Efficient chemotherapy in spite of drug resistance: optimal strategy and robustness

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Outline

- The problem and its modelling by selection-mutation models
- MTD strategy versus "optimal" strategy
- Robustness in the presence of genetic instability

The chemotherapy and its drawbacks

Two main types of chemotherapies

* cytotoxic agents which kill cancer cells,
* cytostatic agents which slow their proliferation down.

Two main drawbacks

* resistance to drugs,
* toxicity to the healthy tissue.

Aims of the mathematical modelling

Modelling must reproduce the clinical observations which show that maximal doses

* cannot be given for too long
* will in the end lead to tumour regrowth because of acquired resistance.

It must also allow for the design of alternative strategies, cf the emerging therapeutical paradigm

Figure: **Change of strategy in the war against cancer.**

Modelling resistance to treatment

What determines the level of resistance to a given drug? It correlates to

* the level of expression of some stem-cell like markers,
* the concentration of transporters eliminating the drug,
* the level of DNA methylation,

... all continuous variables, making a continuous representation of resistance relevant.

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Abstract version:
phenotype variable $x \in [0, 1]$ from sensitiveness ($x = 0$) to resistance ($x = 1$).

Advantages and disadvantages:

* might be a more faithful representation of resistance,
* models much more difficult to parametrise.

From ODEs to IDEs

Let us start from the logistic model

$$\frac{dN}{dt} = [r - dN]\, N$$

* r: intrinsic reaction rate
* $d\,N$: logistic death rate

Generalisation: depending on some (resistance) phenotype, r and d might vary.

x: continuous variable

$r \to r(x)$

$d \to d(x)$

Typical integrodifferential logistic model

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

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

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with

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

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Asymptotic analysis

- of the total number of individuals $\rho(t)$?
- of the phenotypes in the population (*i.e.*, of $n(t,\cdot)$ in $\mathcal{M}^1(0,1)$)?

Motivation: selection of the fittest phenotypes

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

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

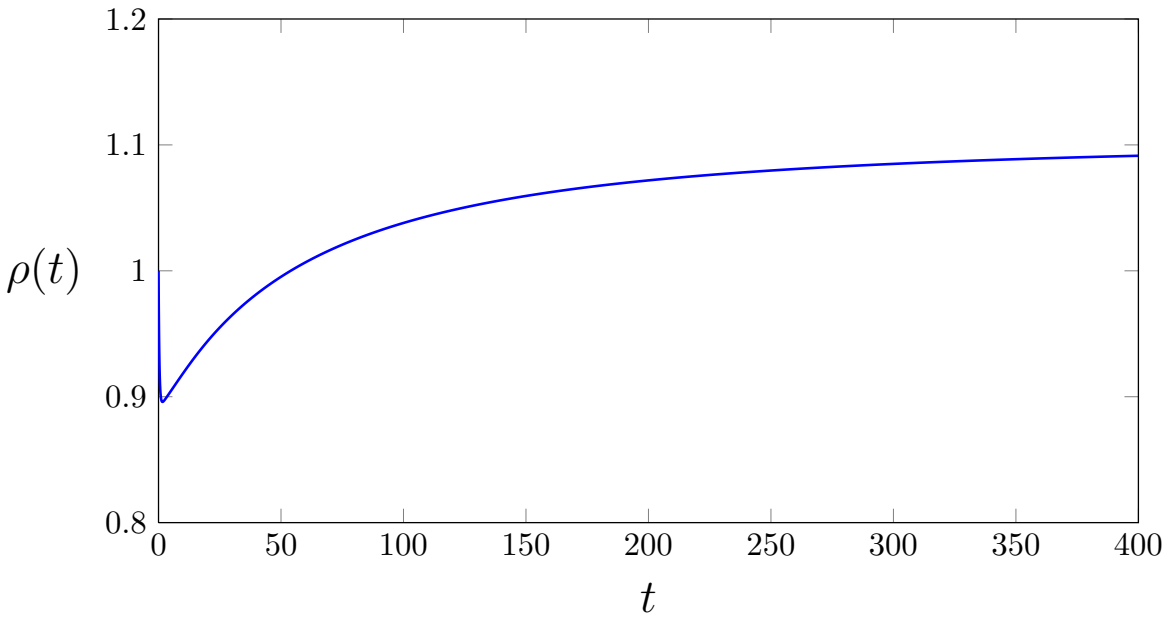

Figure: **Evolution of $\rho(t)$ from $t = 0$ to $t = 400$, with $r(x) = \frac{1}{2}(5 - 3(1-x)^2)$, $d(x) = 1 + 2x$.**

Motivation: selection of the fittest phenotypes

Interest in the field of *adaptive dynamics*.

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

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

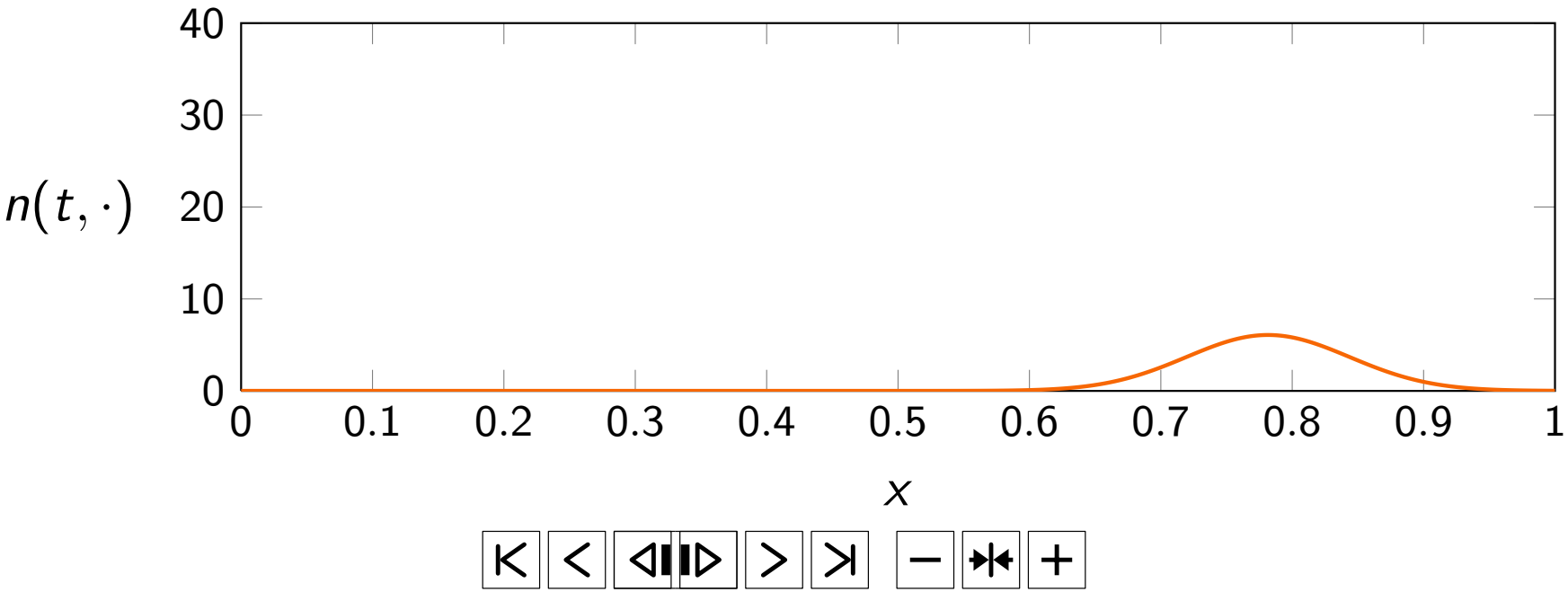

Figure: **Evolution of** $n(t,\cdot)$ **from** $t = 0$ **to** $t = 2000$**, with** $r(x) = \frac{1}{2}(5 - 3(1-x)^2)$, $d(x) = 1 + 2x$**.**

The convergence and concentration theorem

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

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

Theorem (Perthame '07)

ρ converges to $\rho^\infty = \max\left(\frac{r}{d}\right)$. Furthermore, $n(t,\cdot)$ concentrates on $\arg\max\left(\frac{r}{d}\right)$. *In particular, if this set is reduced to a singleton x^∞,*

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

The model [Lorz et al. '13]

$$\frac{\partial}{\partial t} n_H(t,x) = [r_H(x) - d_H(x)\rho_H(t)]\, n_H(t,x),$$
$$\frac{\partial}{\partial t} n_C(t,x) = [r_C(x) - d_C(x)\rho_C(t)]\, n_C(t,x).$$

$x \in [0,1]$ from 0 (sensitiveness) to 1 (resistance)

$n_H(t,x)$: density of healthy cells, of phenotype x.

$n_C(t,x)$: density of cancer cells, of phenotype x.

The model [Lorz et al. '13]

$$\frac{\partial}{\partial t} n_H(t,x) = \big[r_H(x) - d_H(x) \underbrace{(a_{HH}\rho_H(t) + a_{HC}\rho_C(t))}_{=:I_H(t)} \big] n_H(t,x),$$

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* interspecific competition (lower that the intraspecific one), with

$$I_H = a_{HH}\rho_H + a_{HC}\rho_C, \qquad a_{HC} < a_{HH}$$
$$I_C = a_{CC}\rho_C + a_{CH}\rho_H, \qquad a_{CH} < a_{CC}$$

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* cytotoxic agents u_1

The model [Lorz et al. '13]

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

Asymptotic behaviour for constant controls

Theorem (Clairambault, Lorz, Pouchol, Trélat, JMPA '18)

Let $u_1, u_2 \in BV(0,+\infty)$, $\bar{u}_1$, $\bar{u}_2$ their limits as $t \to +\infty$.
Then

- $\rho_H(t)$, $\rho_C(t)$ *converge to* ρ_H^∞, ρ_C^∞,
- $n_H(t,\cdot)$, $n_C(t,\cdot)$ *concentrate on* A_H, A_C.

If $A_H = \{x_H^\infty\}$, $A_C = \{x_C^\infty\}$, *then*

$$n_H(t,\cdot) \rightharpoonup \rho_H^\infty \delta_{x_H^\infty}, \qquad n_C(t,\cdot) \rightharpoonup \rho_C^\infty \delta_{x_C^\infty}.$$

Here $(\rho_H^\infty, \rho_C^\infty)$ *solves the system*

$$\begin{aligned} a_{HH}\rho_H^\infty + a_{HC}\rho_C^\infty &= I_H^\infty, \\ a_{CH}\rho_H^\infty + a_{CC}\rho_C^\infty &= I_C^\infty, \end{aligned} \tag{1}$$

where for $i = H, C$, $I_i^\infty \geq 0$, *is the smallest real such that*

$$\frac{r_i(x)}{1+\alpha_i \bar{u}_2} - \bar{u}_1 \mu_i(x) - d_i(x) I_i^\infty \leq 0. \tag{2}$$

The sets A_H, A_C *are defined for* $i = H, C$ *by*

$$A_i := \left\{ x \in [0,1],\ \frac{r_i(x)}{1+\alpha_i \bar{u}_2} - \bar{u}_1 \mu_i(x) - d_i(x) I_i^\infty \leq 0 \right\}.$$

Strategy with high constant doses

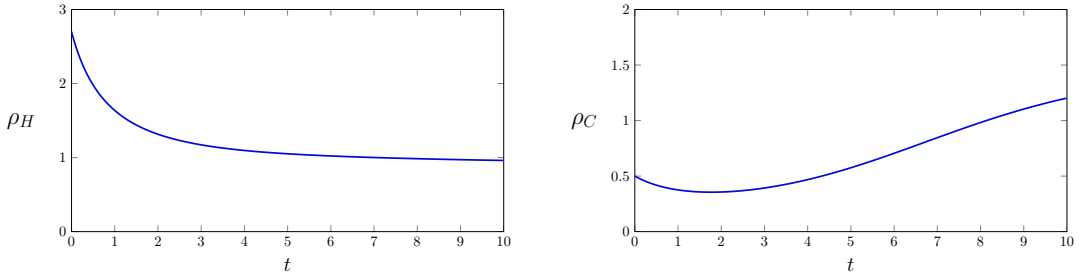
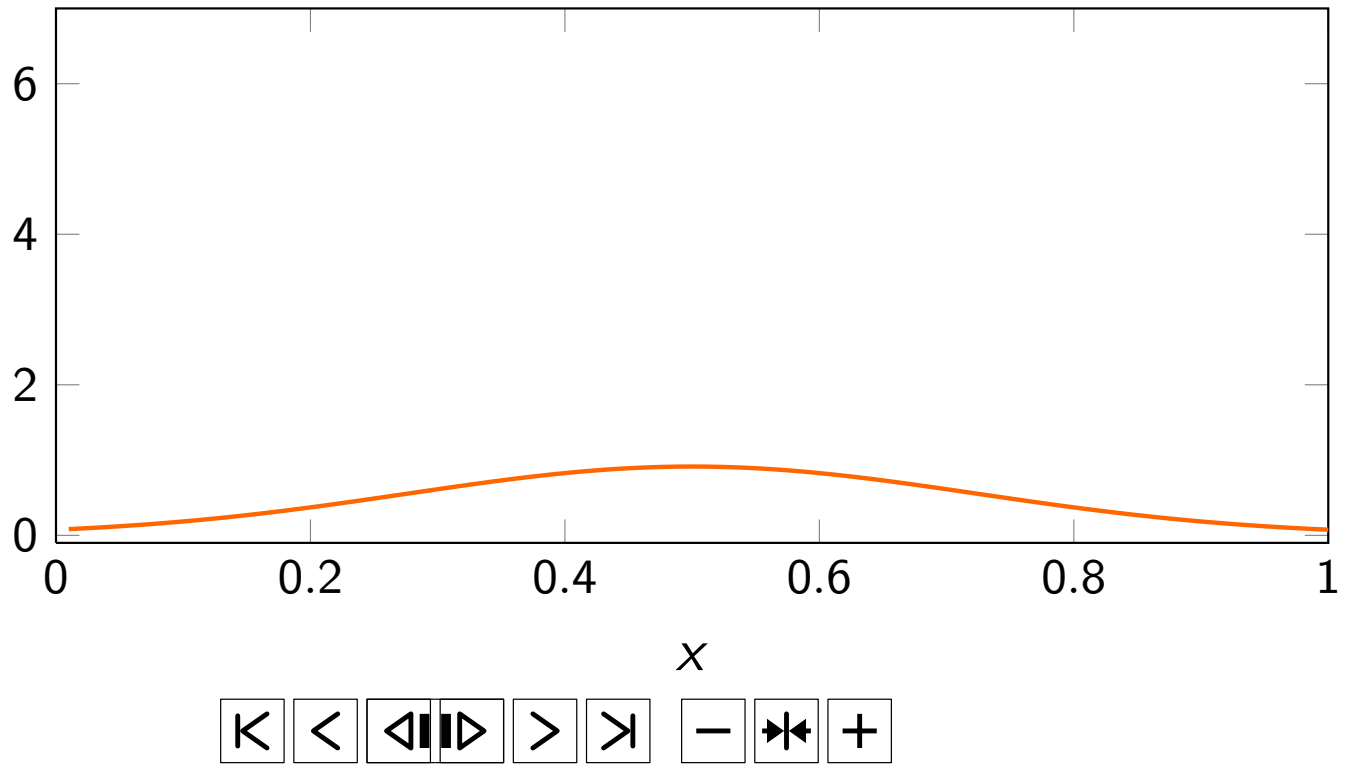


Figure: **Simulation with $u_1 \equiv 2$, $u_2 \equiv 2$.**

$n_C(t, \cdot)$



Optimal control problem ($\mathbf{OCP_1}$)

Let $T > 0$. We define ($\mathbf{OCP_1}$)

$$\inf_{(u_1,u_2)} (1-\lambda_0)\rho_C(T) + \lambda_0 \int_0^T \rho_C(s)\, ds$$

among controls $(u_1, u_2) \in BV(0,T)^2$ such that

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$$\rho_H(t) \ge \theta_H\, \rho_H(0).$$

Numerical simulation of ($\mathbf{OCP_1}$)

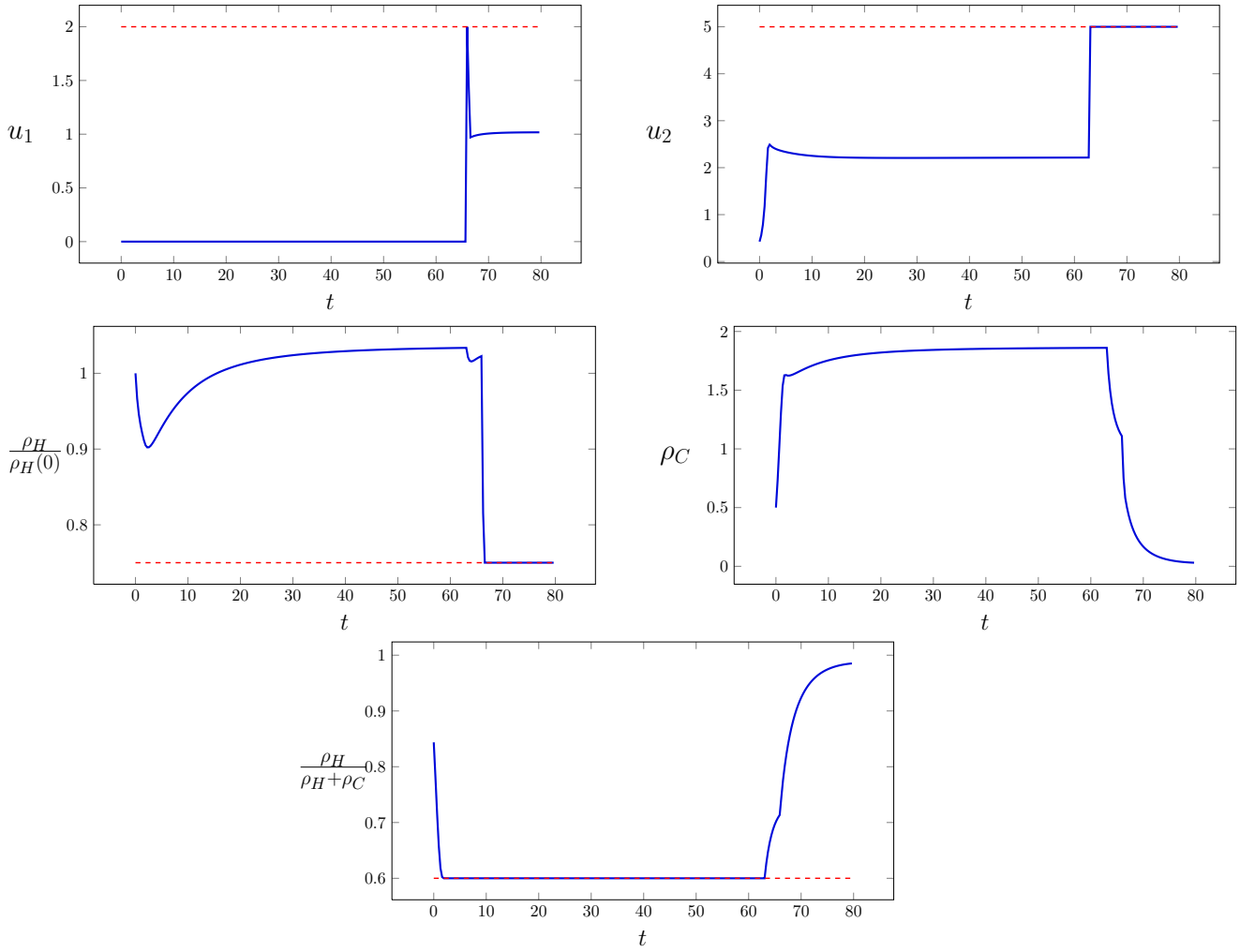
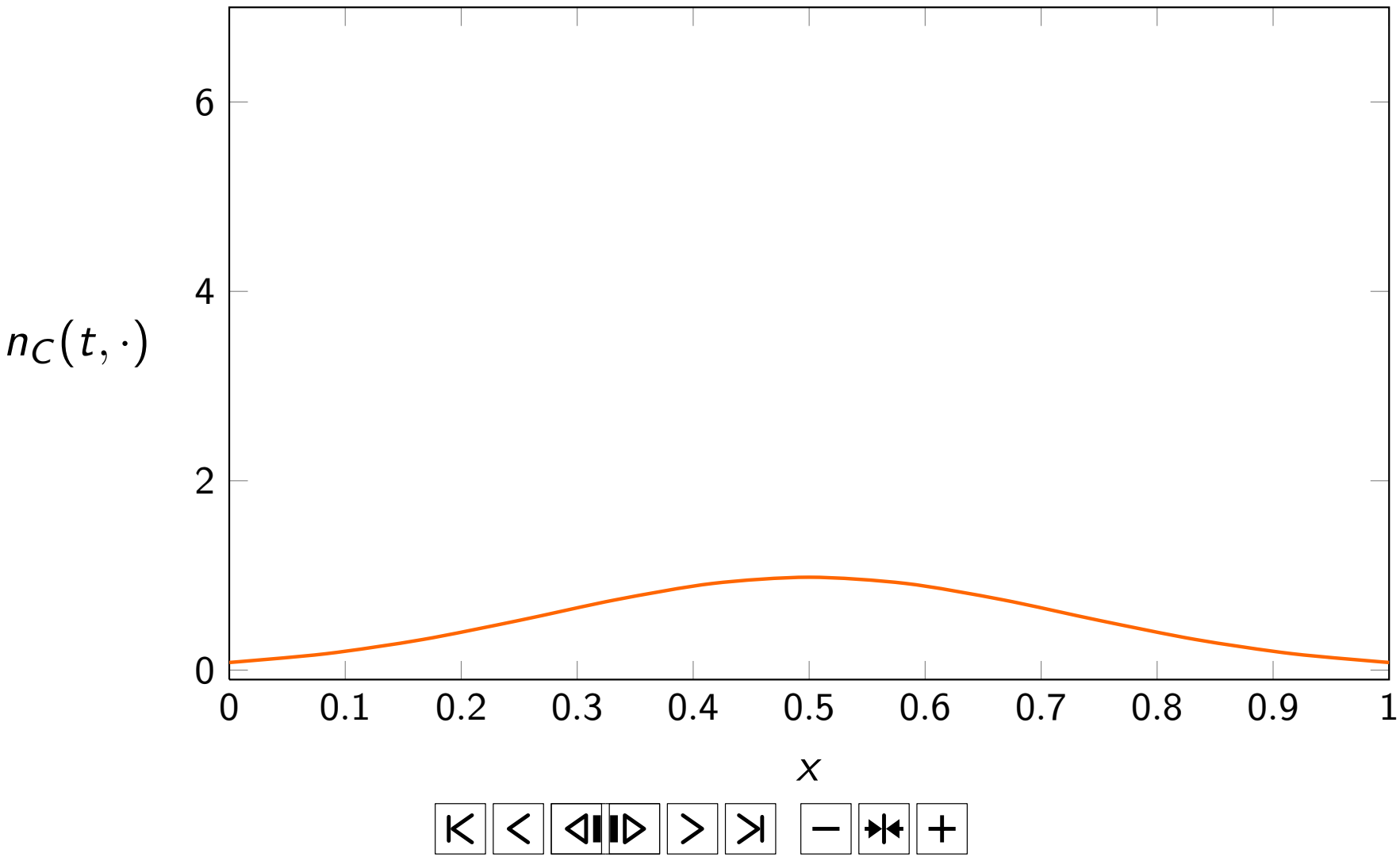


Figure: **Simulation of the optimal solution for $\lambda_0 = 0$.** Done with AMPL + IpOpt.

Numerical simulation of $(\mathbf{OCP_1})$



(Quasi-)optimal strategy in a reduced control set $\mathcal{B}_T$, for T large, $\lambda_0 = 0$:

Theorem (Clairambault, Lorz, Pouchol, Trélat, JMPA '18)

As T tends to $+\infty$, the optimal solution to ($\boldsymbol{OCP_1}$) in $\mathcal{B}_T$ is such that

- *at the end of the first phase, the cancer cell density has concentrated on a sensitive phenotype,*
- *the optimal trajectory is the concatenation of the three following arcs*
  - *a boundary arc with saturation of the quotient $\frac{\rho_H}{\rho_H+\rho_C}$.*
  - *a free arc with $u_1 = u_1^{max}$ and $u_2 = u_2^{max}$,*
  - *a boundary arc on the constraint for the healthy cells, and $u_2 = u_2^{max}$.*

Numerical approach for a generalised model

We consider

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

with Neumann boundary conditions in 0 and 1.

Expected results: same structure of the optimal controls, if mutation rates are small enough.

Difficulties: out of reach theoretically, very costly numerically.

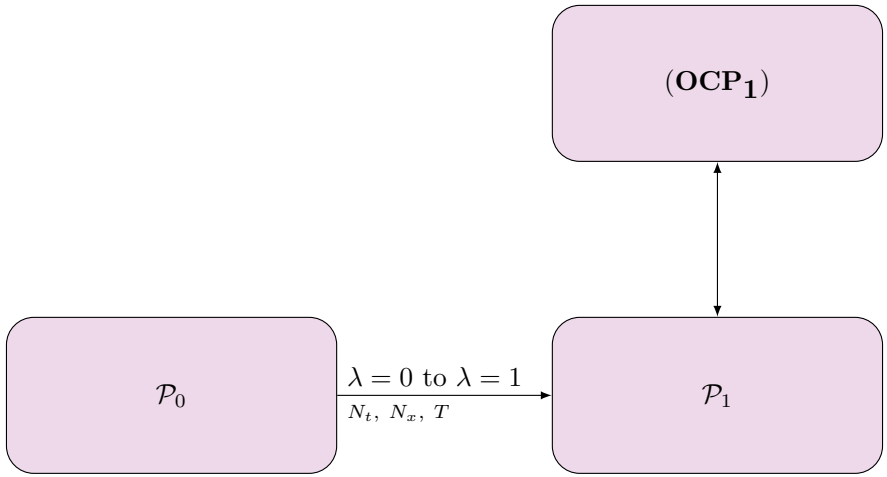


Figure: **Direct methods and continuations: previous method.**

$(\mathcal{P}_\lambda)$ is a family of optimisation problems linking an easy-to-solve problem $\mathcal{P}_0$ and the hard one $\mathcal{P}_1$ that we want to solve.

Algorithm:

1: Solve $\mathcal{P}_0$, and set $\lambda = 0$

2: while $\lambda \leq 1$,
$\lambda \leftarrow \lambda + d\lambda$.
Solve $\mathcal{P}_{\lambda+d\lambda}$ with the solution of $\mathcal{P}_\lambda$ as initial guess.

From $(\mathbf{OCP_1})$ to $(\mathbf{OCP_0})$

$$\frac{\partial n_H}{\partial t} - \beta_H \Delta n_H = \left[\frac{r_H(x)}{1+\alpha_H u_2} - d_H(x)\left(a_{HH}\rho_H + a_{HC}\rho_C\right) - u_1 \mu_H(x) \right] n_H$$

$$\frac{\partial n_C}{\partial t} - \beta_C \Delta n_C = \left[\frac{r_C(x)}{1+\alpha_C u_2} - d_C(x)\left(a_{CC}\rho_C + a_{CH}\rho_H\right) - u_1 \mu_C(x) \right] n_C$$

$$\inf_{(u_1,u_2)} (1-\lambda_0)\rho_C(T) + \lambda_0 \int_0^T \rho_C(s)\, ds$$

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

$$\frac{\rho_H(t)}{\rho_H(t)+\rho_C(t)} \ge \theta_{HC},$$

$$\rho_H(t) \ge \theta_H\, \rho_H(0).$$

Idea: simplify the problem by setting $a_{CH} = \theta_H = \theta_{HC} = \beta_H = \beta_C = 0, \lambda_0 = 0$.

The problem ($\mathbf{OCP_0}$)

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

$$\inf_{(u_1, u_2)} \rho_C(T)$$

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Proposition (Olivier, Pouchol, submitted)

Let $(n_C(\cdot), u(\cdot))$ be an optimal solution for ($\mathbf{OCP_0}$). There exist $t_1 \in [0, T)$ and $t_2 \in [0, T)$ such that

$$u_1(t) = u_1^{max} \mathbb{1}_{[t_1, T]}, \qquad u_2(t) = u_2^{max} \mathbb{1}_{[t_2, T]}.$$

Proof: Pontryagin Maximum Principle in infinite dimension, here in $L^2(0, 1)$.

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Proof: Pontryagin Maximum Principle in infinite dimension, here in $L^2(0, 1)$.

Consequence: ($\mathbf{OCP_0}$) is reduced to a problem from $\mathbb{R}^2$ onto $\mathbb{R}$ with variables (t_1, t_2), leads to an easily solvable problem $\mathcal{P}_0$, even for high discretisation parameters N_t, N_x.

Summary of the method

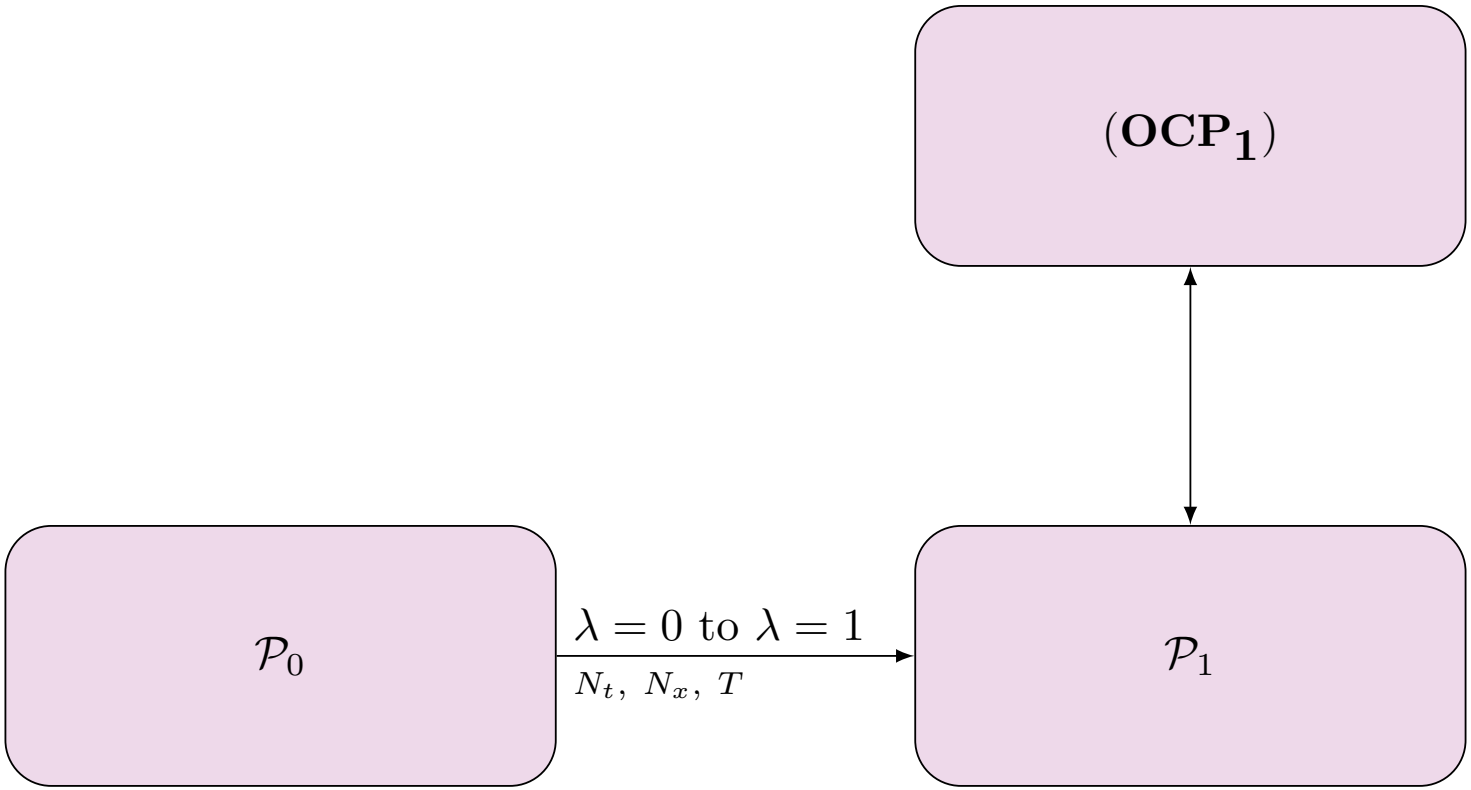

Figure: **Direct methods and continuations: previous method.**

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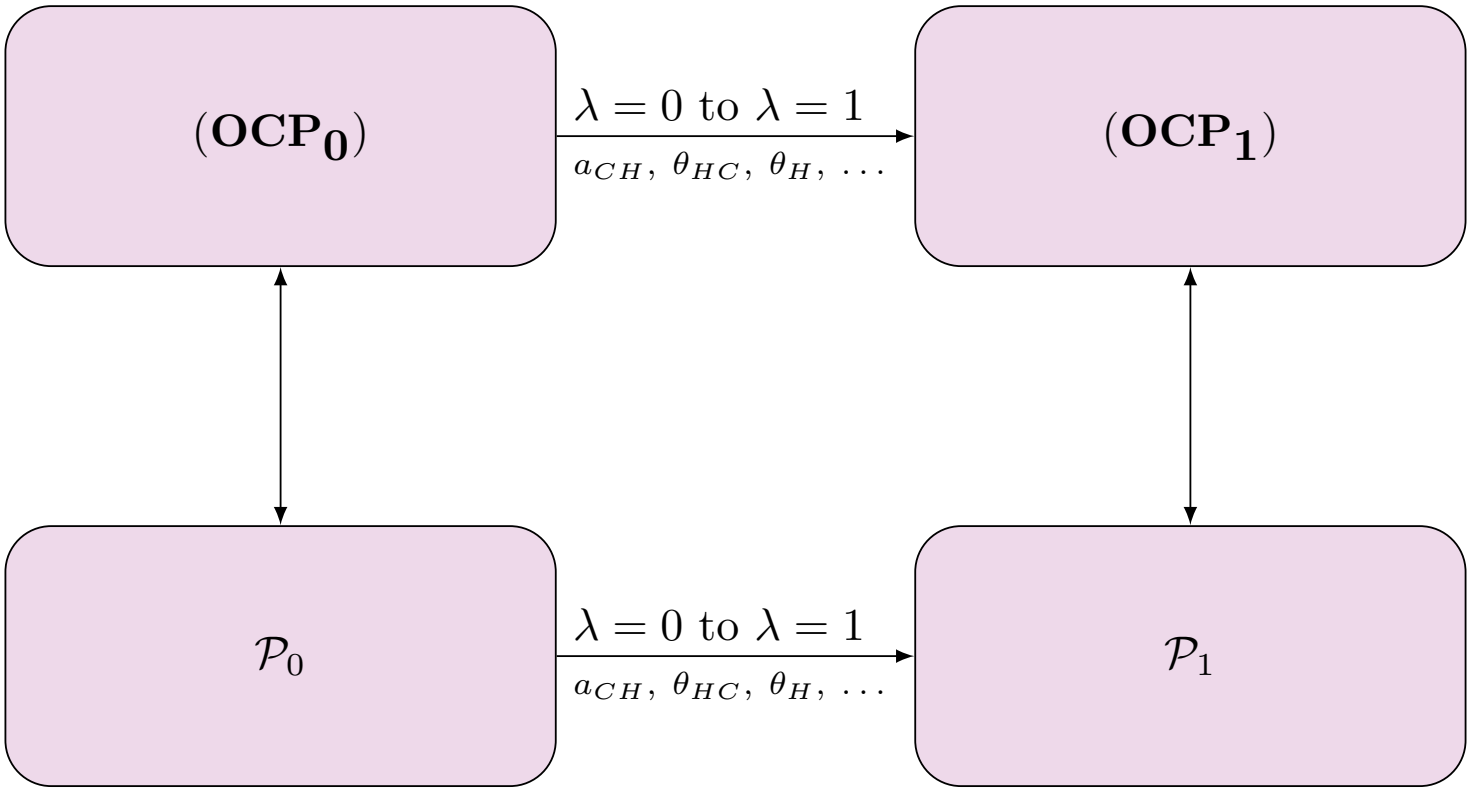

Figure: **Direct methods and continuations: new[1]method [Olivier, Pouchol, submitted].**

[1] cf. the approach with indirect methods in [Cerf-Hakerborn-Trélat '12].

Optimal strategy for ($\mathbf{OCP_1}$): conclusions

Simulations suggest that, for **large** T, there are two main phases:

* A first **long** phase **without cytotoxic drugs** and **intermediate constant doses of cytostatic drugs**, at the end of which cancer cells have concentrated on a sensitive phenotype.

* A second **short** phase with **the maximal doses**, up until the constraint on ρ_H decreases, and then *boundary* controls to saturate the constraint while ρ_C still decreases.

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Very different from the MTD strategy, but also from alternative strategies such as

- metronomic chemotherapy [Scharovsky et al. '09]: infusion of low doses,
- adaptive chemotherapy [Gatenby et al. '09]: decreasing (feedback) doses...

and reminiscent of drug holiday+rechallenge strategies.

References

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