Institute of Natural Sciences, SJTU

Winter School on "Mathematical Models of Tumour and Disease"

From single-cell molecular to cell-populational phenotypically structured models to optimise cancer therapeutics

IV. Drug resistance in cancer, with perspectives in optimal control

Jean Clairambault[†], Tommaso Lorenzi, Alexander Lorz, Benoît Perthame, Camille Pouchol, Emmanuel Trélat

Mamba INRIA team & Laboratoire Jacques-Louis Lions, UPMC, Paris
[†] *http : //who.rocq.inria.fr/Jean.Clairambault/Jean_Clairambault_en.html*

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A general framework to optimise cancer therapeutics: designing mathematical methods along 3 axes

- Modelling the behaviour of growing cell populations on which anticancer drugs act (the targeted cell populations): proliferating tumour and healthy cell populations, including representing functional (not necessarily molecular) targets for pharmacological control
- (When PK-PD models are available) Modelling the external control system, i.e., fate of drugs in the organism, at the level of functional targets (proliferation, death, differentiation) in cell populations by functional, rather than molecular, pharmacokinetics-pharmacodynamics (PK-PD)
- Optimising therapeutic controls: dynamically optimised control of theoretical drug delivery flows representing time-dependent objectives and constraints, making use of known or hypothesised differences between cancer and healthy cell populations

Choosing the constraint to be represented determines the model of proliferation used to optimise drug delivery, aiming to avoid the two main pitfalls of pharmacotherapy:

- *Toxicity issues.* Limiting toxic side effects to preserve healthy cell populations leads to representing proliferating cell populations by ordinary differential equations, or by age-structured models: physiologically structured partial differential equations

- *Drug resistance issues.* Limiting emergence of drug-resistant cell subpopulations in tumour tissues leads to using (evolutionary) phenotypic trait-structured proliferation: physiologically structured evolutionary integro-differential equations

- In fact, one should consider the two issues simultaneously, i.e., two similarly structured cell populations, healthy and cancer, with different characteristics w.r.t. to drug effects and to evolution towards resistance: phenotypic stability of healthy cell populations vs. plasticity of cancer cell populations

Modelling framework: structured population dynamics

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

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

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

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

- Cancer cell populations: (1) tumour growth; (2) asymptotic distribution of trait
- Space is not necessarily a relevant structure variable when studying drug control

Introduction to IDEs: typical 1D IDE logistic model

Prototype model, where $n(t,x)$ stands for the density of cells of phenotype $x \in [0,1]$:

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

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 $n^0 \in L^1([0,1])$

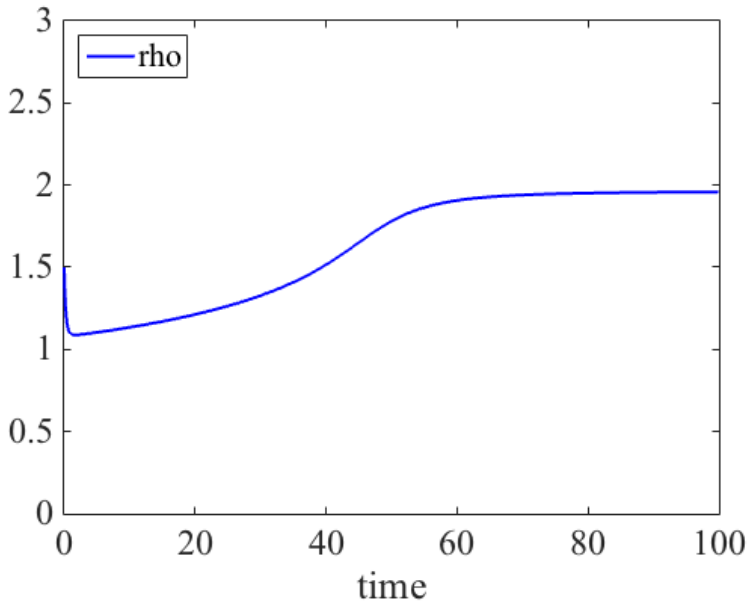
[More general settings for the growth rate $R(x,\rho(t))$, here $\big(r(x) - d(x)\rho(t)\big)$, have been studied in Benoît Perthame's book Transport equations in biology *(2007)]*

Questions: what is the asymptotic behaviour of

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

Introduction to IDEs: convergence and concentration (1D)

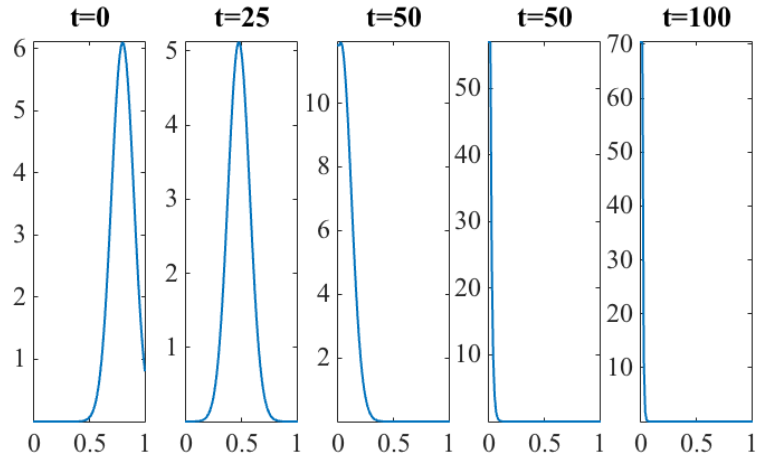
Convergence: Plot of $t \mapsto \rho(t)$



Firstly, it can be shown that: ρ converges to ρ^∞, the smallest value such that $r(x) - d(x)\rho^\infty \leq 0$ on $[0,1]$. *(Idea of proof: show that* $\int_0^{+\infty} \left|\frac{d\rho}{dt}\right|_- dt < +\infty$ *and – with additional hypotheses – that* ρ *is bounded; then convergence follows.)*

Introduction to IDEs: convergence and concentration (1D)

Concentration: 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*

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

[Proof: see Camille Pouchol's internship report: *"Modelling interactions between tumour cells and supporting adipocytes in breast cancer"*, UPMC, September 2015, `https://hal.inria.fr/hal-01252122`]

Drug effects on cell populations and their optimisation
Model with mutations, one cytotoxic drug: cancer cells

- $x =$ level of expression of a drug resistance phenotype (to a given drug)
- $n_H(x,t)$, $n_C(x,t)$ densities of cell populations (H=healthy, C=tumour)

$$\frac{\partial}{\partial t} n_C(x,t) = \Big[\overbrace{(1-\theta_C)\, r(x)}^{\text{growth}} - \overbrace{d(x)}^{\text{death}} - \overbrace{u(t)\mu_C(x)}^{\text{drug effect}} \Big] n_C(x,t)$$

$$+\theta_C \overbrace{\int r(y) M_{\sigma_C}(y,x) n_C(y,t) dy}^{\text{birth with mutation}}$$

- $r(x) =$ basic reproduction rate, $d(x) =$ basic death rate; we assume $r(0) > d(0) > 0, \qquad r'(\cdot) < 0, \qquad r(+\infty) = 0, \qquad d'(\cdot) > 0,$
- $0 \le \theta_{H,C} < 1$ ($\theta_C > \theta_H$) is the proportion of divisions with mutations,
- $\mu_{[H,C]}(x)$ (with $\mu'_C(\cdot) < 0$) represents the phenotype-dependent response to cytotoxic drug, with concentration $u(t)$, designed to target cancer cells.
- Note: assumptions $r(\cdot) > 0, \mu_C(\cdot) > 0$, $\mu'_C(\cdot) < 0$ and $r'(\cdot) < 0$ (cost of resistance: the higher is x, the lower is proliferation) represent an *evolutionary double bind on resistant cancer cell populations*, *i.e., an evolutionary trade-off between growing (thus getting exposed) and keeping still (thus surviving)*

(Lorz et al., M2AN 2013)

Model with mutations, one cytotoxic drug: healthy cells

$$\frac{\partial}{\partial t} n_H(x,t) = \Big[\overbrace{\frac{1-\theta_H}{\left(1+\rho(t)\right)^{\beta}} r(x)}^{\text{growth with homeostasis}} - \overbrace{d(x)}^{\text{death}} - \overbrace{u(t)\mu_H(x)}^{\text{drug effect}} \Big] n_H(x,t)$$

$$+ \frac{\theta_H}{\left(1+\rho(t)\right)^{\beta}} \overbrace{\int r(y) M_{\sigma_H}(y,x) n_H(y,t) dy}^{\text{birth with mutation}},$$

where the total population is defined as

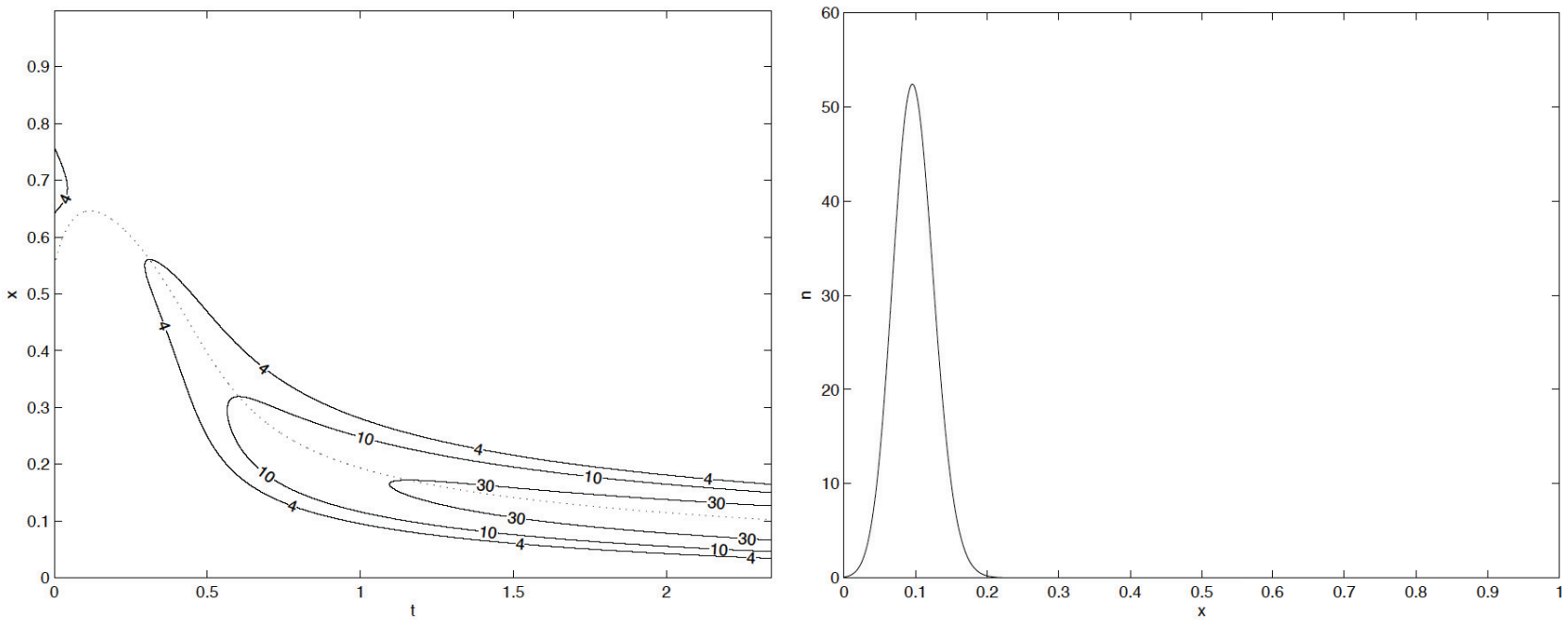
$$\rho(t) = \rho_H(t) + \rho_C(t); \rho_H(t) = \int_{x=0}^{\infty} n_H(x,t)dx; \rho_C(t) = \int_{x=0}^{\infty} n_C(x,t)dx.$$

- $\beta > 0$ to impose healthy tissue homeostasis,
- $u(t)$ denotes the instantaneous dose (concentration) of chemotherapy. We assume in this model that its effect is cytotoxic, i.e., on the death term only.

(Lorz et al., M2AN 2013)

Model with mutations, one cytotoxic drug: illustrations (1)

[Sensitive cell population case: illustration of Gause's exclusion principle]
Theorem: Monomorphic evolution towards drug sensitivity, illustrated here with $\theta_H = 0$, *(no mutations) and* $\mu_H = 0$ *(no drug-induced resistance)*

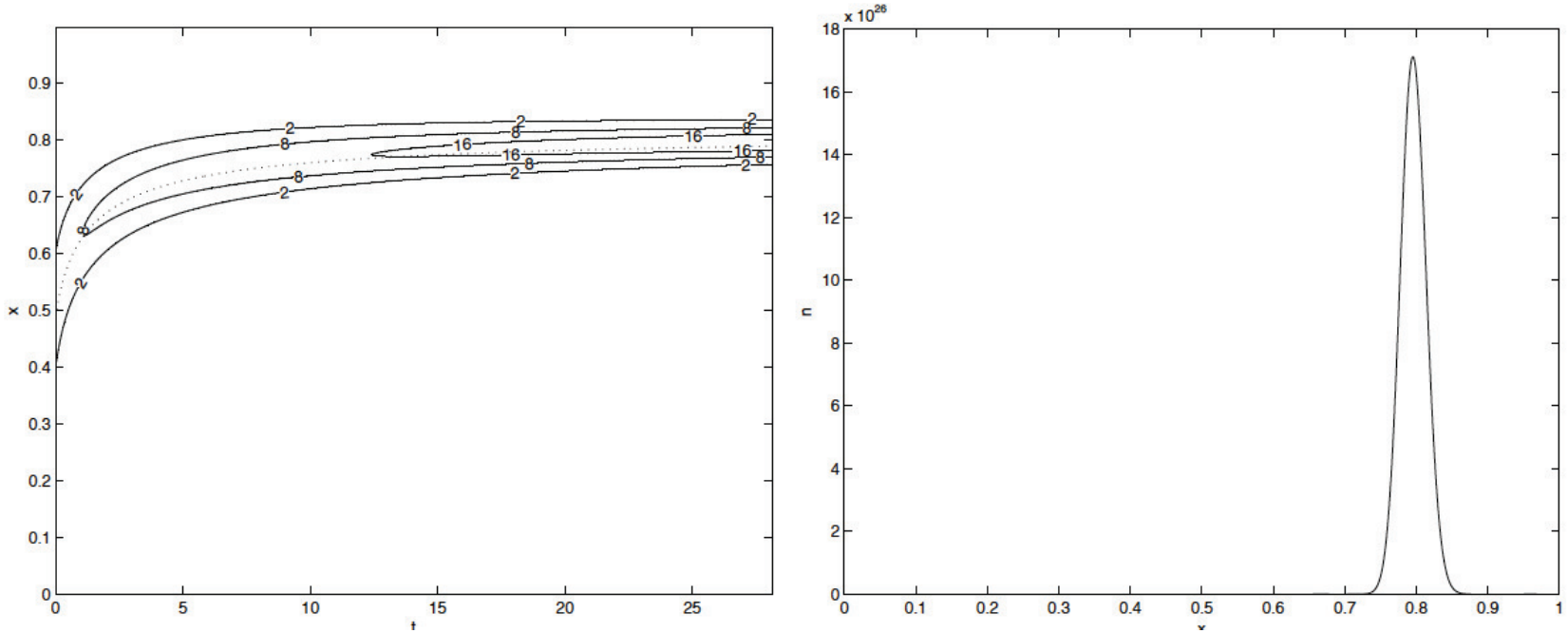


Left panel: starting from a medium phenotype $x = 0.5$, *level sets of a drug-sensitive population in the* (t, x) *plane. Right panel: asymptotic distribution of this drug-sensitive population according to the drug resistance phenotype* x.

(Lorz et al., M2AN 2013)

IModel with mutations, one cytotoxic drug: illustrations (2)

[Resistant cell population case: Gause's exclusion principle again]
Theorem: Monomorphic evolution towards drug-induced drug resistance, here with $\theta_C = 0$, $\mu_C(\cdot) > 0, r'(\cdot) < 0, \mu'_C(\cdot) < 0$ *(costly drug-induced resistance),* $u(t) = Cst$



Left panel: starting from a medium phenotype $x = 0.5$*, level sets of a drug- resistant population in the* (t, x) *plane. Right panel: asymptotic distribution of this drug-resistant population according to the drug resistance phenotype* x*.*

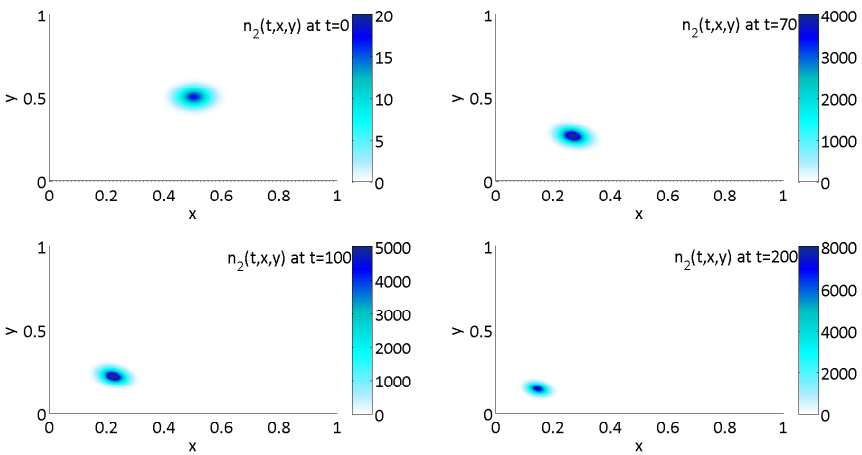
(Lorz et al., M2AN 2013)

IDE model, no mutations: phenotype-structured non-local Lotka-Volterra model with 2 drugs, cytotoxic $u_1(t)$, cytostatic $u_2(t)$, bidimensional resistance phenotype (x, y)

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

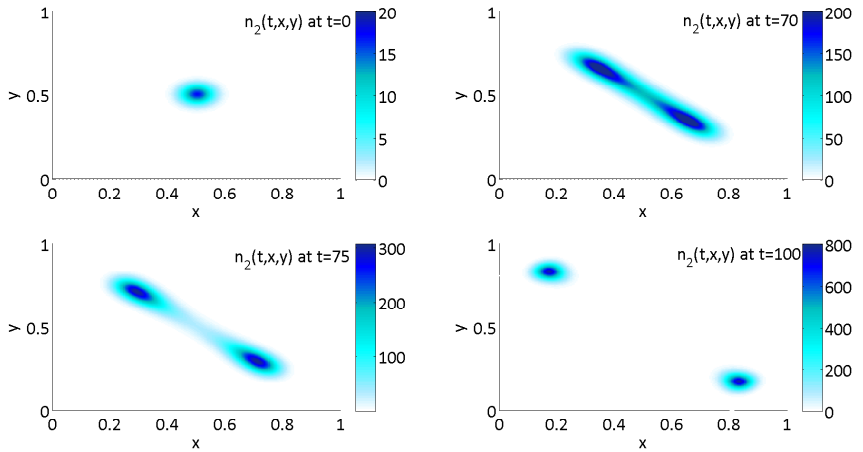
Environment: $I_C(t) = \alpha \int_0^1 \int_0^1 n_C(x,y,t)\, dx\, dy + \beta \int_0^1 \int_0^1 n_H(x,y,t)\, dx\, dy$

Sensitive cell population case:



Convergence toward total sensitivity

Resistant cell population case:



Convergence toward 2 resistant phenotypes

(Lorenzi & Lorz, unpublished)

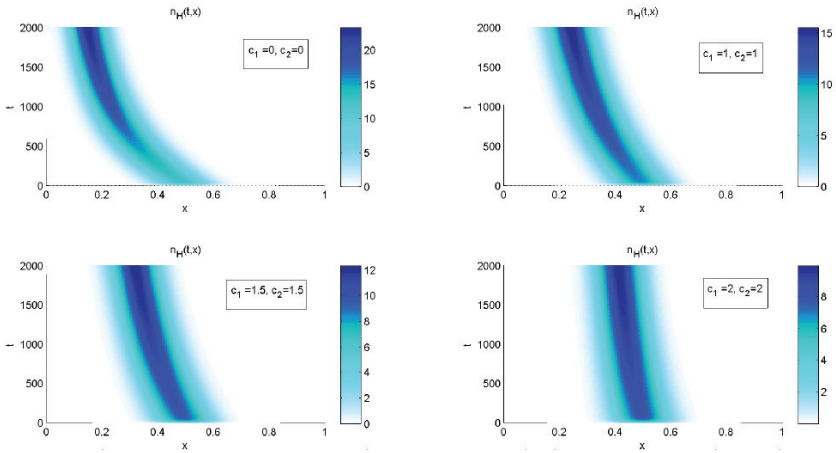
Same phenotype-structured non-local Lotka-Volterra model with 2 drugs and one (scalar) resistance phenotype x

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

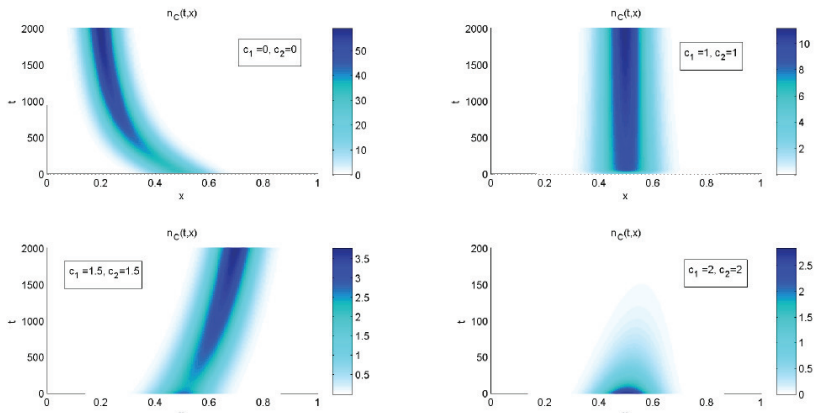
$$\frac{\partial}{\partial t} n_C(x,t) = \left[\frac{r_C(x)}{1 + k_C u_2(t)} - d_C(x) I_C(t) - u_1(t) \mu_C(x) \right] n_C(x,t)$$

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

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



Healthy cells: preserved



Cancer cells: eventually extinct

What about space? Considering both a (1D) resistance phenotype and (1D) space in a tumour spheroid: equations

We assume that the evolution of functions n, s (nutrients), c_1 and c_2 in a 1D radially symmetric tumour spheroid ($r \in [0,1]$) is ruled by the following set of equations:

$$\partial_t n(t,r,x) = \left[\frac{p(x)}{1+\mu_2 c_2(t,r)} s(t,r) - d(x)\varrho(t,r) - \mu_1(x)c_1(t,r)\right] n(t,r,x), \quad (1)$$

$$-\sigma_s \Delta s(t,r) + \left[\gamma_s + \int_0^1 p(x)n(t,r,x)dx\right] s(t,r) = 0, \quad (2)$$

$$-\sigma_c \Delta c_1(t,r) + \left[\gamma_c + \int_0^1 \mu_1(x)n(t,r,x)dx\right] c_1(t,r) = 0, \quad (3)$$

$$-\sigma_c \Delta c_2(t,r) + \left[\gamma_c + \mu_2 \int_0^1 n(t,r,x)dx\right] c_2(t,r) = 0, \quad (4)$$

with zero Neumann conditions at $r = 0$ coming from radial symmetry and Dirichlet boundary conditions at $r = 1$

$$s(t,r=1) = s_1, \partial_r s(t,r=0) = 0, c_{1,2}(t,r=1) = C_{1,2}(t), \partial_r c_{1,2}(t,r=0) = 0. \quad (5)$$

For each t, we also define $\rho(t,r) = \int_0^1 n(t,r,x)\,dx$ (local density at radius r) and $\rho_T(t) = \int_0^1 \rho(t,r)r^2\,dr$ (global density).

Tumour spheroid: simulations with constant drug doses (1)

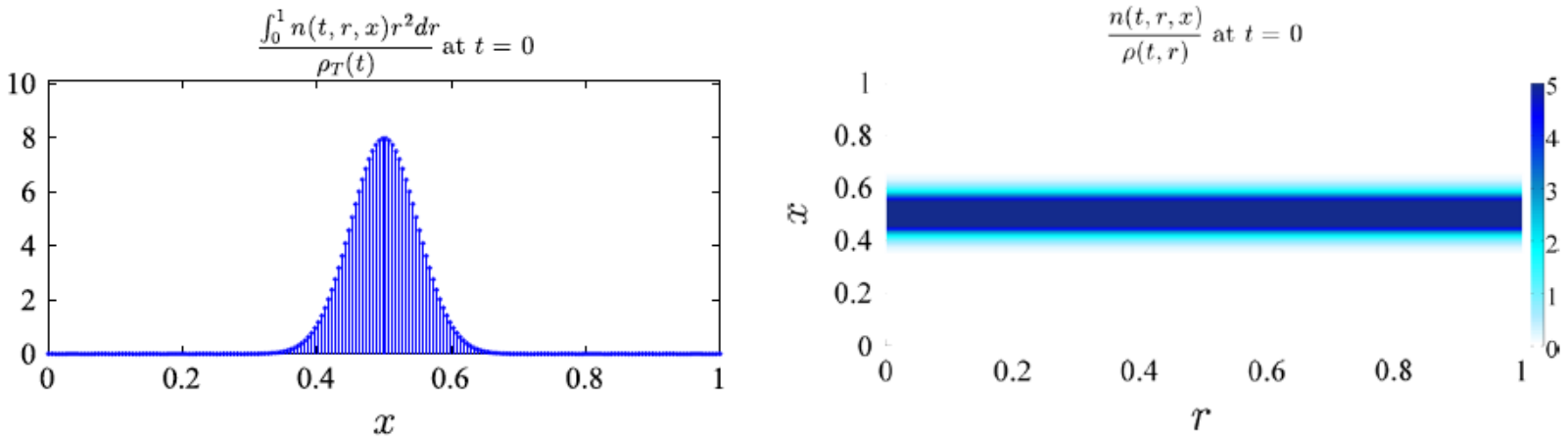
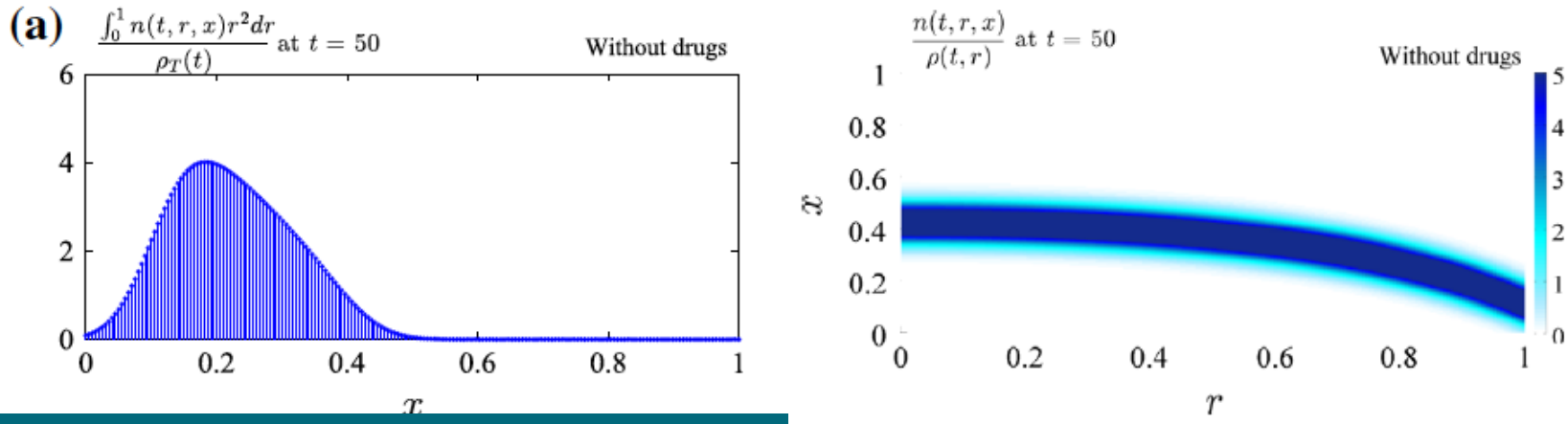
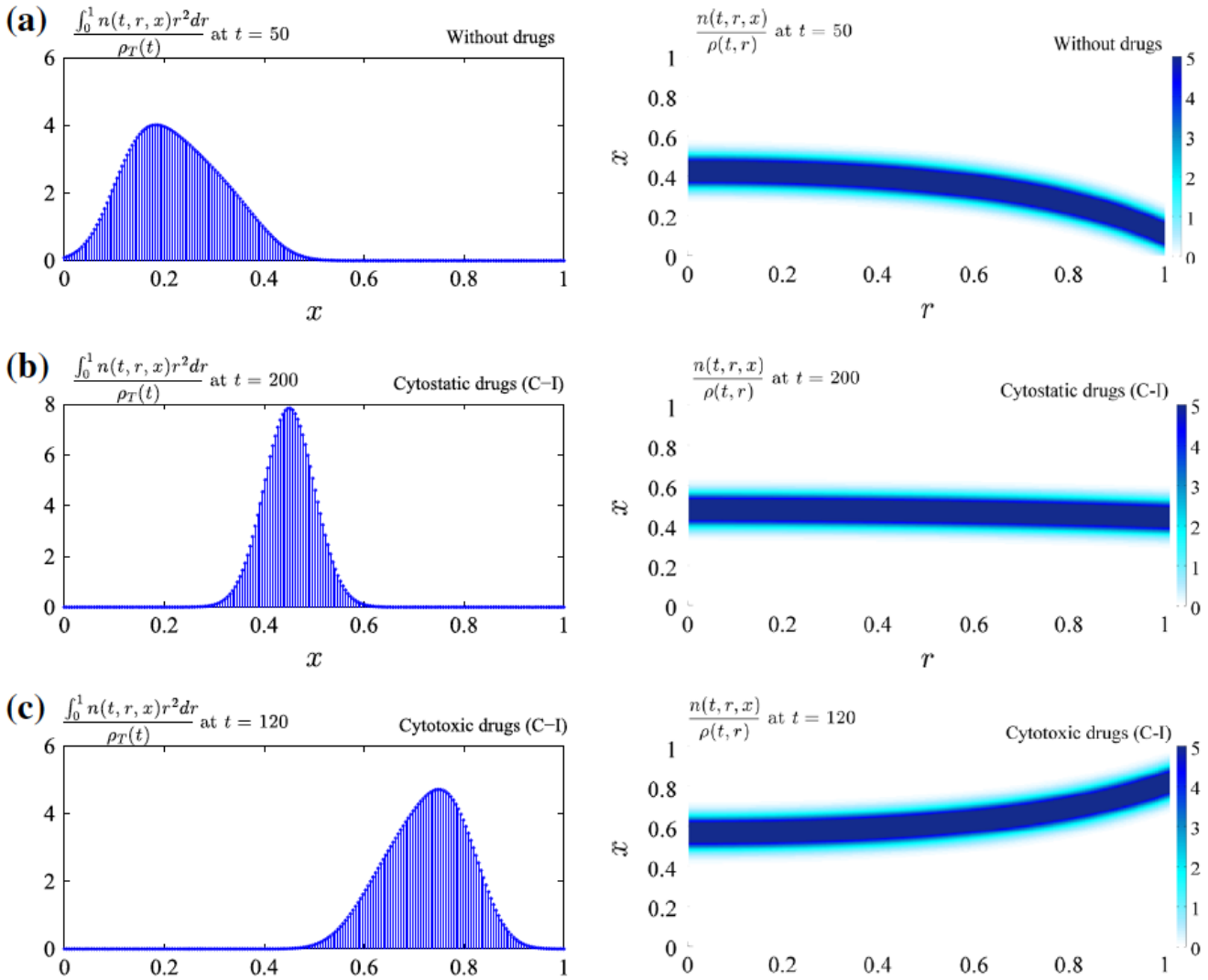


Fig. 1 Initial phenotypic distribution. Plots of $\int_0^1 n(t,r,x)r^2\mathrm{d}r/\rho_T(t)$ (*left panel*) and $n(t,r,x)/\rho(t,r)$ (*right panel*) at $t=0$. The initial cell population is almost monomorphic

Evolution without drugs: towards sensitive phenotype ($x \to 0$)



Tumour spheroid: simulations with constant drug doses (2)



Cytotostatic c_2 has almost no effect / Cytotoxic c_1 clearly induces resistance

(Lorz et al. BMB 2015)

Tumour spheroid (3): constant or bang-bang control?

Therapeutic strategies c_1/c_2: Constant/Bang-bang vs. Bang-bang/Constant

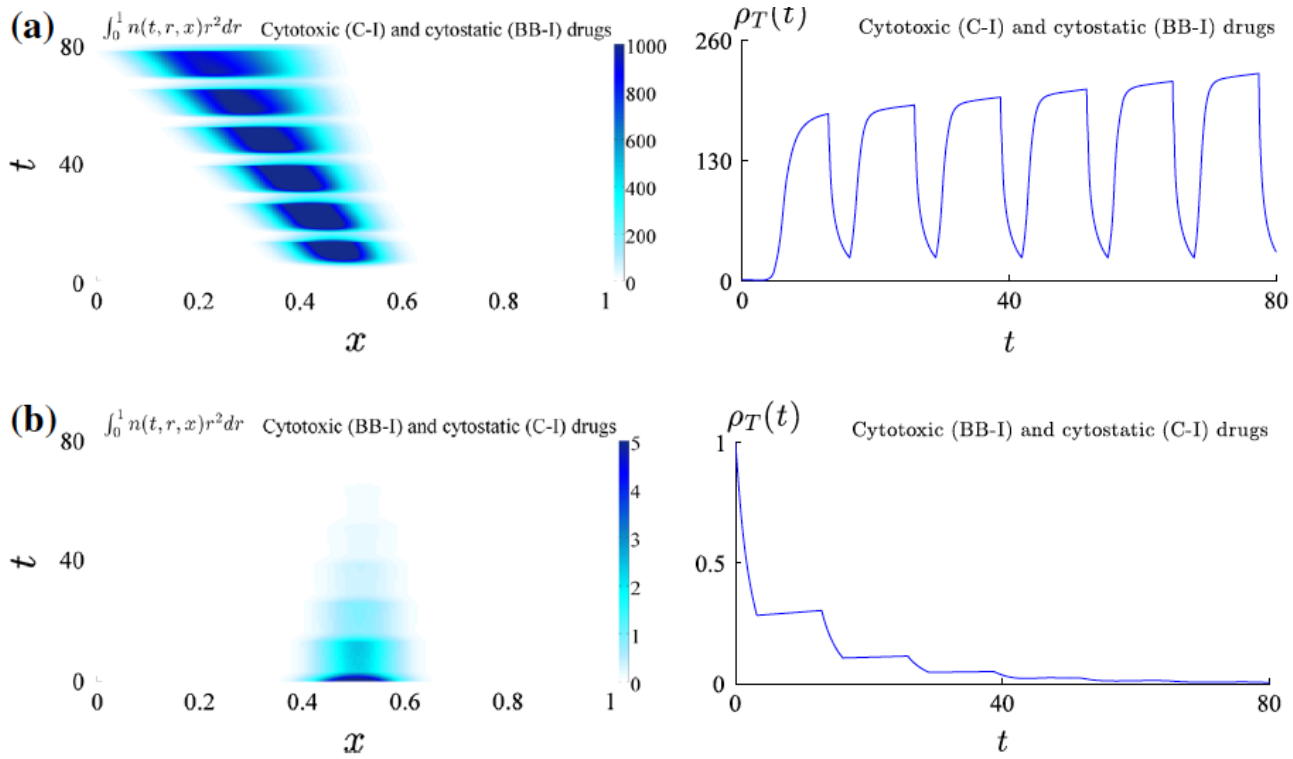


Fig. 11 **a** Cytotoxic (C-I) and cytostatic (BB-I) drugs. Plots of $\int_0^1 n(t, r, x)r^2 \mathrm{d}r$ (*left panel*) and $\rho_T(t)$ (*right panel*). Bang–bang infusion of cytostatic drugs together with constant infusion of cytotoxic drugs weakly affects the dynamics of cancer cells by comparison with the case without therapies, apart from temporary reductions of the global population density. **b** Cytotoxic (BB-I) and cytostatic (C-I) drugs. Plots of $\int_0^1 n(t, r, x)r^2 \mathrm{d}r$ (*left panel*) and $\rho_T(t)$ (*right panel*). Bang–bang infusion of cytotoxic drugs together with constant delivery of cytostatic drugs can push cancer cells toward extinction. The unit of time is days. All values are normalized with respect to the initial global population density

(Lorz et al. BMB 2015)

"What does not kill me strengthens me"

- Note that in the representation of the drug targets on cancer cell populations in the integro-differential equation, with the numerical values chosen for the target functions μ_C and r_C standing for the sensitivities to drugs u_1 and u_2,

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

  the cytostatic drug u_2 only slows down proliferation (softly slowing down velocity in the cell division cycle), but does not arrest it, at least at low doses...

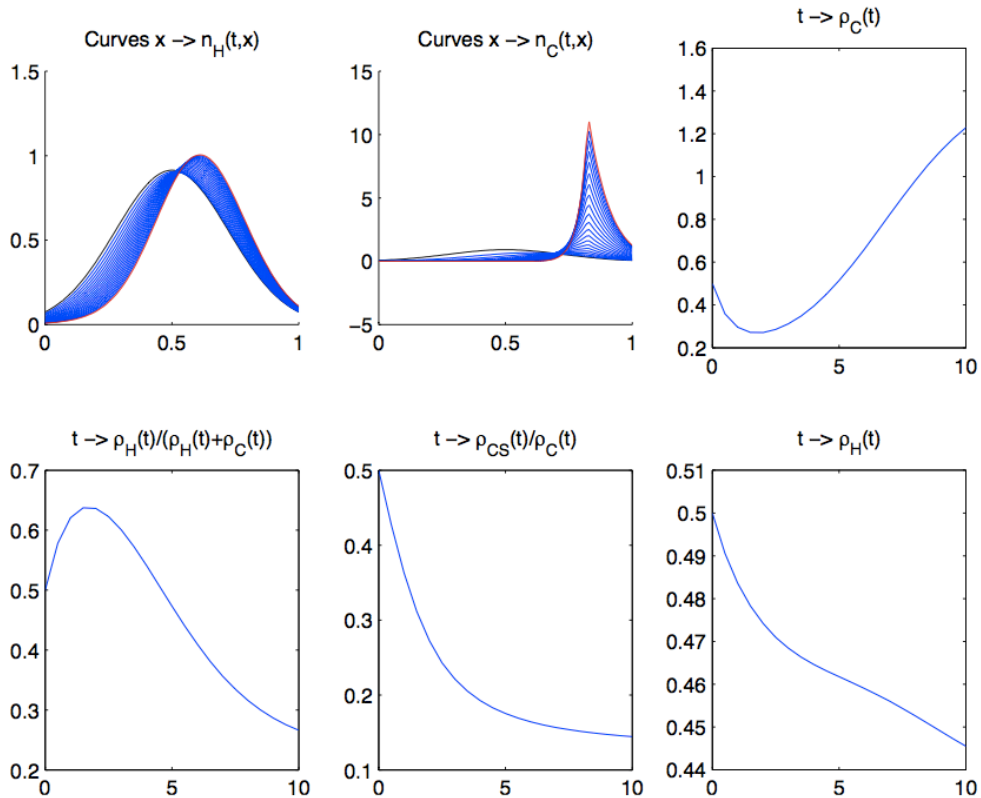
- ...whereas the cytotoxic drug u_1 *kills* the cells by increasing the death term, hence it is actually a direct life threat to the cell population, that 'defends itself' (biological bases under assessment...) by increasing its resistance phenotype x

- This resistance-inducing killing effect should be avoided as long as possible. In summary: limit proliferation but do not try too hard to kill cells, lest the cell population should become resistant, but give cytotoxics only at high doses (MTD) *during a short interval of time only*, thus avoiding to trigger resistance.

- An alternative to such use of MTD (maximum tolerated dose) towards the end of the chemotherapy course is *metronomics*, that also prevents developing resistance by giving low doses of cytotoxics... expecting that the population, thwarted in its proliferation, will be kept in check by the immune system. This has not been represented in an optimal control perspective thus far (however, see Carrère JTB 2017 on metronomics).

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 $T = 10$,
starting from the same medium phenotype $x = 0.5$ for both cell populations:



- Quite small effect of the drug pressure on the phenotype of healthy cells (n_H)
- Cancer cells (n_C) quickly concentrate around a resistant phenotype
- Catastrophic effects on ρ_H, ρ_C and ρ_{CS}

Optimal control algorithms to improve drug delivery in cancer cell populations (with Emmanuel Trélat, LJLL)

Same phenotype-structured non-local Lotka-Volterra model, but instead of a 'pedestrian's optimisation' (i.e., merely using grids), solving an optimal control problem: determining control functions u_1 and u_2 in $L^\infty(0,T)$, satisfying the constraints

$$0 \leq u_1(t) \leq u_1^{\max}, \qquad 0 \leq u_2(t) \leq u_2^{\max}, \tag{6}$$

and minimising the cost functional

$$C_T(u_1,u_2) = \int_0^1 n_C(x,T)\,dx + \gamma_1 \int_0^T u_1(t)\,dt + \gamma_2 \int_0^T u_2(t)\,dt, \tag{7}$$

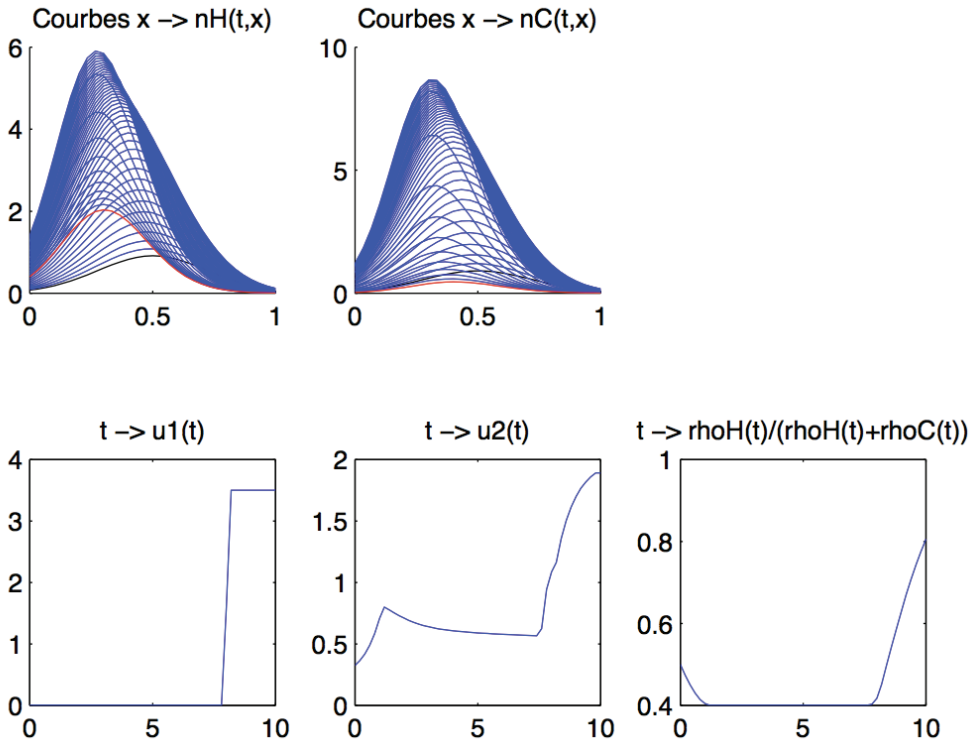
where $(n_C(\cdot,\cdot), n_H(\cdot,\cdot))$ is the unique solution of the system of PDEs corresponding to the controls u_1 and u_2, such that $n_H(0,\cdot) = n_H^0(\cdot)$ and $n_C(0,\cdot) = n_C^0(\cdot)$ and where the trajectory $t \mapsto (n_C(\cdot,t), n_H(\cdot,t))$ is subject to the dynamic state constraint

$$\frac{\rho_H(t)}{\rho_H(t)+\rho_C(t)} \geq \theta_{HC}. \tag{8}$$

(in simulations, e.g., $\theta_{HC} = 0.4$) We use a direct approach, discretising the whole problem and then solving the resulting constrained optimisation problem with AMPL (automatic differentiation) combined with IPOPT (expert optimisation routine)

Numerical solution to this first optimal control problem

Distribution of populations according to phenotype (black: initial; red: final; blue: intermediate steps of the optimisation algorithm)

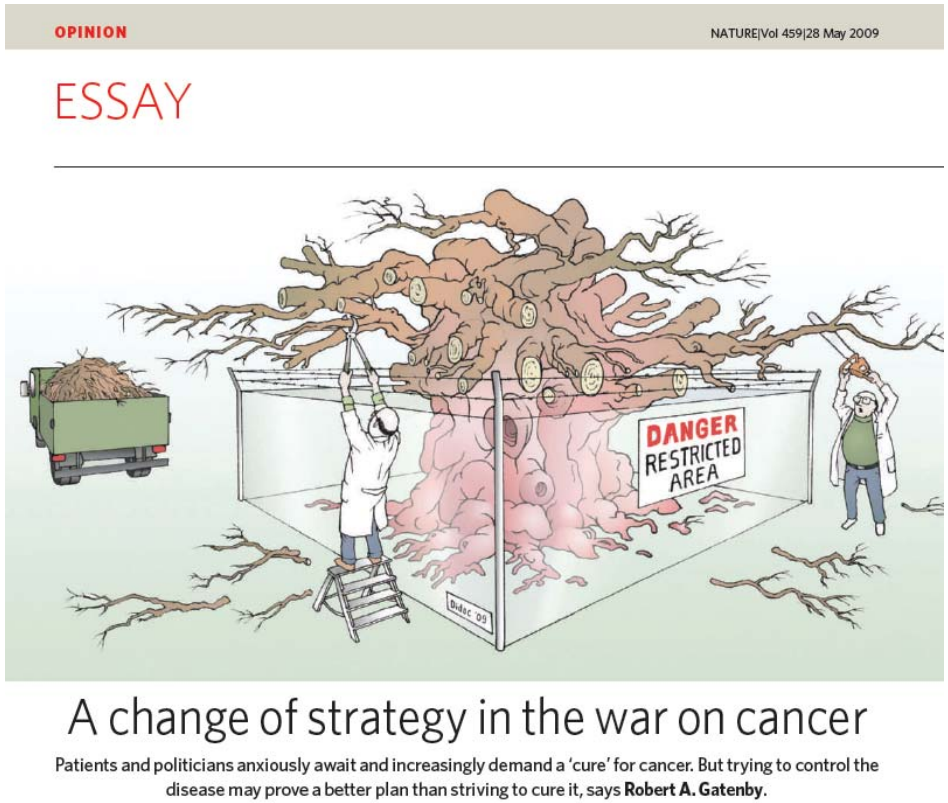


Left and centre panels: optimal drug flows for $u_1(t)$ (cytotoxic) and $u_2(t)$ (cytostatic)

Right panel: satisfaction of dynamic constraint

Introducing 'adaptive therapy', following Robert Gatenby

- Principle: keep alive an objective ally in the enemy place
- Relies on competition for resources between resistant (weakly proliferative) and sensitive cancer cells in the tumour
- Aim: avoid extinction of sensitive tumour cells, that are able to outcompete resistant tumour cells provided that not too high doses of a drug are delivered
- Method: deliver relatively low doses of the drug to prevent thriving of too many sensitive cells and limit emergence of too many (unbeatable) resistant cells
- Objective: controlling total (sensitive + resistant) tumour cell population
- Caveat: not necessarily applicable in the case of fast growing tumours (e.g., acute myeloblastic leukaemia)



Second optimal control problem: same without L^1 cost

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 $\rho_H(t) = \int_0^1 n_H(x,t)\,dx, \rho_C(t) = \int_0^1 n_C(x,t)\,dx$.

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

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

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

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

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)

Note on this second optimal control problem

Note that we might add an "adaptive" constraint

$$\frac{\rho_{CS}(t)}{\rho_C(t)} \geq \theta_{CS}, \quad \textit{where}$$

$$\rho_{CS}(t) = \int_0^1 (1-x) n_C(t,x)\, dx$$

may be seen as the total number at time t of tumour cells that are sensitive, and

$$\rho_{CR}(t) = \int_0^1 x n_C(t,x)\, dx$$

as the total number at time t of tumour cells that are resistant.

However, such constraint seems superfluous, as we show - only numerically so far - that, likely due to phenotype concentration in the first phase of the optimal control, the ratio $t \mapsto \frac{\rho_{CS}(t)}{\rho_C(t)}$ is, *as long as* $u_1(t) = 0$, an increasing function of t without imposing this "adaptive" constraint. Nevertheless, note that when $u_1(t) > 0$, this is no longer granted, and resistance effects (evidenced on decreasing ρ_{CS}) always emerge.

Second optimal control problem: theoretical results

Theorem

(Optimal control theorem)

Under these conditions, the optimal trajectory 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 $u_2 = u_2^{\max}$.

(Proof: Camille Pouchol's PhD thesis work)

Simulations illustrating this theorem

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

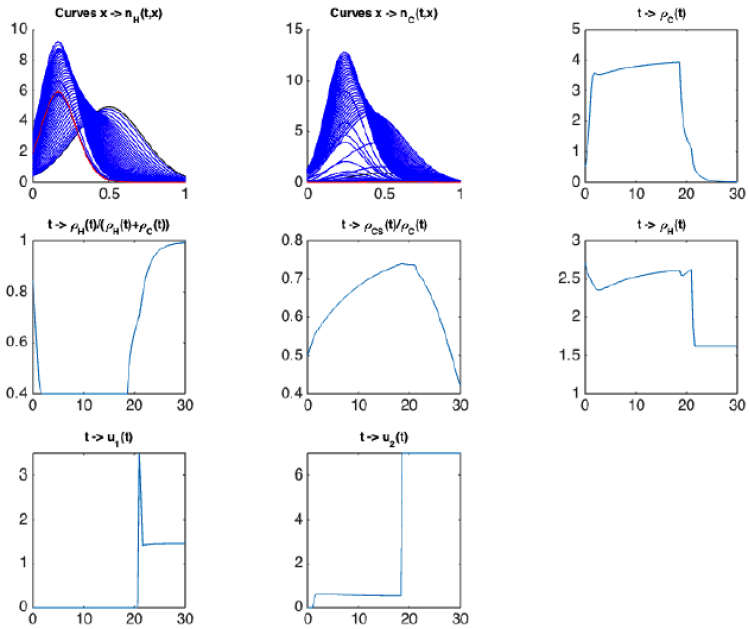


Figure 4: Simulation of (**OCP**) for $T = 30$.

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

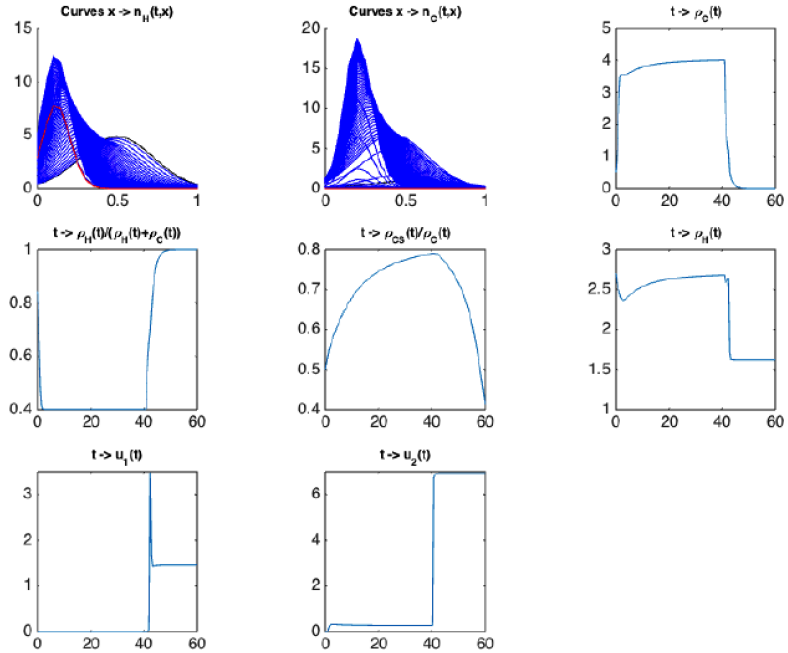


Figure 5: Simulation of (**OCP**) for $T = 60$.

Note that this strategy 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.

Interpretation

In a first approximation the optimal trajectory is made of two parts, the first one with $u_1 = 0$ and the second one with $u_1 = u_1^{\max}$, then u_1 lower than $u_1^{\max}$, and $u_2 = u_2^{\max}$.

Main idea:

1. Let the system naturally evolve to a phenotype concentration (long-time phase).
2. Then, apply the maximal quantity of drugs, during a short-time phase, in order to eradicate as many tumour cells as possible.

The second short-time phase is all the more efficient as the phenotypes are more concentrated (hence, as the time T is large).

We have two facts to prove: 1) convergence and concentration; 2) optimality of the concentrated state to start the final drug delivery phase. We prove the first fact, however the proof of the second fact is still elusive.

Looking for the proof of the theorem, beginning with the simpler case of constant controls, we investigated different tracks. The first attempt failed, but its main ingredients were used in the actual proof (with firstly constant, then piecewise constant controls), which relies on the design of a Lyapunov functional.

I will show only the asymptotic behaviour (=constant controls). The optimal control part relies of Pontryagin's maximal principle and is technical (to be published soon).

Constant controls: asymptotic behaviour

Lemma

Assume that $u_1 = \mathrm{Cst} = \bar{u}_1$ and that $u_2(t) = \mathrm{Cst} = \bar{u}_2$. Then there exist traits x_H^∞ and x_C^∞ such that for some constants ρ_H^∞ and ρ_C^∞, $\forall (n_H(\cdot,0), n_C(\cdot,0))$
$n_H(\cdot,t) \underset{t\to+\infty}{\longrightarrow} \rho_H^\infty \delta_{x_H^\infty}$, $\quad n_C(\cdot,t) \underset{t\to+\infty}{\longrightarrow} \rho_C^\infty \delta_{x_C^\infty}$.

Proof.

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

where we recall that $I_H(t) = a_{HH}.\rho_H(t) + a_{HC}.\rho_C(t)$, $I_C(t) = a_{CH}.\rho_H(t) + a_{CC}.\rho_C(t)$, and $\rho_H(t) = \int_0^1 n_H(x,t)\,dx$, $\rho_C(t) = \int_0^1 n_C(x,t)\,dx$. Firstly, we tried to show, integrating in x and taking lower and upper bounds w.r.t. x, that $(\rho_H(t), \rho_C(t))$ satisfy integral *inequalities* with at each bound the solutions of a coupled system of non-explosive Riccati equations (aka Lotka-Volterra with competition and coexistence)

$$\dot{z}_1(t) = z_1(t)(a_1 - b_{11} z_1(t) - b_{12} z_2(t))$$
$$\dot{z}_2(t) = z_2(t)(a_2 - b_{22} z_2(t) - b_{21} z_1(t)).$$

However, although this argument works in 1D [and in 2D in the case of mutualism, not competition, it implies only the convergence of sub- and supersolutions]. □

Thus this naïve 'proof' fails in our case!

Asymptotic behaviour, (failed) attempt to the proof (1)

Indeed, even if we have such boundaries for the solutions, oscillatory behaviour between boundaries cannot not be excluded! Note that *if nevertheless convergence of* $(\rho_H(t), \rho_C(t))$ *were granted*, then concentration would then follow from the exponential behaviour of $n_H(\cdot, t)$ and $n_C(\cdot, t)$, as we will show next.

1. Convergence towards what? Assume that $u_1(t) = \mathrm{Cst} = \bar{u}_1$, $u_2(t) = \mathrm{Cst} = \bar{u}_2$ and that for any initial population of healthy and of tumour cells, convergence of $(\rho_H(t), \rho_C(t))$ when $t \to +\infty$ is taken for granted. Then the equilibrium point $(\rho_H^\infty, \rho_C^\infty)$ towards which $(\rho_H(t), \rho_C(t))$ converges can be exactly computed as follows. Let $a_1 \geq 0$ and $a_2 \geq 0$ be the smallest nonnegative real numbers such that

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

(Remark: for $\bar{u}_1, \bar{u}_2$ *fixed, call* $R_{H,C}(x_0, a_{1,2}) \leq 0$ *the two inequalities above and assume* ab absurdo *that* $\forall a \in \mathbb{R}_+, \exists x_0$ *s.t.* $R_{H,C}(x_0, a) > 0$*, then by continuity, this would be true on a whole interval around* x_0*, hence there would be exponential blow-up of the population, which is excluded by the convergence hypothesis.)*

Then $(\rho_H^\infty, \rho_C^\infty)$ is the unique solution of the system (invertible as a consequence of the fact that intraspecific competition is assumed higher than interspecific competition)

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

Asymptotic behaviour, (failed) attempt to the proof (2)

2. Concentration. Furthermore, if $A_H \subset [0,1]$ (resp., $A_C \subset [0,1]$) is the set of all *points such that equalities hold in (1)*, then the supports of the probability measures $\nu_H(t) = \frac{n_H(x,t)}{\rho_H(t)}\,dx$ and $\nu_C(t) = \frac{n_C(x,t)}{\rho_C(t)}\,dx$ converge respectively to A_H and A_C. In particular, if A_H is reduced to a singleton x_H^∞, and if A_C is reduced to a singleton x_C^∞ (cases of our simulations), then $\nu_H(t)$ and $\nu_C(t)$ converge for the vague topology respectively to the Dirac masses $\delta_{x_H^\infty}$ and $\delta_{x_C^\infty}$ for some $x_H^\infty \in [0,1]$ and $x_C^\infty \in [0,1]$ as t tends to $+\infty$.

This theorem (that still remains to be proved) asserts that, under generic conditions that are satisfied here with the numerical data that we have chosen and under a constant drug treatment, the populations of healthy and of tumour cells concentrate to some respective phenotypes that can be exactly computed.

Asymptotic behaviour, (failed) attempt to the proof (3)

Indeed, by integration, we would have

$$n_H(x,t) = n_H^0(x)\exp\left(\left(\frac{r_H(x)}{1+\alpha_H\bar{u}_2} - \bar{u}_1\mu_H(x)\right)t - d_H(x)\left(a_{HH}\int_0^t \rho_H(s)\,ds + a_{HC}\int_0^t \rho_C(s)\,ds\right)\right),$$

$$n_C(x,t) = n_C^0(x)\exp\left(\left(\frac{r_C(x)}{1+\alpha_C\bar{u}_2} - \bar{u}_1\mu_C(x)\right)t - d_C(x)\left(a_{CH}\int_0^t \rho_H(s)\,ds + a_{CC}\int_0^t \rho_C(s)\,ds\right)\right).$$

Now, *if convergence were granted*, since for large t, we have $\int_0^t \rho_H(s)\,ds \sim \rho_H^\infty t$ and $\int_0^t \rho_C(s)\,ds \sim \rho_C^\infty t$, the asymptotic behaviour of $n_H(x,t)$ and of $n_C(x,t)$ depends on the functions

$$b_H(x) = \frac{r_H(x)}{1+\alpha_H\bar{u}_2} - \bar{u}_1\mu_H(x) - d_H(x)(a_{HH}\rho_H^\infty + a_{HC}\rho_C^\infty),$$

$$b_C(x) = \frac{r_C(x)}{1+\alpha_C\bar{u}_2} - \bar{u}_1\mu_C(x) - d_C(x)(a_{CH}\rho_H^\infty + a_{CC}\rho_C^\infty),$$

whose maxima on $[0,1]$ may be shown to be both zero.The points at which these maxima are attained (A_H and A_C, generically singletons x_H^∞ and x_C^∞) are the supports of the announced Dirac masses.

Actual proof of asymptotic behaviour: a Lyapunov functional

We follow an argument by P.-E. Jabin & G. Raoul (*J Math Biol 2011*) to prove at the same time convergence and concentration by designing a Lyapunov functional.

Theorem

(Asymptotic behaviour theorem, no prior convergence assumed)

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 tumor 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) 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 $+\infty$.

Basis of proof (constant controls): a Lyapunov functional

Firstly, the correspondence $(a_1, a_2) \mapsto (\rho_H^\infty, \rho_C^\infty)$ being bijective and controls $\bar{u_1}$, $\bar{u_2}$ being constant and omitted in the sequel, one can write the two inequalities above as

$$\forall x \in [0,1], \quad R_H(x, \rho_H^\infty, \rho_C^\infty) \leq 0 \quad \text{and} \quad \forall x \in [0,1], \quad R_C(x, \rho_C^\infty, \rho_H^\infty) \leq 0$$

with, furthermore

$$\forall x \in A_H, \quad R_H(x, \rho_H^\infty, \rho_C^\infty) = 0 \quad \text{and} \quad \forall x \in A_C, \quad R_C(x, \rho_C^\infty, \rho_H^\infty) = 0$$

Then, for $m_{H,C} := \dfrac{1}{d_{H,C}}$, define the Lyapunov functional $V(t) := V_H(t) + V_C(t)$ where

$$V_{H,C}(t) = \lambda_{H,C} \int_0^1 m_{H,C}(x) \left[n_{H,C}^\infty(x) \ln \left(\frac{1}{n_{H,C}(t,x)} \right) + \left(n_{H,C}(t,x) - n_{H,C}^\infty(x) \right) \right] dx.$$

where $n_{H,C}^\infty(x)$ are measures with support in $A_{H,C}$ such that $\displaystyle\int_0^1 n_{H,C}^\infty(x)\, dx = \rho_{H,C}^\infty$, the positive constants λ_H and λ_C being adequately chosen to make V decreasing along trajectories. The functional V yields simultaneously convergence and concentration.

(Part of PhD thesis work by Camille Pouchol, to be submitted soon as an article)

About the 'cooking recipes' used in the simulations (1)

In this version of the simulations (used throughout in the sequel)

$$r_H(x) = \frac{1.5}{1+x^2}, \quad r_C(x) = \frac{3}{1+x^2},$$

$$d_H(x) = \frac{1}{2}(1-0.1x), \quad d_C(x) = \frac{1}{2}(1-0.3x),$$

$$u_1^{\max} = 3.5, \quad u_2^{\max} = 7,$$

and the initial data are

$$n_H(0,x) = C_0 \exp(-(x-0.5)^2/\varepsilon), \quad n_C(0,x) = C^0 \exp(-(x-0.5)^2/\varepsilon),$$

with $\varepsilon > 0$ small (typically, we will take either $\varepsilon = 0.1$ or $\varepsilon = 0.01$), and where

$$\rho_H(0) = 2.7, \quad \rho_C(0) = 0.5$$

About the 'cooking recipes' used in the simulations (2)

The closer to 1 is the variable x, the more resistant are the tumour cells. The choice done in *Lorz et al. 2013* (where no optimal control is considered) is

$$\mu_H(x) = \frac{0.2}{0.7^2 + x^2}, \quad \mu_C(x) = \frac{0.4}{0.7^2 + x^2}.$$

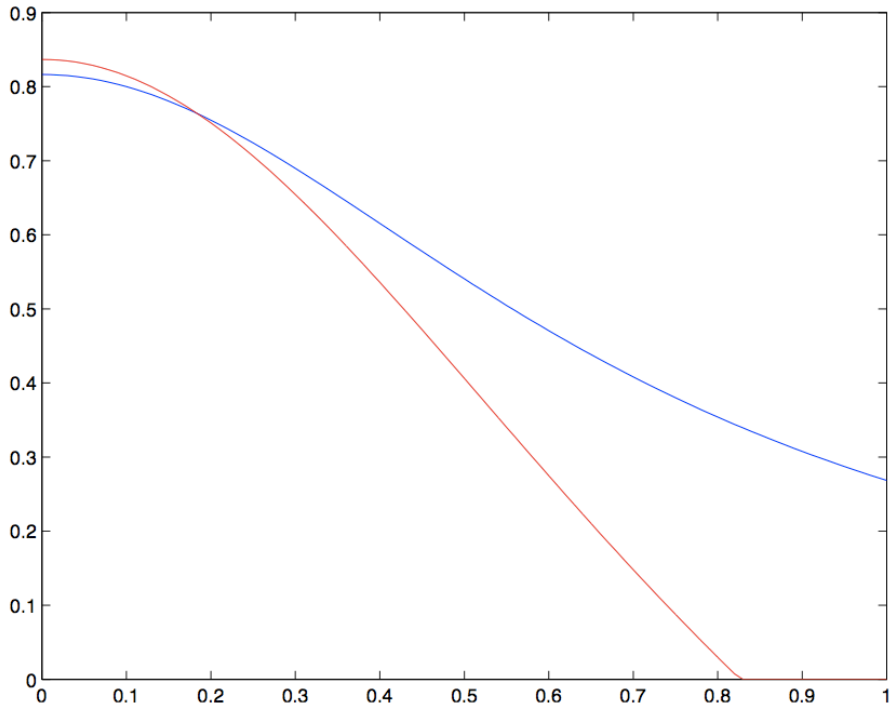
Note that, with this choice of functions, if we take constant controls u_1 and u_2, with

$$u_1(t) = \mathrm{Cst} = u_1^{\max} = 3.5, \qquad u_2(t) = \mathrm{Cst} = 2,$$

then we can kill all tumour cells (at least, they decrease exponentially to 0), and no optimisation is necessary - not clinically realistic, so that the function μ_C was modified to be zero for x close to the maximum value of the drug resistance phenotype (i.e., 1), becoming $\mu_C(x) = \max\left(\frac{0.9}{0.7^2 + 0.6x^2} - 1, 0\right)$:
μ_C thus decreases to zero and is zero from $\simeq 0.83$ to 1, i.e., the sensitivity $\mu_C(x)$ to the cytotoxic drug is constantly nil for $0.83 \leq x \leq 1$ in the cancer cell population.

About the 'cooking recipes' used in the simulations (3)

On the figure below, the former function μ_C is in blue, and the new one is in red.



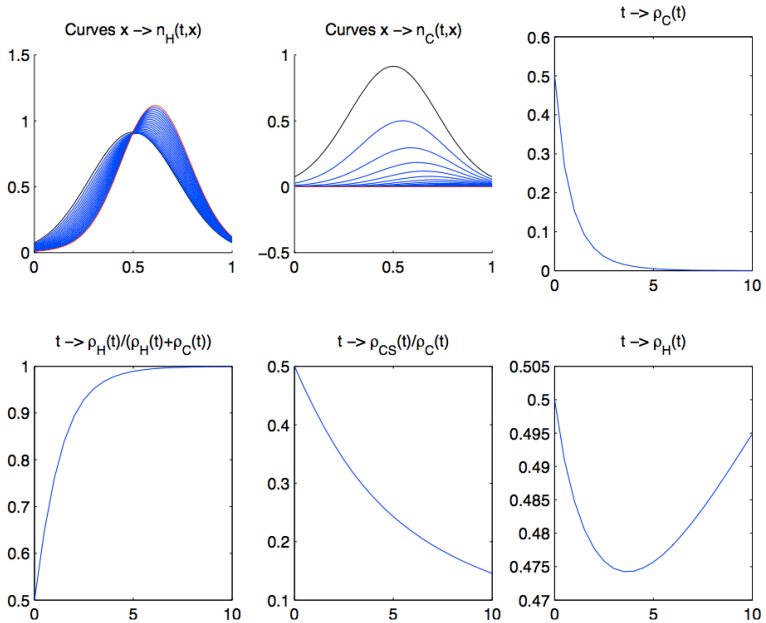
This new function μ_C is nonnegative and decreasing on $[0, 1]$, and vanishes identically on the subinterval $[0.83, 1]$. This reflects a saturation phenomenon of the sensitivity function μ_C: once cancer cells have acquired total resistance, increasing the doses has no effect any more.

About the 'cooking recipes' used in the simulations (4)

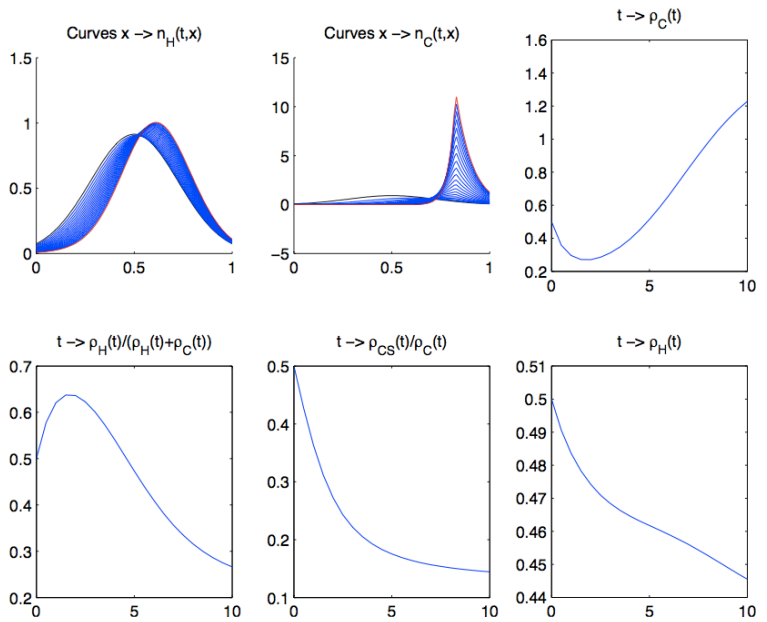
Comparison between the two choices for μ_C with constant controls

Simulations with $u_1(t) = \mathrm{Cst} = 3.5$ and $u_2(t) = \mathrm{Cst} = 2$, in time $T = 10$. At the top, left and middle: evolution in time of the curves $x \mapsto n_H(t,x)$ and $x \mapsto n_H(t,x)$, with the initial conditions in black, and the final ones in red. At the right, top and bottom: graphs of $t \mapsto \rho_C(t)$ and of $t \mapsto \rho_H(t)$. At the bottom, left and middle: graphs of $t \mapsto \frac{\rho_H(t)}{\rho_H(t)+\rho_C(t)}$ and of $t \mapsto \frac{\rho_{CS}(t)}{\rho_C(t)}$. Note that with the value $u_1 \neq 0$ chosen, the ratio of sensitive cells is constantly decreasing ("What does not kill me strengthens me").

With the first (non realistic) function μ_C



With the new function μ_C



About the 'cooking recipes' used in the simulations (5)

The environment variables $I_{[H,C]}(t)$ defined by

$$\begin{aligned} I_H(t) &= a_{HH}\rho_H(t) + a_{HC}\rho_C(t), \\ I_C(t) &= a_{CH}\rho_H(t) + a_{CC}\rho_C(t), \end{aligned} \tag{2}$$

and

$$\rho_H(t) = \int_0^1 n_H(x,t)\,dx, \qquad \rho_C(t) = \int_0^1 n_C(x,t)\,dx.$$

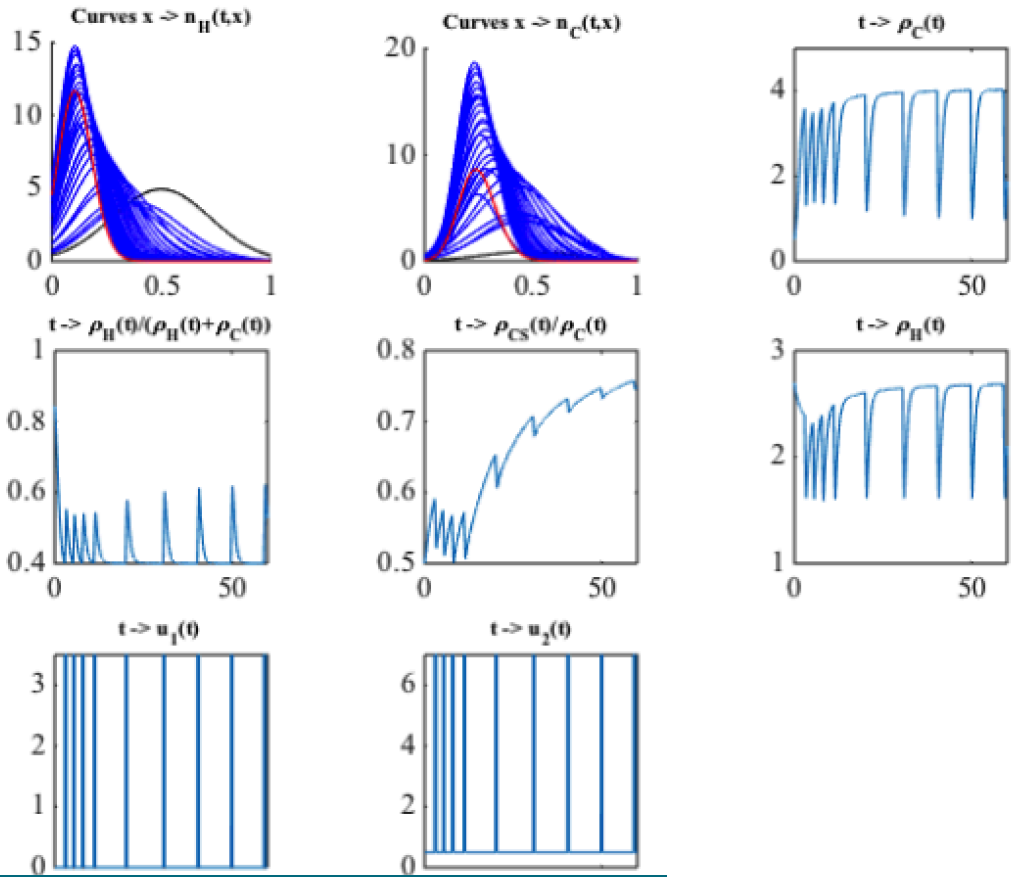
have been chosen (with $\alpha_H = 0.01$, $\alpha_C = 1$) such that

$$a_{HH} = 1, \quad a_{CC} = 1, \quad a_{HC} = 0.07, \quad a_{CH} = 0.01,$$

which means in particular that in the limiting logistic terms in the model, intraspecific competition is overwhelmingly higher than interspecific competition, i.e., cell growth is mainly limited by access to resources, and very little by frontal competition between cancer and healthy cells, a choice done on biological grounds (*cancer cells and healthy cells are not thriving on the same metabolic niche, e.g., aerobic vs. glycolytic metabolisms*). As a consequence, as in classical Lotka-Volterra models with competition, the choice of these parameters will lead in the simulations to asymptotic coexistence of the two species, healthy and cancer, in a non trivial equilibrium state.

Comparison with "almost periodic" therapeutic strategies

We mimic actual clinical settings: as long as $\frac{\rho_H}{\rho_H + \rho_C} > \theta_{HC}$, we follow the 'drug holiday' strategy by choosing $u_1 = \bar{u_1} = 0$, $u_2 = \bar{u_2} = 0.5$. Then, as long as $\rho_H > \theta_H.\rho_H(0)$, we use the maximal amount of drugs. As soon as $\rho_H = \theta_H.\rho_H(0)$, back to the drug holiday strategy. Results (note stabilised ρ_C and increasing ρ_{CS}):



Comparison with "almost periodic" therapeutic strategies

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

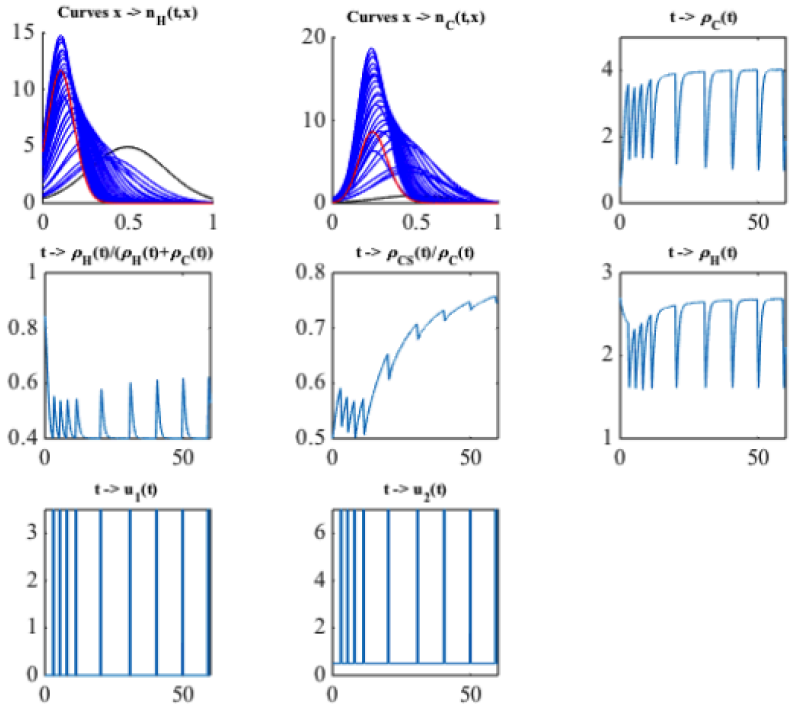


Figure 6: Quasi-periodic strategy, for $T = 60$.

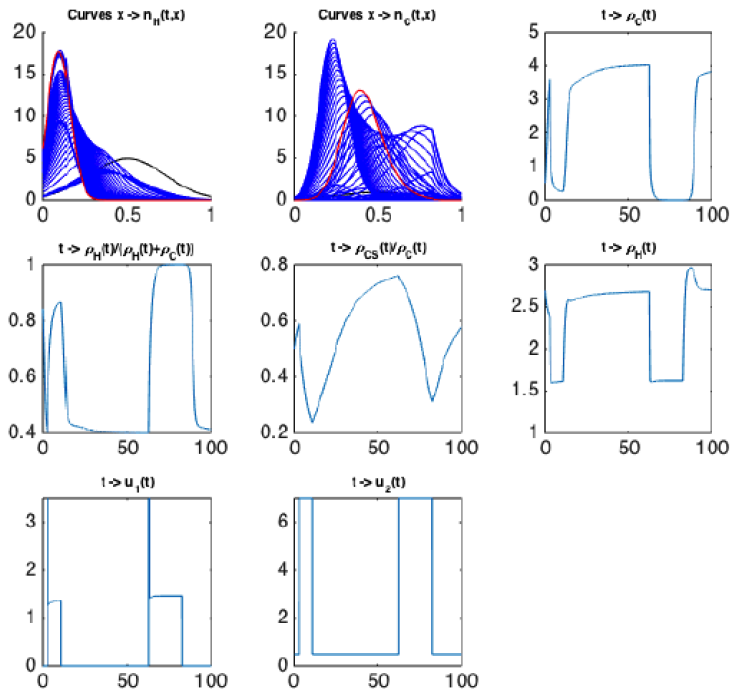
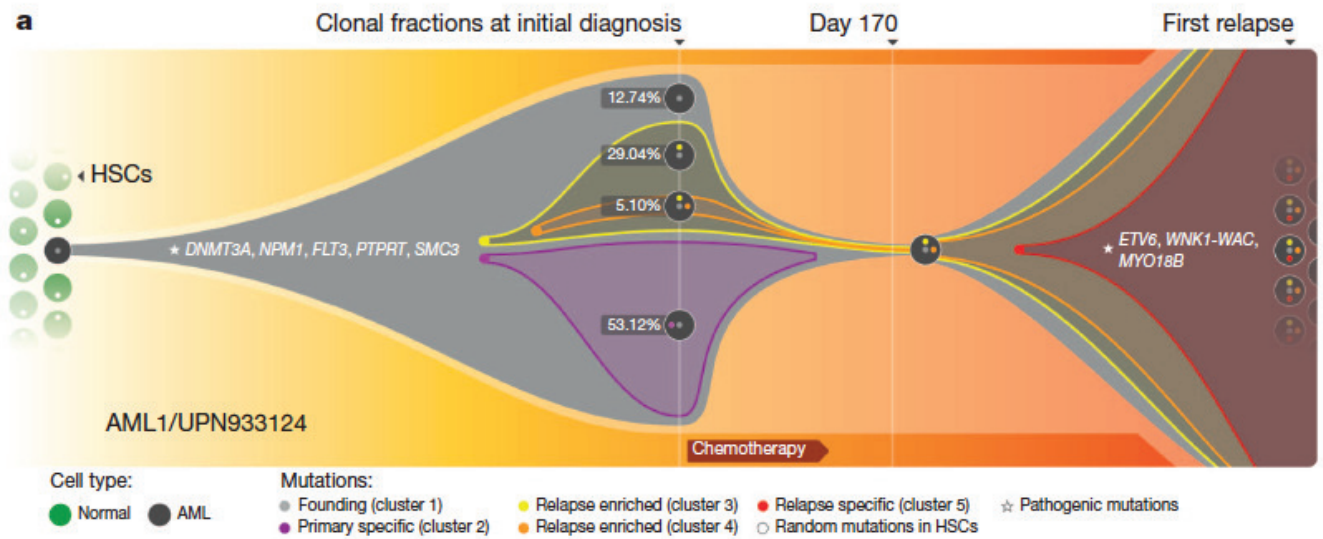


Figure 7: Second quasi-periodic strategy, for $T = 100$.

First (unsatisfying) periodic strategy: stabilisation of ρ_C only. 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 (eradication of the tumour?).

Limitations of this optimisation procedure, owing to the fact that the trait represents resistance to only one drug

- The model assumes *one* trait of resistance corresponding to *one* cytotoxic drug.
- However, overcoming resistance using such strategy may not be successful if too many types of resistance coexist, due to high phenotype heterogeneity.
- Phenotype heterogeneity (e.g., multiclonality) within the tumour may reduce such strategy to nothing, unless a multidimensional phenotype is considered.
- ... Unless also one could act very early to avoid the development of transient drug-resistant cell clones by epigenetic drugs or metabolism-modifying strategies.



(AML relapse, cf. *Ding et al. Nature 2012*)

A possible extension: adding phenotype instability

As done in *Chisholm et al. Cancer Resear Research 2015*, we may in a more realistic way than in sheer IDE Lotka-Volterra-like models, introduce non-genetic instability in a PDE model for evolution in phenotype x due to effects of cytotoxic drug $u_1(t)$ with second order terms:

$$\frac{\partial}{\partial t} n_H(x,t) = \left(\frac{r_H(x)}{1+\alpha_H u_2(t)} - d_H(x) I_H(t) - u_1(t)\mu_H(x) \right) n_H(x,t) + D \frac{\partial^2 n_H}{\partial x^2}(x,t)$$

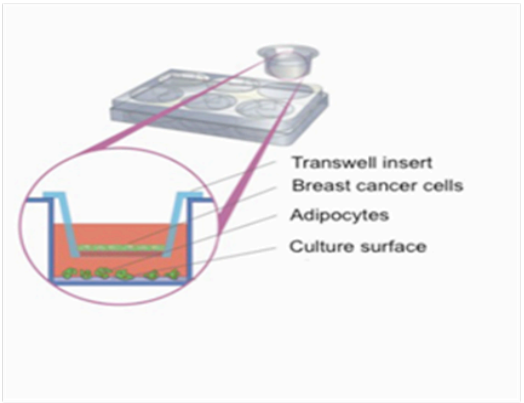
$$\frac{\partial}{\partial t} n_C(x,t) = \left(\frac{r_C(x)}{1+\alpha_C u_2(t)} - d_C(x) I_C(t) - u_1(t)\mu_C(x) \right) n_C(x,t) + E \frac{\partial^2 n_C}{\partial x^2}(x,t)$$

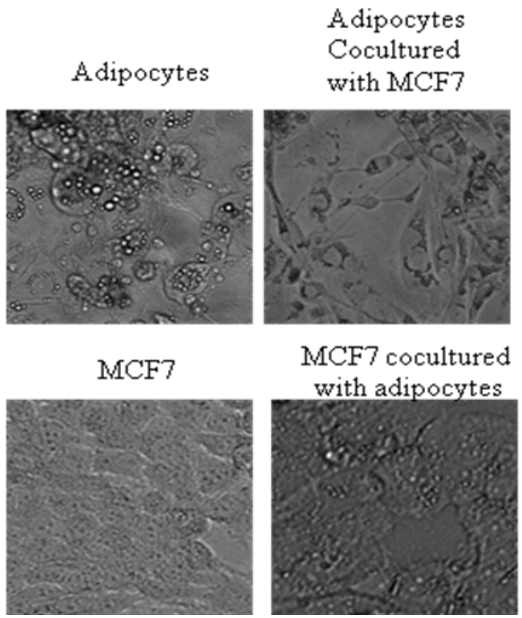
We might in this way allow for the possibility of evolution towards stable coexistence of stationary concentrated phenotypes, which may be closer to the actual behaviour of tumours, assuming that phenotype polyclonality precedes genotype polyclonality.

Also, of course, phenotypes accounting for drug resistance might be more realistically multidimensional. We are exploring with biological partners (F. Vallette's team about resistance of GBM to TMZ) gene expression changes triggered by exposure to drugs, with the hope to elicit functionally defined gene expression clusters that could ultimately be interpreted as phenotypes accounting for the evolution towards heterogeneity (with possible stochastic bet hedging?) in drug-resistant cancer cell populations.

Extension of the IDE model: tumour micro-environment

Breast cancer cell line MCF7 in symbiosis with adipocytes (work 2015)





A mutualistic model with control by drugs: cytostatic $v_r(t)$, cytotoxic $v_d(t)$, plus blockade of receptors to intercellular soluble factors $\varphi_A(t), \varphi_C(t)$ by other drugs, e.g., oestrogen receptor blockers $w_{sC}(t)$, antiinflammatory molecules $w_{sA}(t)$

$$\frac{\partial}{\partial t} n_C(u,t) = \left[\frac{r_C}{1+v_r(t)} + \varphi_A(t) \frac{s_C(u)}{1+w_{sC}(t)} - (1+v_d(t)) d_C(u) \rho_C(t) \right] n_C(u,t),$$

$$\frac{\partial}{\partial t} n_A(x,t) = \left[r_A + \varphi_C(t) \frac{s_A(x)}{1+w_{sA}(t)} - d_A \rho_A(t) \right] n_A(x,t).$$

(Camille Pouchol's PhD thesis 2015-...)

Other possible extensions: representing the immune response

- Remarkable recent and longlasting therapeutic results have been obtained in various cancers by using immune checkpoint inhibitors (anti-CTLA-4, anti-PD1, anti-PDL1), monoclonal antibodies that *inhibit inhibition* of immune effector cells, see, e.g., Naidoo *et al.* in Br J Cancer 2014

- However, remarkable though they are, these results remain limited, long survivors (18 months) in melanoma passing from 0 to 25-40 % in the best cases (Nivolumab in melanoma without *BRAF* mutation, *C. Robert NEJM 2015*)

- Using chemotherapies to decrease cancer cell populations, not to eradicate them, but to make them amenable to be kept in check by the immune system, raises reasonable hopes to increase these (already remarkable) results

- This calls for models of the immune response in cancer to optimise cancer treatments by combining chemo- and immunotherapies...

- ... Keeping in mind the urge by Charles Lineweaver, Paul Davies and Mark Vincent (Bioessays 2014) to *target cancer's weaknesses (not its strengths)* by triggering the adaptive immune response

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