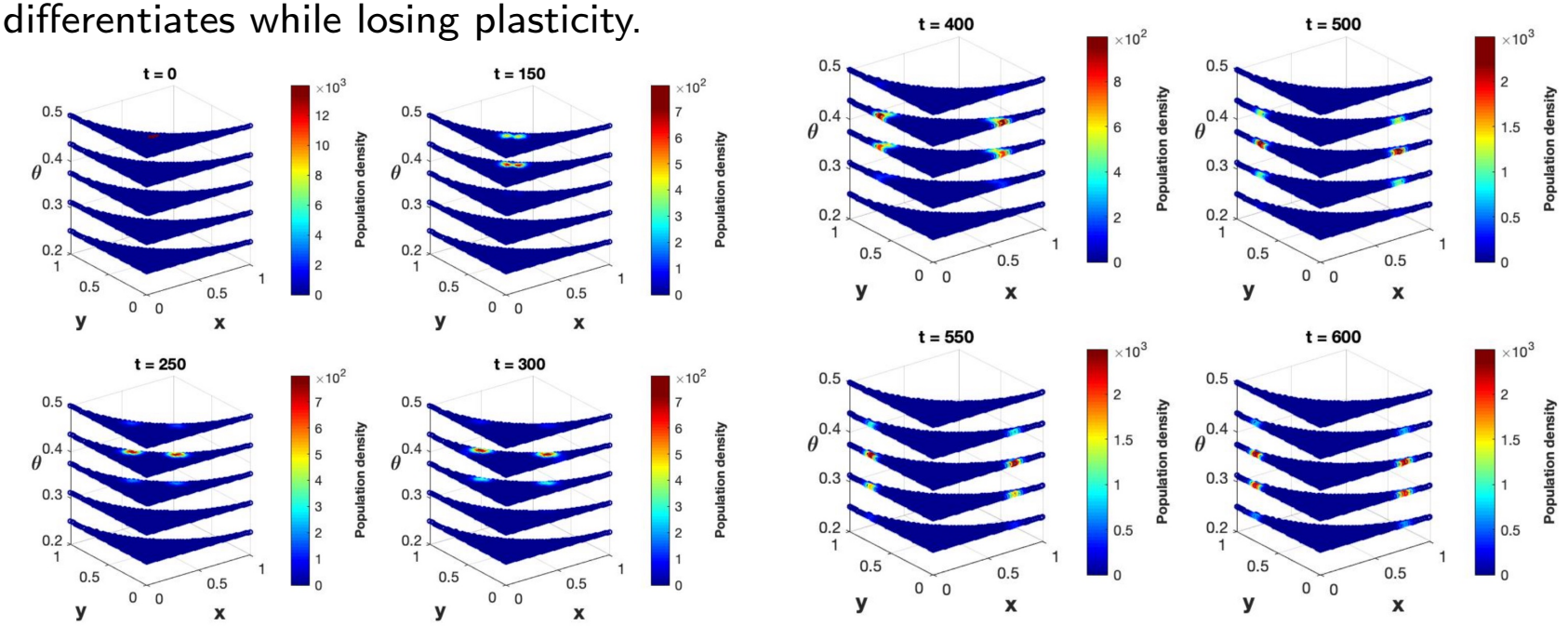
We choose the diffusion matrix

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

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

Phenotypic divergence: illustration (first stages)

The "push" towards specialisation imposed by V is negatively 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.

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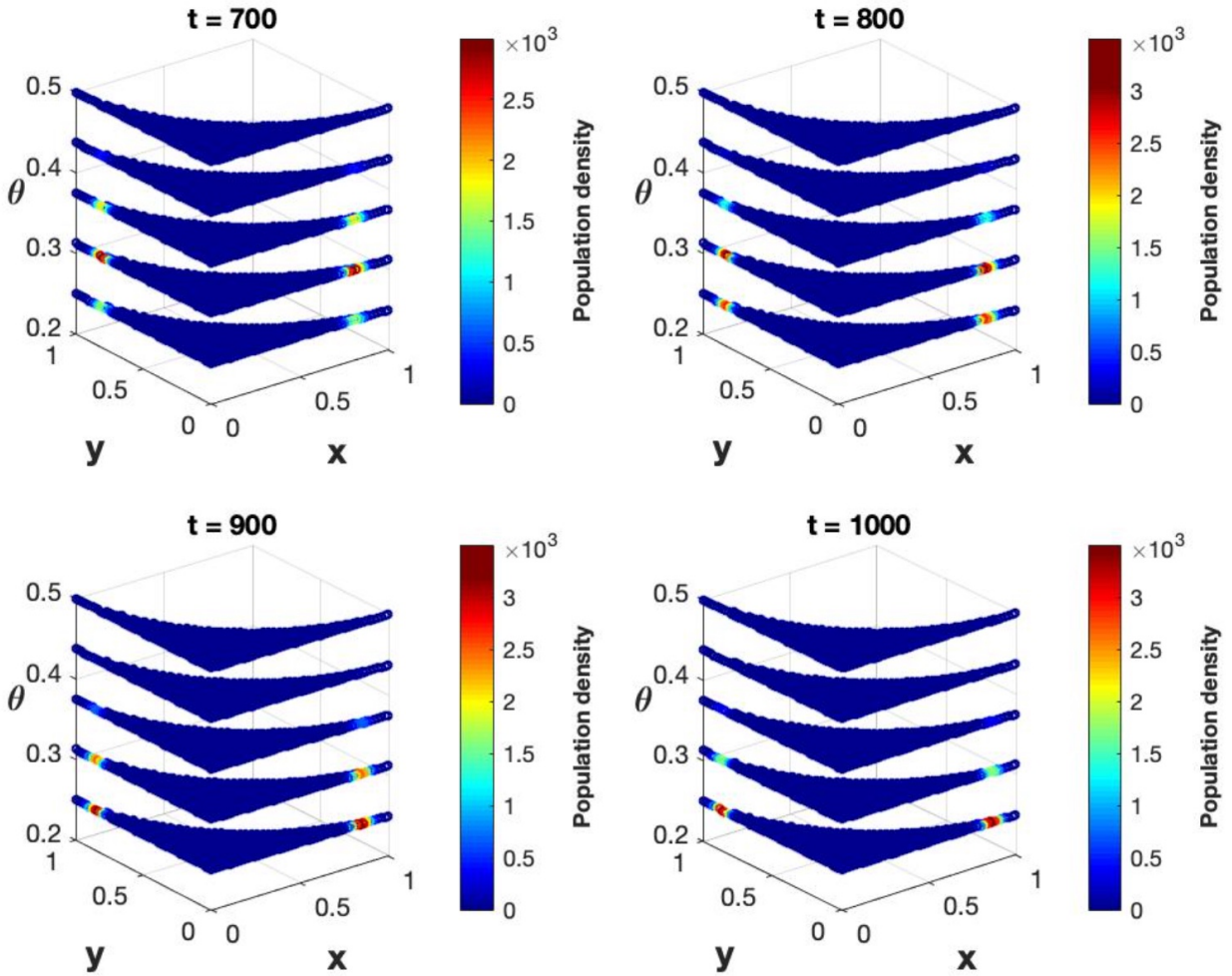
Phenotypic divergence: illustration (final stages)



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 time $t = 1000$ (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.

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Cooperation: the prisoner's dilemma paradigm

An initial intention for cooperation and the existence of reciprocity are crucial for the evolution of cooperation (Axelrod & Hamilton, 1981).
Consider two players involved in the repeated prisoner's dilemma game with cooperation probabilities p_k and q_k at turn k. Player A will initially cooperate with probability $p_0 > 0$ while player B will do so with probability $q_0 > 0$ (initial intention for cooperation).
Both players will modify their probabilities of cooperation at turn $k+1$ by following the rule:

$$p_{k+1} = \begin{cases} p_k + \varepsilon_{11}(1-p_k), & \text{if player B cooperated in turn } k \text{ (increase in cooperation)}, \\ p_k(1-\varepsilon_{12}), & \text{if not (decrease in cooperation)}, \end{cases}$$

and

$$q_{k+1} = \begin{cases} q_k + \varepsilon_{21}(1-q_k), & \text{if player A cooperated in turn } k \text{ (increase in cooperation)}, \\ q_k(1-\varepsilon_{22}), & \text{if not (decrease in cooperation)}, \end{cases}$$

where $0 < \varepsilon_{ij} < 1$ for $i, j \in \{1, 2\}$ are reciprocity coefficients (existence of reciprocity).
We recall that the so-called *payoff matrix* of the prisoner's dilemma game is given by

$$\begin{pmatrix} b-c & \textit{(both prisoners cooperate)} & -c & \textit{(I cooperate, the other defects)} \\ b & \textit{(I defect, the other cooperates)} & 0 & \textit{(both prisoners defect)} \end{pmatrix},$$

where b is the benefit and c is the cost of cooperation ($b > c$) from an "I" viewpoint.

Cooperation: the prisoner's dilemma paradigm (continued)

Hence, the expected gains for players A and B at turn k are given by

$$E_A^k = (b-c)p_k q_k + b(1-p_k)q_k - cp_k(1-q_k) = bq_k - cp_k \text{ and } E_B^k = bp_k - cq_k,$$

respectively. Therefore, the average expected gain at turn k is given by the relation

$$E_k = \frac{(b-c)}{2}(p_k + q_k).$$

Given that the probability of both players cooperating at turn k is equal to $p_k q_k$, our interest falls then on the question: What are the conditions over the values ε_{ij}, $i, j \in \{1, 2\}$, such that the sequence (p_k, q_k) converges towards a non trivial limit ? In such cases, when does the average expected gain can be expected to increase ?
In order to answer these questions we first explicitly give the values of p_{k+1} and q_{k+1} as functions of p_k and q_k. Thanks to the law of total probability, we get the relations

$$\begin{aligned} p_{k+1} &= q_k(p_k + \varepsilon_{11}(1-p_k)) + (1-q_k)p_k(1-\varepsilon_{12}) \\ &= (1-\varepsilon_{12})p_k + \varepsilon_{11}q_k + (\varepsilon_{12}-\varepsilon_{11})p_k q_k =: f_1(p_k, q_k), \\ q_{k+1} &= p_k(q_k + \varepsilon_{21}(1-q_k)) + (1-p_k)q_k(1-\varepsilon_{22}) \\ &= (1-\varepsilon_{22})q_k + \varepsilon_{21}p_k + (\varepsilon_{22}-\varepsilon_{21})p_k q_k =: f_2(p_k, q_k). \end{aligned}$$

If this sequence has a limit (p^*, q^*), it must satisfy the relation

$$\begin{cases} p^* &= f_1(p^*, q^*), \\ q^* &= f_2(p^*, q^*). \end{cases}$$

Cooperation: the prisoner's dilemma paradigm (stable steady states)

In the following proposition we identify the possible values for (p^*, q^*) and their stability:

Consider a couple (p_0, q_0) and the value $e = \varepsilon_{11}\varepsilon_{21} - \varepsilon_{12}\varepsilon_{22}$.

i) If $e < 0$, then the only possible steady states are $(0,0)$ (stable) and $(1,1)$ (unstable).

ii) If $e > 0$, then the only possible steady states are $(0,0)$ (unstable) and $(1,1)$ (stable).

iii) If $e = 0$ then the steady state is the unique solution of

$$\varepsilon_{22} p_0 + \varepsilon_{11} q_0 = \varepsilon_{22} p^* + \varepsilon_{11} q^*,$$

$$q^* = \frac{\varepsilon_{12} p^*}{\varepsilon_{11} + (\varepsilon_{12} - \varepsilon_{11}) p^*},$$

and it is a stable steady state.

Cooperation: the prisoner's dilemma paradigm (illustration)

Leaving aside the study of the effect of the average expected gain E_k on the evolution of the couple (p_k, q_k) (work underway), we plainly illustrate here its convergence towards its limit (p^*, q^*) in the third case of the previous proposition.

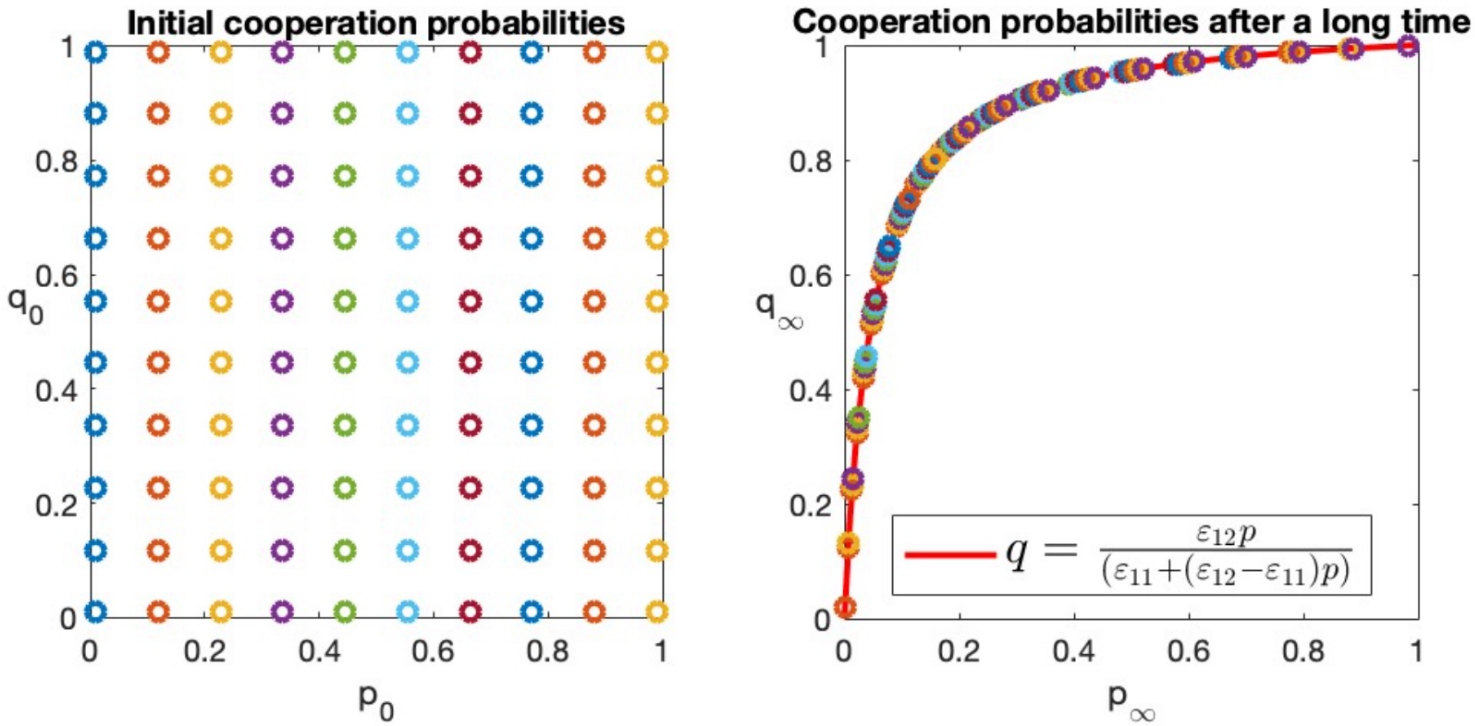


Illustration of the stable limit (p^*, q^*) in the case $e = \varepsilon_{11}\varepsilon_{21} - \varepsilon_{12}\varepsilon_{22} = 0$. Left panel: Several initial configurations of cooperation probabilities. Right panel: Limiting values of the sequences (p_k, q_k) associated to initial values showcased on the previous figure.

Cooperation between subpopulations: a first PDE model

Let $p \in [0,1]$ be a continuous structure variable representing the probability of cooperation. Consider two populations A and B, each one composed by individuals with different probabilities of interspecific cooperation. Let $n_A(t,p)$ and $n_B(t,p)$ be their respective population densities.
For the two total population masses at time t :

$$\rho_A(t) := \int_0^1 n_A(t,p)dp, \quad \rho_B(t) := \int_0^1 n_B(t,p)dp,$$

the mean cooperation probabilities are

$$\tilde{p}_A(t) := \frac{\int_0^1 p n_A(t,p)dp}{\rho_A(t)}, \quad \tilde{p}_B(t) := \frac{\int_0^1 p n_B(t,p)dp}{\rho_B(t)},$$

with global expected gains in each population:

$$\begin{aligned} E_A(t) :=& (b-c)\tilde{p}_A(t)\tilde{p}_B(t) + b(1-\tilde{p}_A(t))\tilde{p}_B(t) - c\tilde{p}_A(t)(1-\tilde{p}_B(t)) \\ =& b\tilde{p}_B(t) - c\tilde{p}_A(t), \\ E_B(t) :=& b\tilde{p}_A(t) - c\tilde{p}_B(t). \end{aligned}$$

where b and c are the benefit and cost, respectively, of cooperation in the prisoner's dilemma setting.

Cooperation between subpopulations: a first PDE model

The two population densities evolve according to the PDE system

$$\begin{cases} \partial_t n_A(t,p) + \varepsilon_A \partial_p \left((\tilde{p}_B(t) - p) n_A(t,p) \right) = & g_A(p, E_A(t)) n_A(t,p), \\ \partial_t n_B(t,p) + \varepsilon_B \partial_p \left((\tilde{p}_A(t) - p) n_B(t,p) \right) = & g_B(p, E_B(t)) n_B(t,p), \\ n_A(0,p) = n_A^0(p), \quad n_B(0,p) = n_B^0(p), \end{cases}$$

where ε_A, ε_B are reciprocity coefficients and g_A, g_B are continuous and increasing functions of E_A and E_B respectively.
For example, we can set:

$$\begin{aligned} g_A(p, E_A(t)) &:= r_A(p) + \gamma_A(p) E_A(t) = r_A(p) + \gamma_A(p)(b\tilde{p}_B(t) - c\tilde{p}_A(t)), \\ g_B(p, E_B(t)) &:= r_B(p) + \gamma_B(p) E_B(t) = r_B(p) + \gamma_B(p)(b\tilde{p}_A(t) - c\tilde{p}_B(t)), \end{aligned}$$

where γ_A and γ_B are functions of the structure variable p, tuning the nonlocal cooperation terms $b\tilde{p}_B(t) - c\tilde{p}_A(t)$ for $n_A(p,t)$ and $b\tilde{p}_A(t) - c\tilde{p}_B(t)$ for $n_B(p,t)$.

Cooperation between subpopulations: a first PDE model

Consider the simple case $\varepsilon_A = \varepsilon_B = 0$ (no advection terms in the previous equations), $\gamma_A(p) \equiv \gamma_A \geqslant 0$ and $\gamma_B(p) \equiv \gamma_B \geqslant 0$ (p-constant dependence on the nonlocal terms).

Suppose that $r_A(p)$, $r_B(p)$, $n_A^0(p)$ and $n_B^0(p)$ belong to $C([0,1])$, and furthermore

$$\arg \max_{p \in supp\ n_A^0} r_A(p) = \{p_A^*\} \text{ and } \arg \max_{p \in supp\ n_B^0} r_B(p) = \{p_B^*\}.$$

Then it can be shown (*FEA* and *JC* 2024) that

i) If $r_A(p_A^*) + \gamma_A(bp_B^* - cp_A^*) < 0$, population A will go extinct.
ii) If $r_A(p_A^*) + \gamma_A(bp_B^* - cp_A^*) > 0$, there exists a non void interval I satisfying $p_A^* \in I \subset [0,1]$ such that population A will blow up for all $p \in I$.
iii) The same is true for population B, depending on the sign of $r_B(p_B^*) + \gamma_B(bp_A^* - cp_B^*)$.

This result serves solely to illustrate the - sometimes dramatic - effect of cooperation on the dynamics of the two populations. However, this model only accounts for the effect of cooperation and it does so independently of the population sizes. These are two flaws to be overcome if more realistic scenarios are to be represented. These can be achieved, for example, by integration with the phenotypic divergence model and considering the parameters b, c, γ_A and γ_B as functions of ρ_A and ρ_B.

Combining PDE models of cooperation?

- At this step of modelling, we can combine the two PDE models by identifying $n_A(p)$ with $n(0.1, 0.9, p)$ and $n_B(p)$ with $n(0.9, 0.1, p)$ in the phenotype divergence model presented above, identifying plasticity θ with the probability of cooperation p. This would mean that an initially undivided cell population firstly diverges in two phenotypes, i.e., specialises on given phenotypes, and that only secondly (and independently of phenotype divergence) cooperation may emerge.

- However, admitting that cooperation with division of work is what makes the meaning of developing multicellularity in the deterministic body plan, one may put the problem the other way round: division of work is a way to optimise a global fitness (only global proliferation doing better that the sum of two isolated ones? or enhanced by the cooperative production of a common good, as in a sociological metaphor?), relying on growing specialisation and cooperation of two complementary populations communicating together, to be properly defined.

- It thus remains for us to define - and solve - an optimisation problem of global fitness, that should lead from a phenotypically homogeneous cell population to a split one, consisting of two subpopulations, specialised and cooperating, doing better in fitness that the initial one. Which is our present goal in modelling physiological multicellularity, before considering the case of cheating cancer cells.

In conclusion, what possible consequences for cancer?

- A long-term perspective: modelling the body plan with its cohesion mechanisms (gene regulatory networks) that ensure the global and local (tissue) stability of the animal multicellular organism, result of its unfolding in embryogenesis, and that also ensure maintenance of its cohesion in the constituted animal.

- In a more local way, at the scale of each tissue rather than at the scale of the organism, there is a need to explore and represent mechanistically the gene regulatory networks that are physiologically at work in tissues, controlling local cell differentiations and proliferation, and that are impaired in all cancers.

- Genetic mechanisms in the body plan have been explored by biologists (*W.E.G. Müller; E.H. Davidson and colleagues*) from the point of view of Darwinian evolution, but not from that, developmental, of their alterations in cancer.

- When alteration of differentiation control is located within the cancer cell itself, in particular by chromosome translocations (such as in Acute Promyelocytic Leukaemia or in Chronic Myelogenous Leukaemia), full therapeutic successes have been obtained (ATRA and AsO_2 for APL, Imatinib and other molecules for CML). But can we change the focus from the cancer cell to the cancer tissue?

- In particular, clonal cooperation mechanisms in tumours, among others, likely remnants in tumour cells of the species body plan cohesion mechanisms, have been evidenced (*Cleary, Polyak & Marusyk Nature Lett. 2014*), hardly exploited so far, to the best of our knowledge.

... and further cancer therapeutics?

- Plasticity in tumour cells leads them to deploy defence mechanisms resulting in various drug resistance mechanisms, in de-differentiation and plastic bet hedging with different cell phenotypes adapted to different insults or to cooperation between different tumour clones to survive, or in transdifferentiation (like EMT).

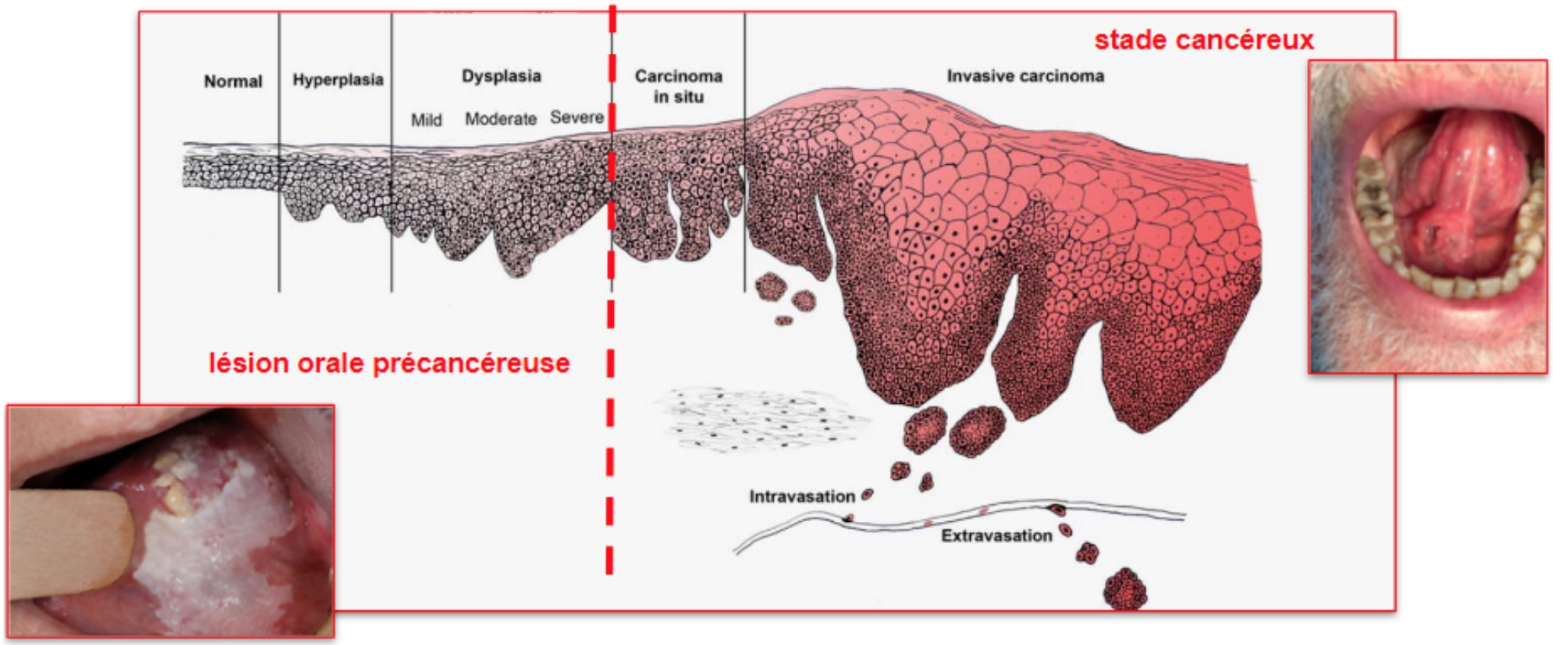
- As EMT, drug-induced drug resistance in cancer, in particular, is, initially at least, a reversible phenomenon, likely of epigenetic nature, that can be thwarted in combined treatments minimising drug exposure by *optimal control methods*, as proposed in *[Pouchol, JC, Lorz & Trélat, J Maths Pures Appl. 2018]*.

- Using epigenetic drugs to thwart EMT, or drugs susceptible to alter cooperation between subclones in tumours are other tracks to explore and further develop.

- Exploring and re-establishing, whenever possible, deterministic tissue control mechanisms may be of no avail when letal driver mutations have occurred in the genome of cancer cells, leading them to complete escape from external control. But is it constantly so? Could not re-established control by local epigenetic barriers at least limit cancer cell proliferation at the expense of healthy tissues?

- Supposing that the axes explored in this presentation resort more to cancer prevention than to cancer treatment, then immunotherapies *[Kaid, Pouchol & JC, MMNP 2023]*, not involving drug resistances, can be used. But, while drug-induced resistance is in principle excluded, toxicity issues limit their application.

Exploring medical realities: epithelial tissue evolutions in precancerous and cancerous lesions of the oral cavity



(Courtesy of Jean-Philippe Foy, St. Antoine Hospital, Paris)

- Unclear, possibly reversible, evolution from epithelial hyperplasia and dysplasia towards cancer in the oral cavity. At-risk lesions or benign ones? Feasiblity of preventive immunotherapies? Identifiability of our mathematical models?
- A co-supervised interdisciplinary PhD thesis (E. Trélat, applied maths, LJLL, Sorbonne University, and J.-Ph. Foy, biology and medicine, St Antoine and Pitié-Salpêtrière hospitals, Paris) begins in October 2024 on these topics.

References

- Aktipis, C.A., Boddy, A.M., Jansen, G., *et al.*. (2015). Cancer across the tree of life: cooperation and cheating in multicellularity. *Phil. Trans. Roy. Soc. B* 370: 20140219
- *FEA* & *JC* (2024). Phenotype divergence and cooperation in isogenic multicellularity and in cancer. *Mathematical Medicine and Biology A Journal of the IMA, online, July 2024, https://doi.org/10.1093/imammb/dqae005. Authors' proof https://hal.science/hal-04638544.*
- *FEA*, Carrillo, J.A., & *JC*. (2022). Evolution of a structured cell population endowed with plasticity of traits under constraints on and between the traits. *J. Math. Biol.* 85:64 (49 pp.).
- Axelrod, R., & Hamilton, W. D. (1981). The evolution of cooperation. *Science* 211(4489):1390–1396.
- Bertolaso, M. (2016). *Philosophy of cancer. A dynamic and relational view.* Springer, Dordrecht.
- Brunet, T & King, N. (2017). The origin of animal multicellularity and cell differentiation. *Dev. Cell* 43:124–140.
- *JC*. (2020). Plasticity in cancer cell populations: biology, mathematics and philosophy of cancer. In: G. Bebis, M. Alekseyev, H. Cho, J. Gevertz, M. Rodriguez Martinez (Eds.), Springer LNBI 12508, pp. 3-9, October 2020. https://hal.science/hal-03066491
- Cleary, A.S., et al. (2014). Tumour cell heterogeneity maintained by cooperating subclones in Wnt-driven mammary cancers. *Nature Lett.* 508:111–117.
- Davies, P.C.W. & Lineweaver, C.H. (2011). Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors. *Phys. Biol.* 8:015001 (7pp).
- Erkenbrack, E.M., Davidson, E.H., & Peter, I.S. (2018). Conserved regulatory state expression controlled by divergent developmental gene regulatory networks in echinoids. *The Company of Biologists* 145, dev167288. doi:10.1242/dev.167288
- Müller, W.E.G., Wiens, M., Adell,T., *et al.* (2004). Bauplan of Urmetazoa: basis for genetic complexity of Metazoa. *Int. Rev. Cytol.* 235:53–92.
- Nedelcu, A.M. (2020). The evolution of multicellularity and cancer: views and paradigms. *Biochem. Soc. Trans.* 48(4):1505–1518.
- Nedelcu, A.M. & Michod, R.E. (2020). Stress responses co-opted for specialized cell types during the early evolution of multicellularity. *Bioessays*, 2000029. doi:10.1002/bies.2000029
- Shen, S. & *JC*. (2020). Cell plasticity in cancer cell populations. *F1000 Research* 9 (F1000 Faculty Rev):635. doi:10.12688/f1000research.24803.1
- Wagner, G.P., Erkenbrack, E.M., & Love, A.C. (2019). Stress-induced evolutionary innovation: A mechanism for the origin of cell types. *Bioessays* 41(4): e1800188.