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Mathematical modelling of cancer growth and drug treatments: taking into account cell population heterogeneity and plasticity.
Part I: a quick overview with examples

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Plan of the talk

1. *Heterogeneity* w.r.t. what? Continuous cell functional phenotypes governing cell population fate; *plasticity* w.r.t. one or more phenotypes defined as uncertainty in the determination of phenotypes

2. The *basic nonlocal logistic model* in 1D: BV arguments or a Lyapunov functional

3. 1st example: a reaction-diffusion-advection model of cell differentiation in a heterogeneous cell population with *phenotype divergence*; its interest in representing bet hedging in cancer according to viability, fecundity, plasticity

4. 2nd example: a model of *tumour-immune interactions* with traits of malignancy and of anti-tumour efficacy, with possible introduction of immune checkpoint inhibitors to fight immunoediting by cancer cells

5. 3rd example: a model of *optimal drug control of cancer growth* taking into account the two main pitfalls of cancer therapeutics: drug-induced drug tolerance in cancer cell populations and toxic side effects in healthy cell populations

6. Conclusion: In the framework of nonlocal Lotka-Volterra cell population models, heterogeneity, i.e., biological variability within cell populations w.r.t. relevant continuous traits, has been used to study adaptive dynamics of cell populations

Heterogeneity with respect to what?

- Heterogeneity is just biological between-cell variability in cell populations. Numerous continuous models of structured cell populations exist, using cell size, cell cycle age, time since last neuronal fire, expression of drug resistance...
- Heterogeneity is meant here as structuring populations w.r.t. continuous cell functional phenotypes governing cell population fate; it may be understood as between-individual variability identified in *phenotypic* (not Cartesian) space.
- Chosen traits in a structured cell population model, aka cell phenotypes, are assumed to be *continuous* and to characterise cells in the population in a way that is relevant to a given biological question.
- They may be identified as linked to biological gene expressions and/or protein concentrations, but more fundamentally (and abstractly in these mathematical models) such traits are *functional*, supposed to govern cell population fate.
- They are *adaptive*, continuously changing according to changes in the environment of the cell population; following their distribution (e.g., yielding concentration on asymptotic phenotype values) allows to identify such adaptation in the long run.

What is meant by plasticity?

- In a representation of cell population behaviour by phenotype-structured equations, phenotypes are adaptive towards environmental pressure, i.e., plastic.

- Plasticity w.r.t. one or more phenotypes may be thus defined as uncertainty in the determination of phenotypes, which is naturally present in the reaction term of continuous phenotype-structured equations, and may be also represented, in models involving diffusion, as a Laplacian (second-order derivative w.r.t. phenotypes); it may also impinge on an advection term, representative of cellular stress due to environmental pressure.

- Biologically, it is related to non genetic, i.e., of epigenetic nature, uncertainty in the differentiation status of cells governed by expression of genes. Gene expression, controlled by epigenetic enzyme activity, is by nature continuous.

- In physiology, cell plasticity w.r.t. phenotype expression is present, strictly organismically controlled from one phenotype to some other, in embryological development, in wound healing and in tissue repair, such as regeneration of a missing limb in Axolotl.

- In cancer, plasticity may be biologically defined as loss of organism control on cell differentiation (de-differentiation and re-differentiation such as in EMT-MET, or transdifferentiation, tumour-controlled). All cancer cells escape organism regulation and are amenable to phenotype plasticity.

Where does environmental pressure impinge in the model equations?

- *Reaction* terms in the equations may be diversely affected by external variables representing the input from the cell population environment of local biophysical or chemical densities on proliferation or death terms.
- Optional *advection* terms, standing for the velocity with which cells vary w.r.t. their content in phenotypes, may be considered, affected by the same changes in environmental settings.
- Optional *diffusion* terms may also be affected, e.g., by functions of the environment multiplying them, adding or substracting uncertainty in the determination of phenotypes.

The basic reaction-[diffusion]-[advection] population model

The basic model for a density of cells $n(t,z)$, at time t with phenotype $z \in D$, runs

$$\partial_t n = (r(z) - d(z)\rho(t))n,$$

where $\rho(t) = \int_D n(t,z)\, dz$, $r(z)$ and $d(z)$ instantaneous growth and death terms.

If one adds an advection term $\nabla V(z).n$ and a diffusion term $\nabla(A(z)\nabla n)$, it runs

$$\partial_t n + \nabla(V(z).n - A(z)\nabla n) = (r(z) - d(z)\rho(t))n,$$

where $V(z)$ is a real-valued vector and $A(z)$ is a diffusion matrix.

The simplest nonlocal logistic model in 1D

- Population dynamics *in time t and in relevant phenotype* $x \in [0,1]$:

$$\partial_t n = (r(x) - d(x)\rho(t))n$$

- 'Structure variable' $x \in [0,1]$: trait chosen as bearing the biological variability
- Variable : $n(t,x)$ population density of individuals bearing trait x at time t
- (1) Evolution in mass of individuals constituting the population

$$t \mapsto \rho(t) = \int_0^1 n(t,x)\, dx$$

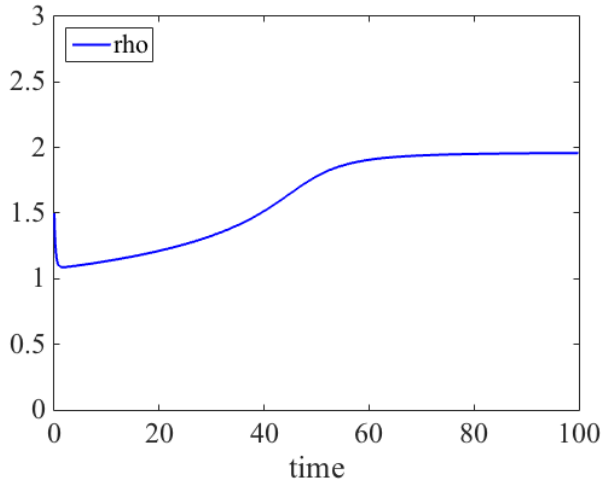
- (2) Asymptotics of distribution of the trait in the population

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

- Cancer cell populations: (1) tumour growth; (2) asymptotic distribution of trait
- Cartesian space is not here a relevant structure variable, but it may added.

Non-local logistic 1D model: convergence in time

Convergence: plot of $t \mapsto \rho(t)$



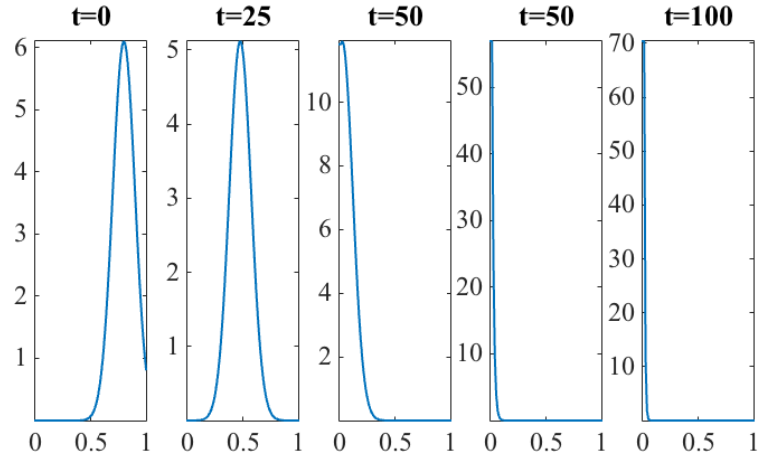
Firstly, it can be shown that: ρ converges to $\rho^\infty = \max_{[0,1]} \frac{r}{d}$, i.e., to the smallest value ρ such that $r(x) - d(x)\rho \leq 0$ on $[0,1]$.

Remark: If drugs u_1 (cytotoxic) and u_2 (cytostatic) modify the net growth rate $\frac{\partial_t n}{n} = r(x) - d(x)\rho$ to $\frac{r(x)}{1+u_2} - d(x)\rho - \mu(x)u_1$, then the new stationary value will become $\rho^\infty = \max_{[0,1]} \frac{r_1}{d}$, where $r_1(x) = \frac{r(x)}{1+u_2} - \mu(x)u_1$.

Non-local logistic 1D model: concentration in trait x

But also: asymptotic concentration on a phenotype x^∞

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*

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

Remark: In the same way, adding drugs u_1 and u_2 changes concentration in x to the set $\{x \in [0,1],\ r_1(x) - d(x)\rho^\infty = 0\}$, where $r_1(x) = \dfrac{r(x)}{1+u_2} - \mu(x)u_1$. This is where is induced phenotype adaptation.

Non-local logistic 1D model: convergence (in mass 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]

Phenotype divergence: Bet hedging in tumours (1)

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 $z = (x, y, \theta)$, 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 $(\text{Vn-A}(\theta)\nabla n\Big) \cdot \mathbf{n} = 0$ 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, 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 $\rho(t) = \int_D n(t,z)dz$ stands for the total amount of individuals in the population at time t.

(FE Alvarez, JA Carrillo, JC, J. Math. Biol. 2022)

Bet hedging as phenotypic divergence (2): 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

$$n_0(z) = a1_{\{f(z)<1\}} e^{-\frac{1}{1-f(z)}},$$

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

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

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

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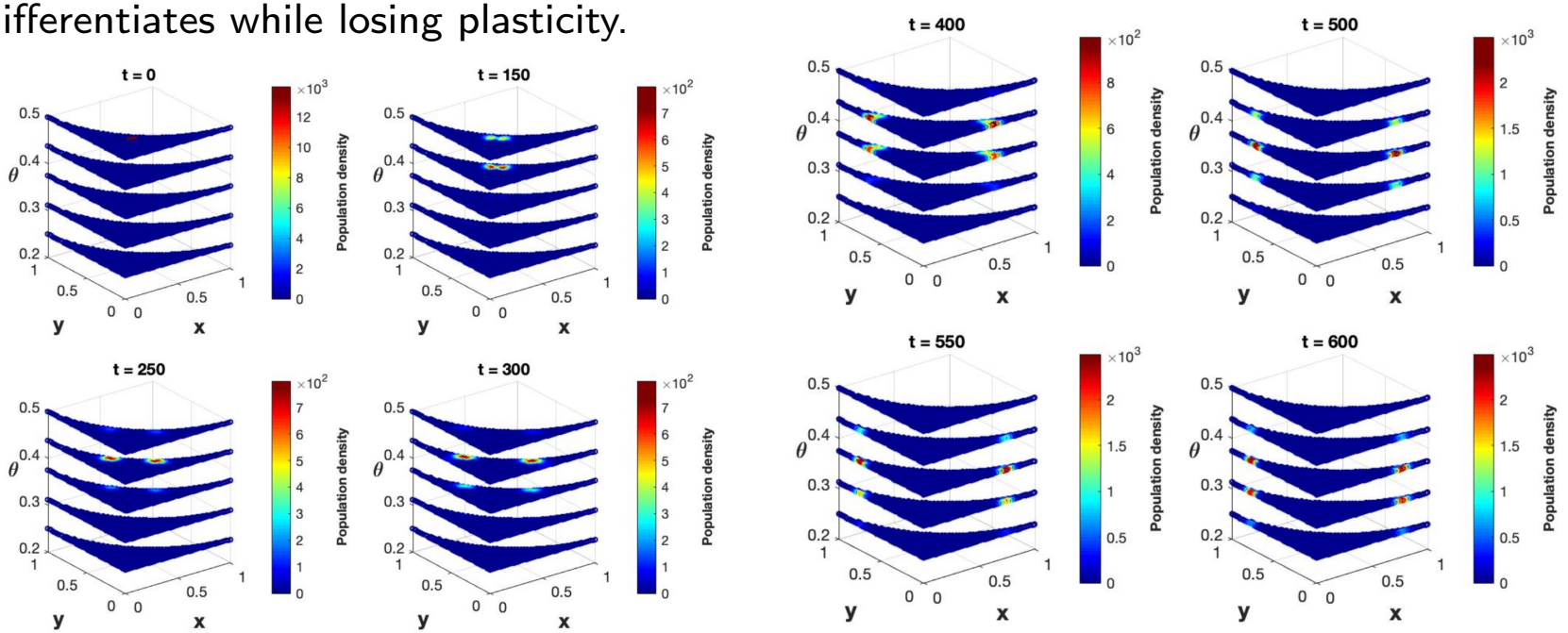
Phenotypic divergence: illustration (first stages)

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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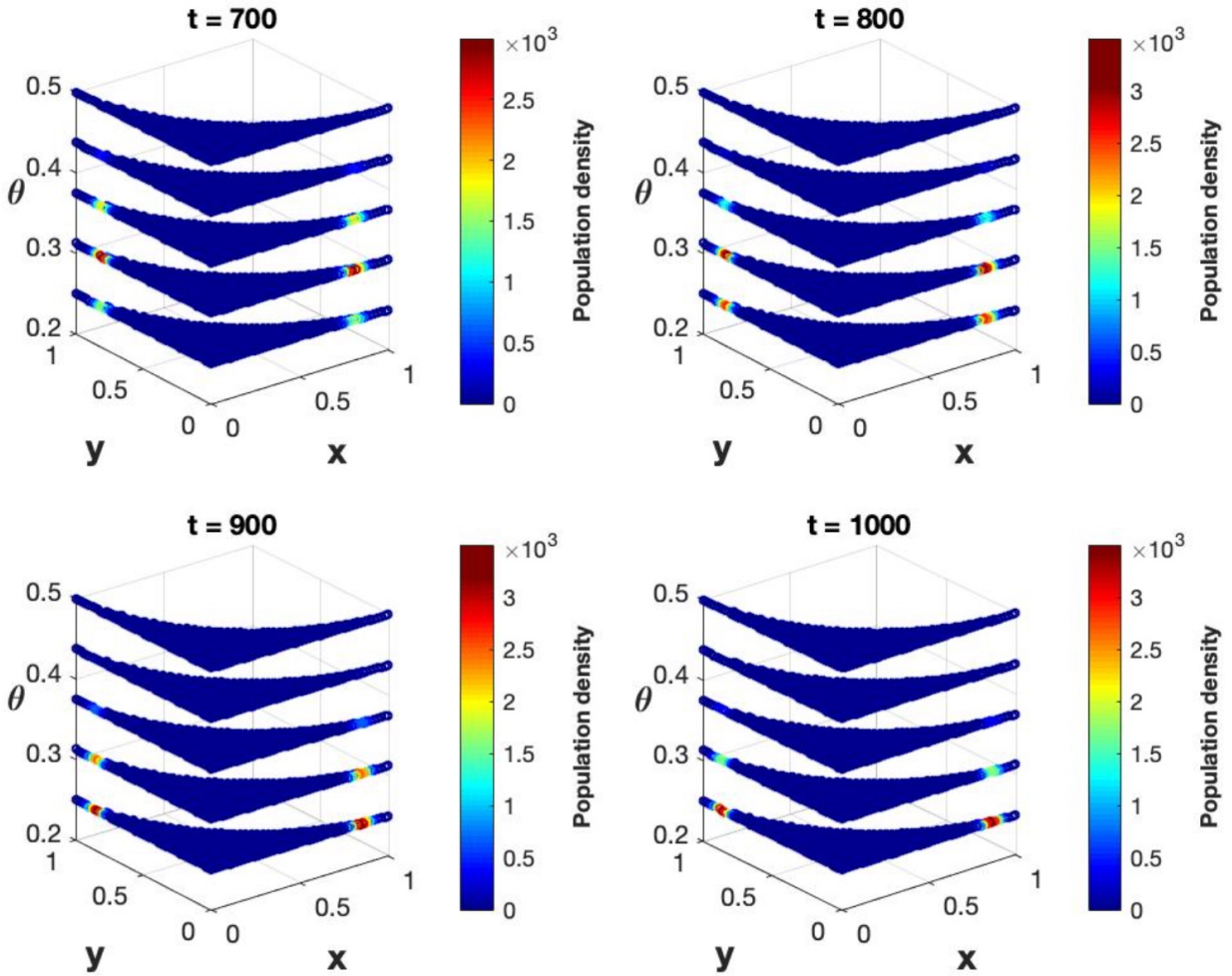
Phenotypic divergence: illustration (final stages)



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 $t = 1000$ (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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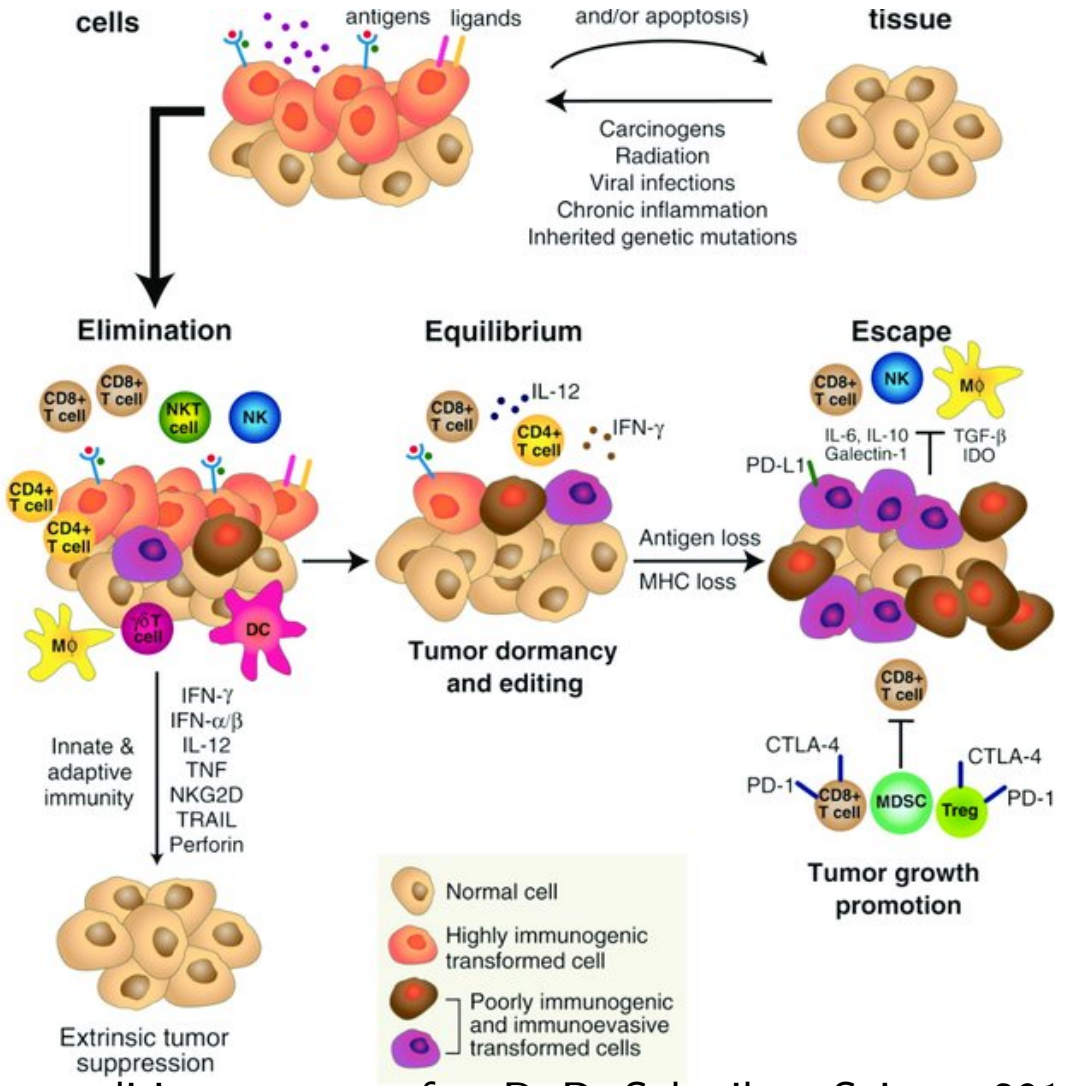
Immunoediting: elimination, equilibrium or escape



The cancer immunoediting process, after R. D. Schreiber, Science 2011, proceeds according to three possible asymptotic situations: elimination, equilibrium or escape.

A model of tumour-immune interactions

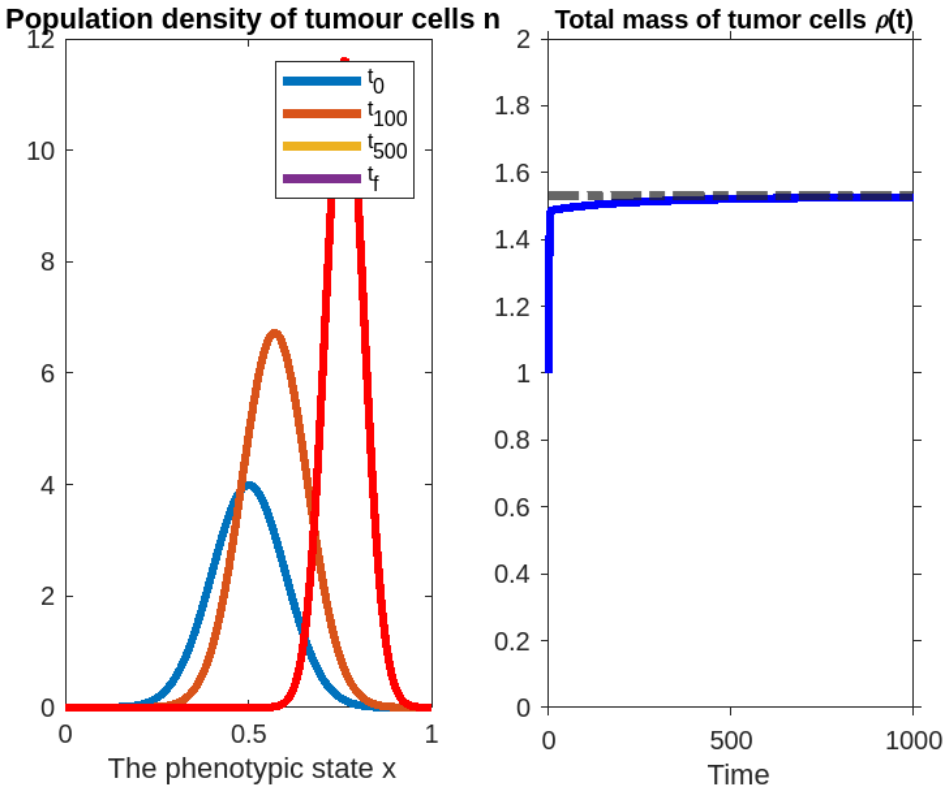
Structure variables for a population of tumour cells and a population of lymphocytes:
x, malignancy trait (adaptive, stemness-like, for de-differentiation in tumour cells)
y, anti-tumour aggressiveness trait (adaptive, in competent NK and T-lymphocytes)

$n(t,x)$ cancer cells, $\ell(t,y)$ competent lymphocytes at tumour site with $\nu(y)$ sensitivity of NK/T-lymphocytes to weakening molecules (PD ligands) emitted by tumour cells, $p(t,y)$ sourcing lymphocytes produced in lymphoid organs, $\chi(t,y)$ APC-borne or molecular identification message from tumour cells to lymphoid organs, *ICI* immune checkpoint inhibitor therapy

$$\begin{cases} \dfrac{\partial n}{\partial t}(t,x) = \left[r(x) - d(x)\rho(t) - \mu(x)\varphi_\lambda(t,x)\right] n(t,x), \\ \dfrac{\partial \ell}{\partial t}(t,y) = p(t,y) - \left(\dfrac{\nu(y)\rho(t)}{1+hICI(t)} + k_1\right)\ell(t,y), \\ \dfrac{\partial p}{\partial t}(t,y) = \chi(t,y)p(t,y) - k_2 p^2(t,y). \end{cases}$$

with the total mass of cancer cells at time t: $\rho(t) := \int_0^1 n(t,x)dx$,
$\chi(t,y) = \int_0^1 \omega(x,y)n(t,x)dx$, $\quad \omega(x,y) = \frac{1}{s}e^{-|x-y|/s}$ and
$\varphi_\lambda(t,x) = \int_0^1 \Psi_\lambda(x,y)\ell(t,y)dy$, where $\Psi_\lambda(x,y) = \left((1-\lambda) + \lambda\frac{1}{v}e^{-|x-y|/v}\right)\psi(y)$,
with immune mixing NK/T response parameter $\lambda \in [0,1]$ ($\lambda = 0$: nonspecific, innate NK-cells only; $\lambda = 1$: specific, adaptive T-cells only), ψ nondecreasing function of y.
Parameters s and v tune the precision of tumour antigen detection (s) /targeting (v).

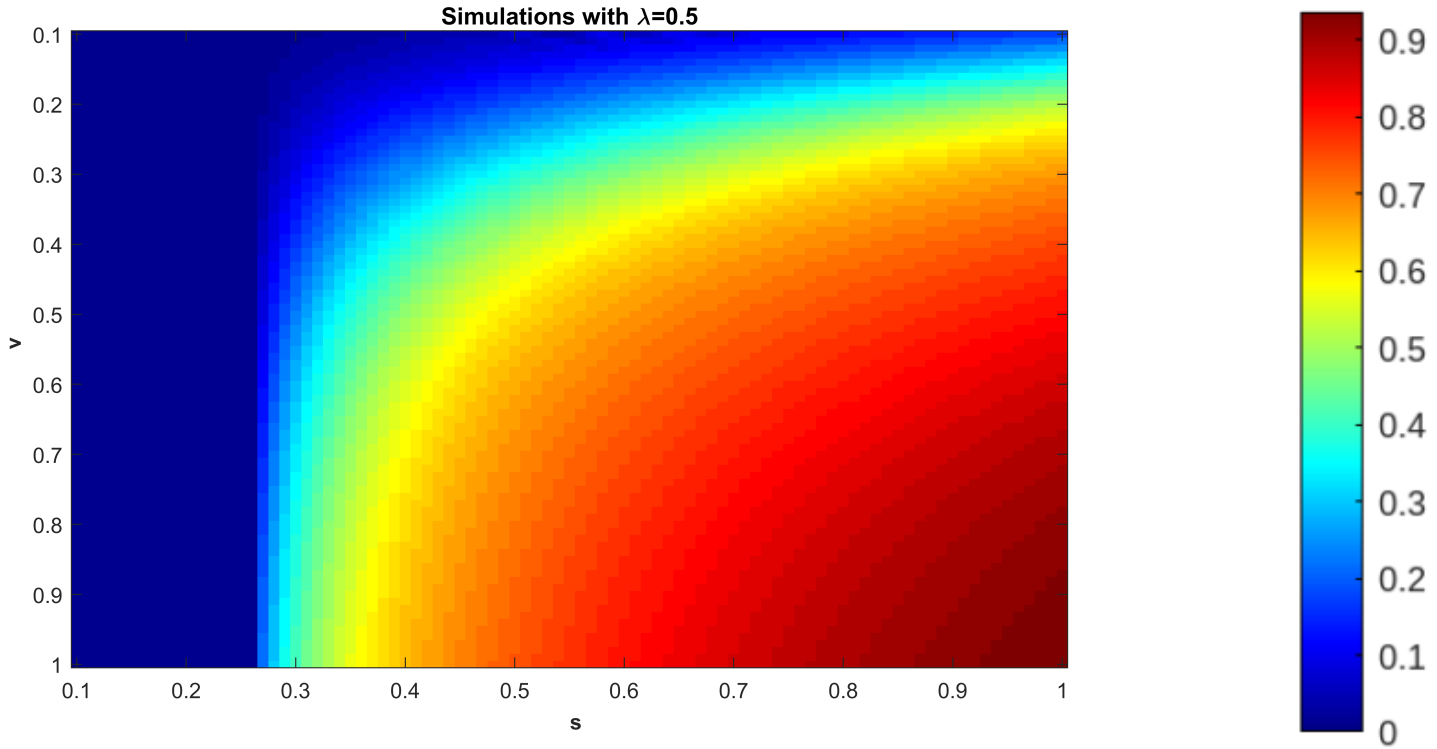
Tumour-immune interactions: simulation results (1)



Numerical simulation of the solution *in complete absence of immune response* (e.g., setting $\psi(y) = 0$). **Left panel**, plots of cell densities $n(t, \cdot)$ at different times up to $T = t_f = 1000$ (in red): the phenotype x evolves towards more and more malignancy (i.e. de-differentiated status). **Right panel**, dynamics of the total density of tumour cells $\rho(t)$. The black dashed line highlights a numerical estimation of the tumour cell carrying capacity $\rho^\star$, with $\rho(0) = 1$.

with Z. Kaid and C. Pouchol, 2023 submitted

Tumour-immune interactions: simulation results (2)



Precision of detection parameter s vs. precision of targeting parameter v in the innate-adaptive case (i.e., $\lambda = 0.5$): Heatmap representation of the contribution of the two localisation kernel parameters s and v to the final relative density $\frac{\rho^{\infty}}{\rho^{\star}}$ of total tumour cells at the end of simulations (where $\rho^{\star}$ is the tumour carrying capacity), in the case without treatment by *ICI*s. Of note, relatively wide s values (up to 0.3) for the detection of the malignancy phenotype, whatever the targeting precision v, clearly yield good immune efficacy. The case $\lambda = 1$ (T-cells only) would give similar results.

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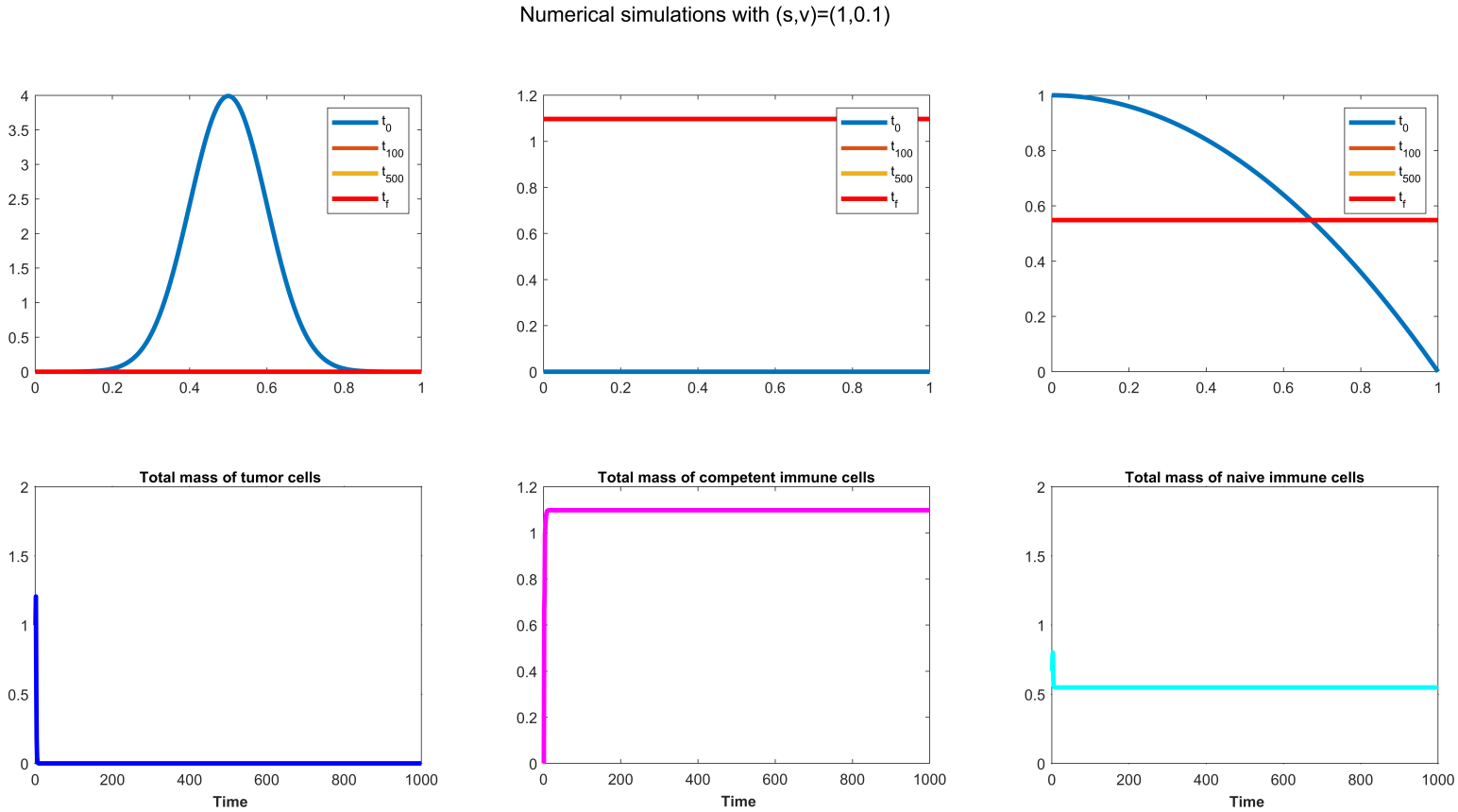
Tumour-immune interactions: simulation results (3)



Case of eradication: mixed innate/adaptive case ($\lambda = 0.5$). Simulations with $(s, v) = (1, 0.1)$ for $T = 500$.

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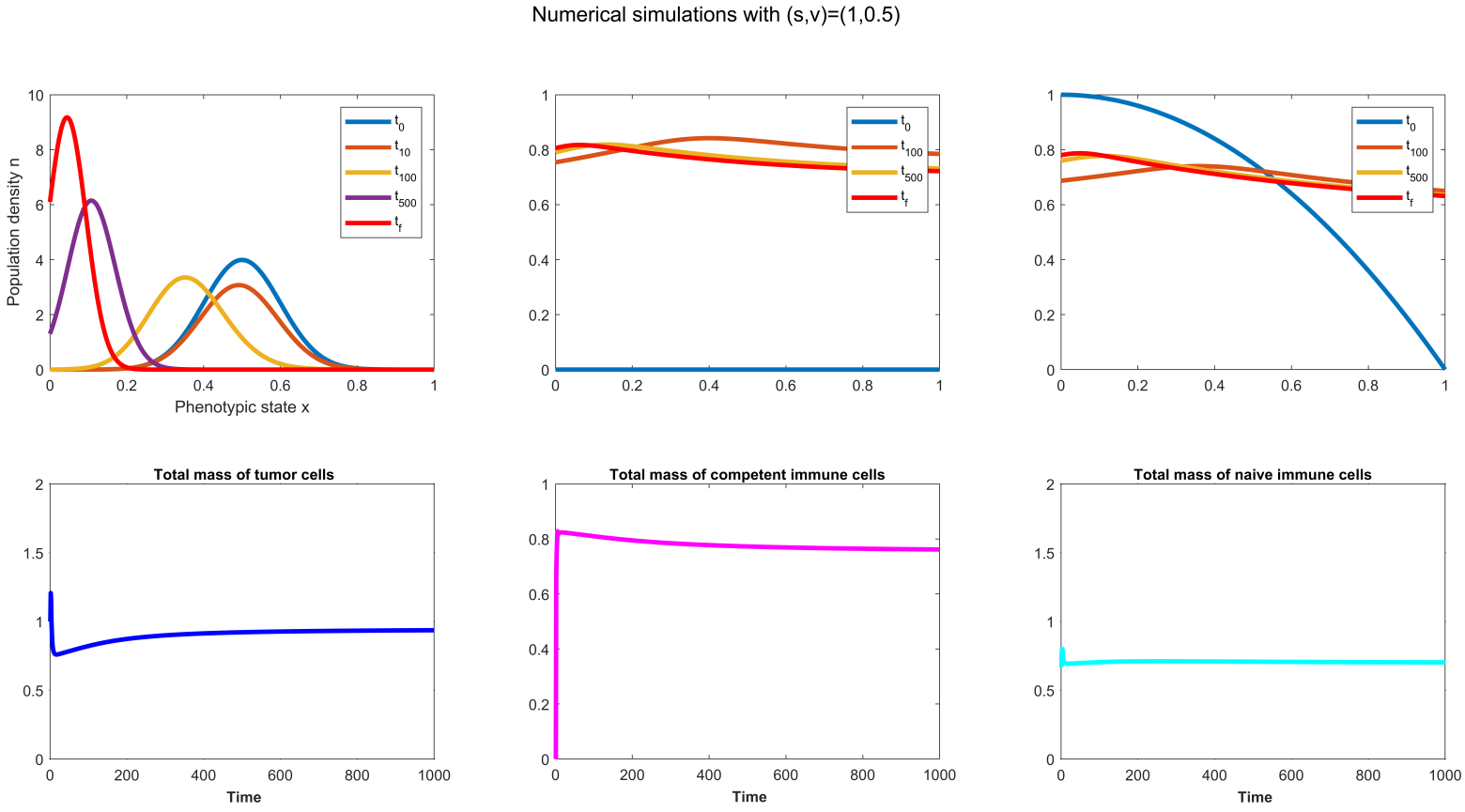
Tumour-immune interactions: simulation results (4)



Case of equilibrium: mixed innate/adaptive case ($\lambda = 0.5$). Simulations with $(s, v) = (1, 0.5)$ for $T = 500$. Note that the malignancy phenotype x concentrates onto a phenotype close to 0.

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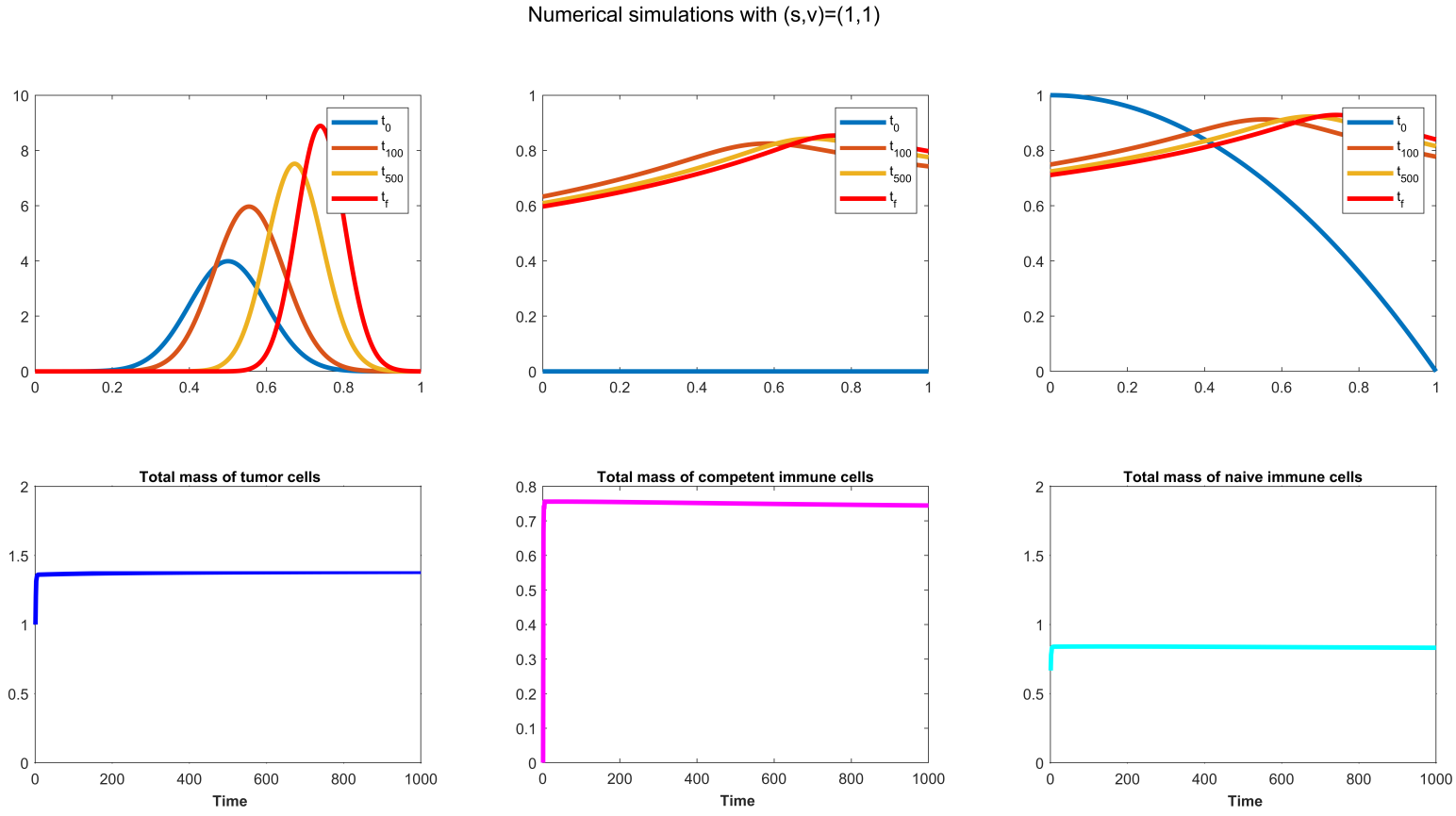
Tumour-immune interactions: simulation results (5)



Case of escape: mixed innate/adaptive case ($\lambda = 0.5$). Simulations with $(s, v) = (1, 1)$ for $T = 500$. Note that the malignancy phenotype x concentrates onto a phenotype close to 1.

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Tumour-immune interactions: simulation results (6)

Increasing levels of *ICI*s: here, $ICI = 0$

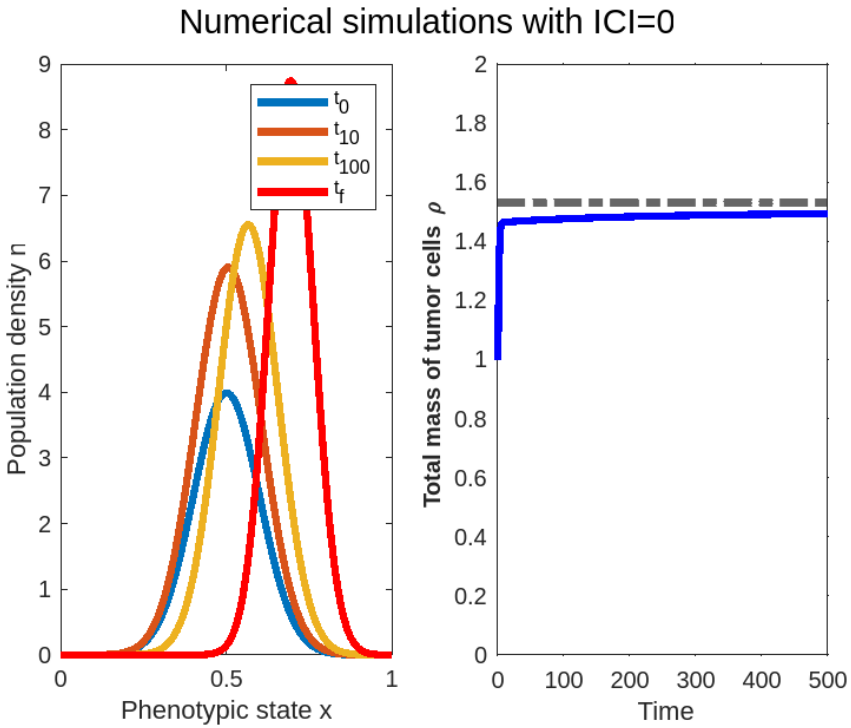

Figure: Escape. Simulation with $ICI = 0$.

Simulations with $\lambda = 1$ (only T-cells), $(s, v) = (1, 2)$ and increasing levels of *ICI*s, up to time $T = 500$. The black dashed line stands for the tumour carrying capacity $\rho^\star$.

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Tumour-immune interactions: simulation results (7)

Increasing levels of *ICI*s: here, $ICI = 1$

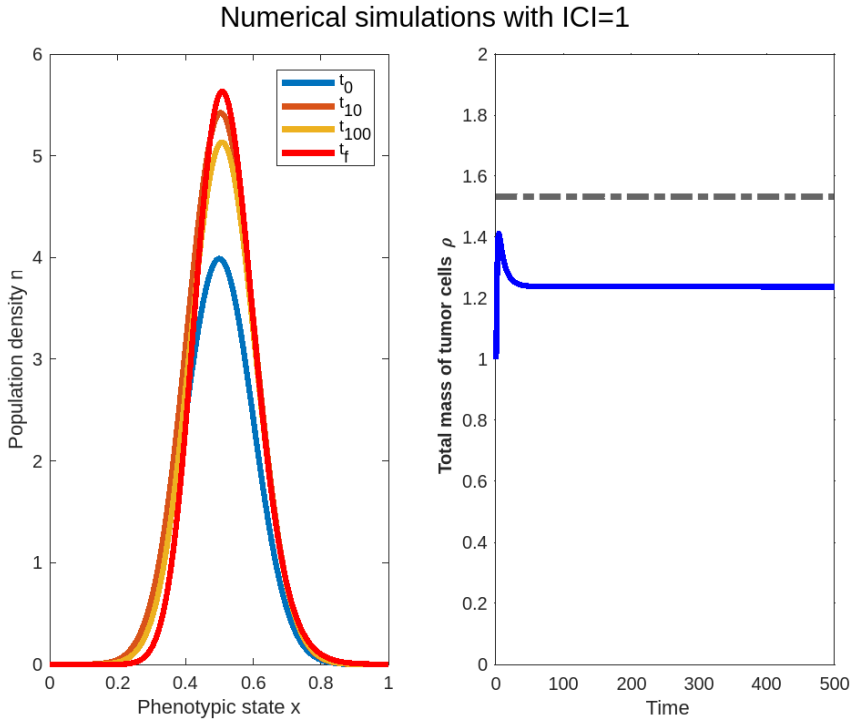

Figure: Equilibrium. Simulation with $ICI = 1$.

Simulations with $\lambda = 1$, $(s, v) = (1, 2)$ and increasing levels of *ICI*s, up to time $T = 500$. The black dashed line stands for the tumour carrying capacity $\rho^\star$.

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Tumour-immune interactions: simulation results (8)

Increasing levels of *ICI*s: here, $ICI = 10$

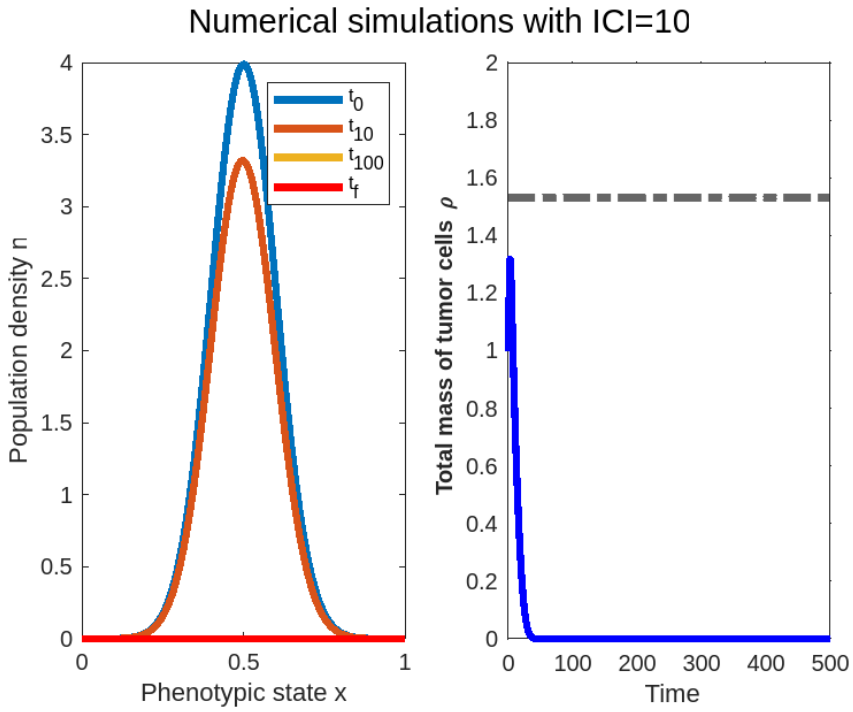

Figure: Eradication. Simulation with $ICI = 10$.

Simulations with $\lambda = 1$, $(s, v) = (1, 2)$ and increasing levels of *ICI*s, up to time $T = 500$. The black dashed line stands for the tumour carrying capacity $\rho^\star$.

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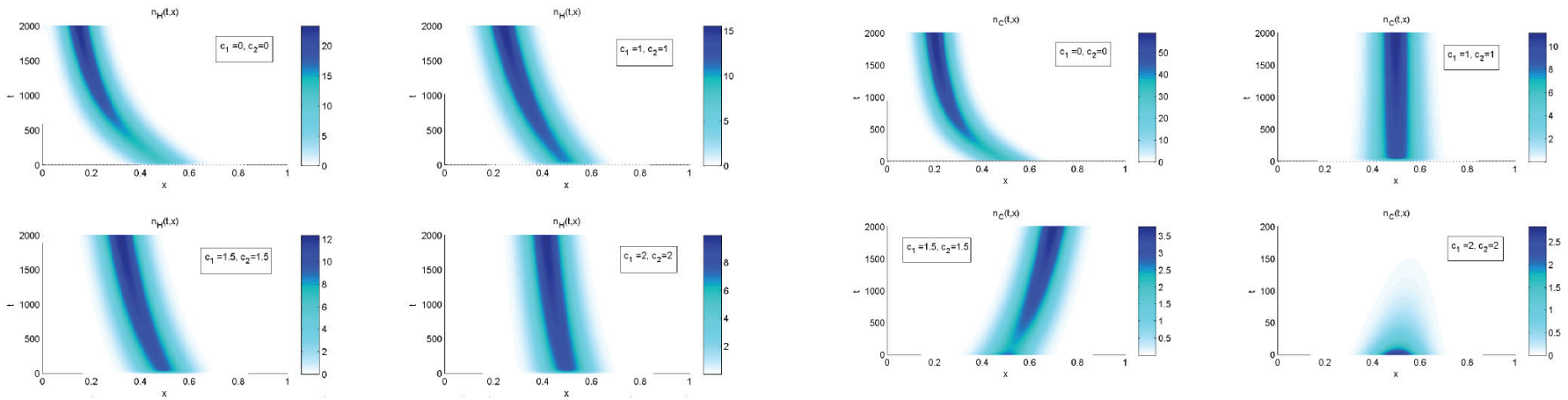
Non-local Lotka-Volterra model of treatment for 2 cell populations, 2 different drugs and a resistance phenotype x

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

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

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

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

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 holds 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* $+\infty$.

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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)

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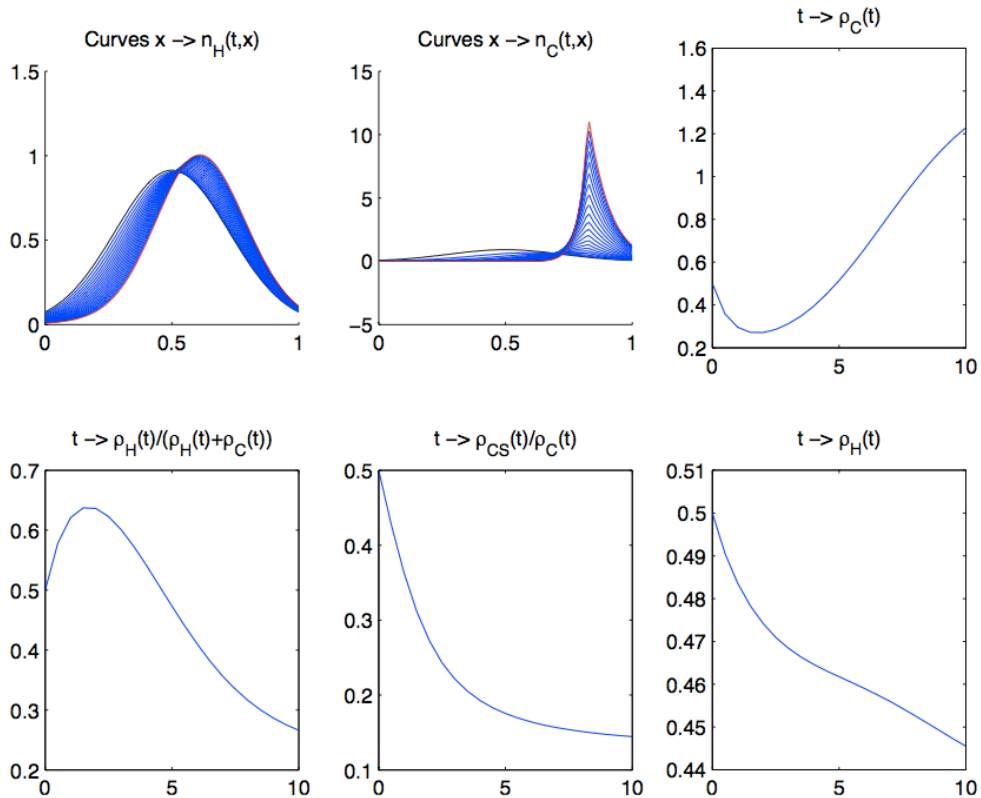
How to be deleterious by using constant doses of drugs

[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}.

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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:

- 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 uses the Pontryagin maximum principle.

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Simulations illustrating this theorem

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

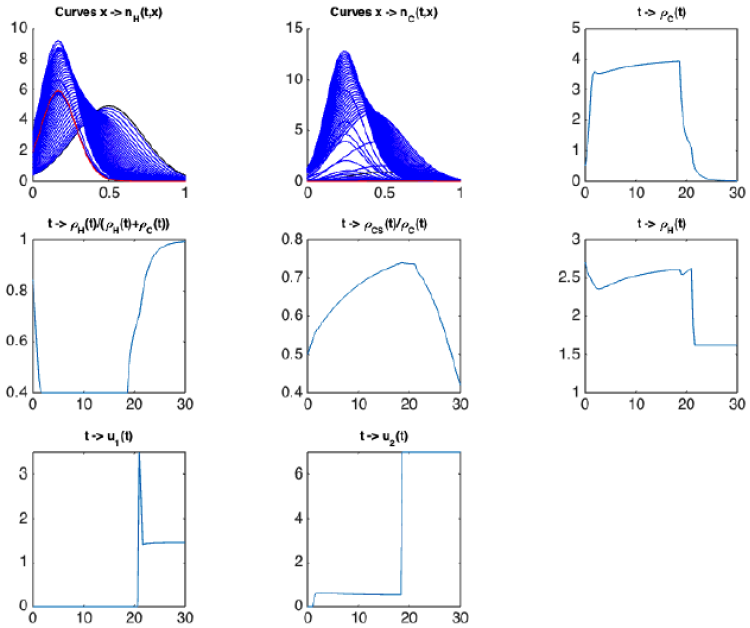

Figure 4: Simulation of (**OCP**) for $T = 30$.

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

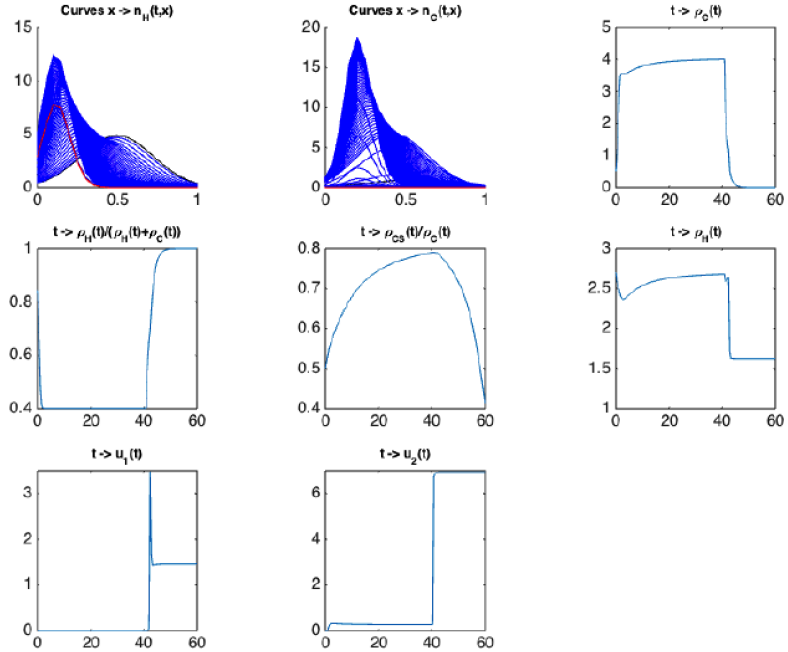

Figure 5: Simulation of (**OCP**) for $T = 60$.

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.

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Comparison with "almost periodic" therapeutic strategies

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

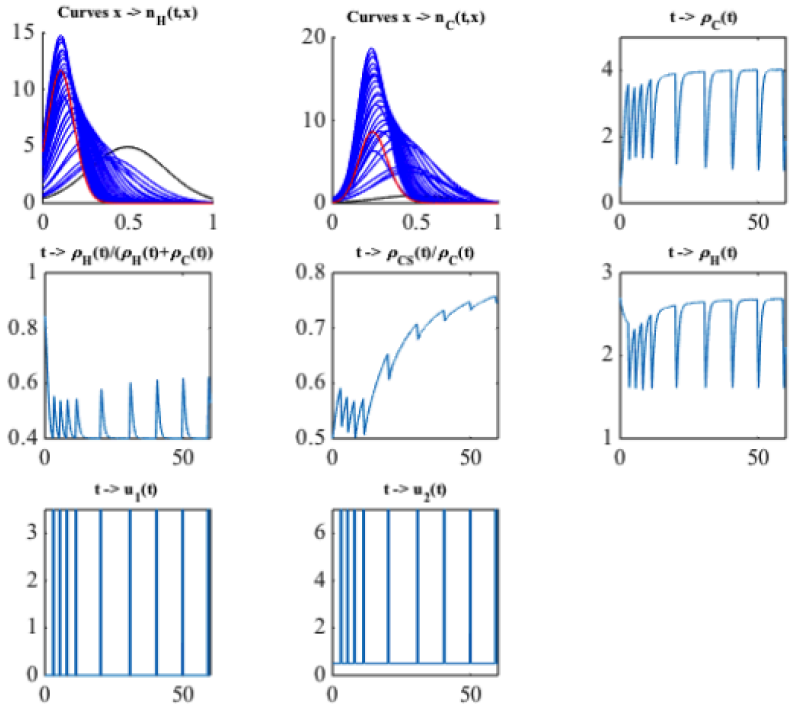

Figure 6: Quasi-periodic strategy, for $T = 60$.

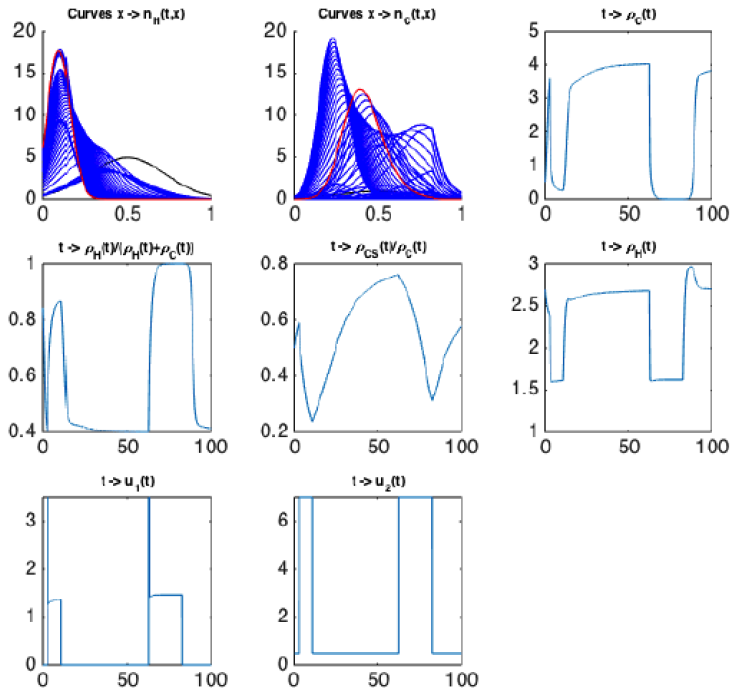

Figure 7: Second quasi-periodic strategy, for $T = 100$.

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?).

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Conclusion on the interest of continuous phenotype-structured cell population models

- Capture any sort of relevant heterogeneity related to a given biological question
- May represent phenotype plasticity by adding diffusion/advection in equations
- Often of the nonlocal Lotka-Volterra type, well-studied systems
- Analysable in terms of asymptotic behaviour
- Can result from agent-based models by passage to the limit ($\varepsilon \to 0$, $N \to +\infty$)
- Conversely, may be transformed in compartmental ODE systems by discretisation of the phenotype space
- However, note that structuring biological variables are by nature continuous
- Amenable to control and optimal control methods, in particular for therapeutics

References

- Kaid, Z., Pouchol, C., *JC*. A phenotype-structured model for the tumour-immune response. https://hal.science/hal-03936993 (authors' preprint), Submitted, January 2023.
- Alvarez Borges, F.E., Carrillo, J.A., *JC*. Evolution of a structured cell population endowed with plasticity of traits under constraints on and between the traits. https://hal.science/hal-03344894 (authors' proof) *J. Math. Biol.*, 85:64, September 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.
- Lorenzi, T., Chisholm, R.H., *JC*. Tracking the evolution of cancer cell populations through the mathematical lens of phenotype-structured equations. Biology Direct, Online, August 2016. Available online in open access
- 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.