# Asymptotic analysis and optimal control of an integro-differential system modelling healthy and cancer cells exposed to chemotherapy

Jean Clairambault, Alexander Lorz, *Camille Pouchol*, Emmanuel Trélat

*Laboratoire Jacques-Louis Lions, UPMC and Mamba INRIA team, Paris*

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# Chemotherapy and its drawbacks

Two main types of chemotherapeutic drugs

- cytotoxic drugs kill cancer cells
- cytostatic drugs lower their proliferation

Two main pitfalls

- Resistance to drugs: the cancer cell population acquires resistance
- Toxicity to healthy cells: no exclusive targeting of cancer cells

# Objectives of a mathematical modelling approach

Modelling must reproduce the clinical observations that the maximum tolerated doses

- cannot be given for too long because of the side-effects
- can lead to the regrowth of the tumour even with further treatment because resistance has been acquired

It must also provide optimal strategies, to be compared with an emerging therapeutical paradigm:


Figure : **A change of strategy in the war on cancer**

# Modelling drug resistance: adaptive dynamics

Heterogeneity inside a solid tumour can be understood through the principles of Darwinian evolution, which leads to use tools from adaptive dynamics.

We focus on

- deterministic models where the structuring variable $x$ is a *continuous* phenotype,
- because drug resistance can be linked, for example, to DNA methylation

# Introduction to IDEs: starting from ODEs

Start from the logistic model

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

- $r$: proliferation rate
- $d\,N$: death rate (increasing with N: **intra-specific competition**)

*What if individuals have different phenotypes?*

$x$: continuous phenotype

- $r \to r(x)$
- $d \to d(x)$

(*Perthame, Transport equations in biology, 2006*)

# Introduction to IDEs: typical IDE logistic model

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

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

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

with

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

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**Asymptotic behaviour** of

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

# Introduction to IDEs: convergence and concentration

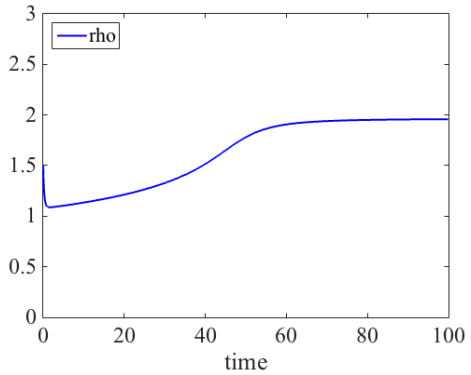


Figure : **Plot of** $t \mapsto \rho(t)$ for $r(x) = 2 + x$, $d(x) = 1 + 2x$.

# Introduction to IDEs: convergence and concentration

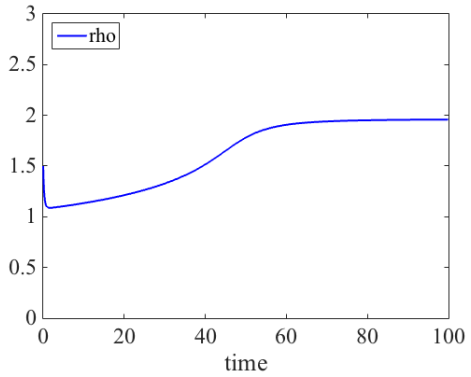


Figure : **Plot of** $t \mapsto \rho(t)$ for $r(x) = 2 + x$, $d(x) = 1 + 2x$.

## Theorem

*$\rho$ converges to $\rho^\infty$ defined as the smallest value such that $r(x) - d(x)\rho^\infty \leq 0$ on $[0, 1]$.*

# Introduction to IDEs: convergence and concentration

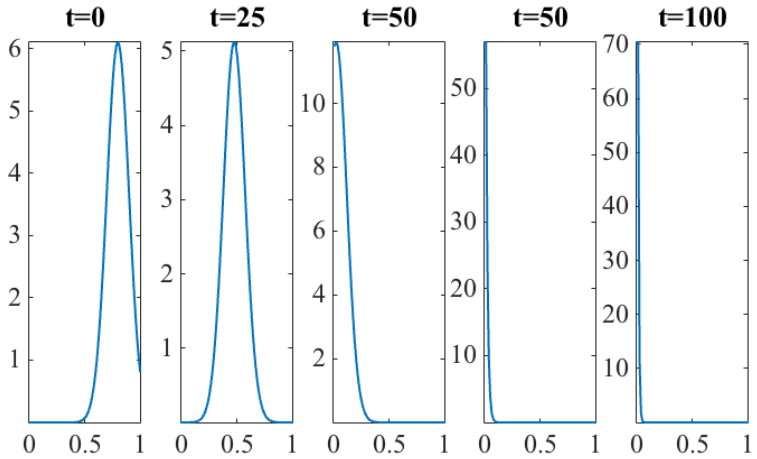


Figure : **Plot of $x \mapsto n(t,x)$ for different times**

# Introduction to IDEs: convergence and concentration

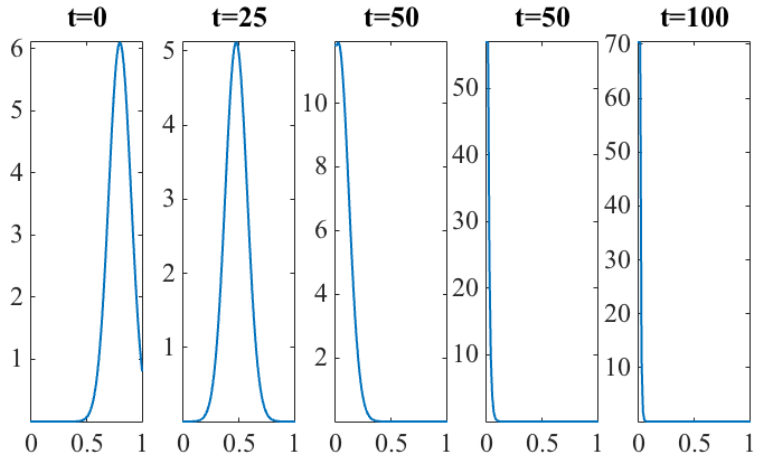


Figure : **Plot of $x \mapsto n(t,x)$ for different times**

## Theorem

*$\rho$ converges to $\rho^\infty$, defined as the smallest value $\rho$ 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 $x^\infty$, then*

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

# Model construction

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

$x \in [0,1]$ from 0 (sensitive) to 1 (resistant)

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

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

# Model construction

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

$$\frac{\partial}{\partial t} n_C(t,x) = \left[ r_C(x) - d_C(x) \underbrace{\left( a_{CC}\rho_C(t) + a_{CH}\rho_H(t) \right)}_{=: I_C(t)} \right] n_C(t,x)$$

- Interspecific competition (smaller than intraspecific competition), with

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

# Model construction

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

- Interspecific competition (smaller than intraspecific competition), with

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

- Cytotoxic drugs $u_1$

# Model construction

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

- Interspecific competition (smaller than intraspecific competition), with

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

- Cytotoxic drugs $u_1$
- Cytostatic drugs $u_2$

# Difficulties for the asymptotic analysis of the model

With **constant controls**, the asymptotic analysis requires to understand systems of the following type:

$$\begin{aligned} \frac{\partial n_H}{\partial t}(t,x) &= \big(r_H(x) - d_H(x) I_H(t)\big) n_H(t,x) \\ \frac{\partial n_C}{\partial t}(t,x) &= \big(r_C(x) - d_C(x) I_C(t)\big) n_C(t,x) \end{aligned} \tag{1}$$

where the coupling comes from $I_H = a_{HH}\rho_H + a_{HC}\rho_C$, $I_C = a_{CC}\rho_C + a_{CH}\rho_H$.

Do we still have convergence for $\rho_H$, $\rho_C$, and concentration for $n_H$, $n_C$?

# Convergence and concentration hold, and with a wide class of controls

## Theorem

*Let $u_1, u_2$ be any functions in $BV(\mathbb{R}_+)$, and let $\bar{u}_1$, $\bar{u}_2$ be their limits. Then $(\rho_H(t), \rho_C(t))$ converges to the equilibrium point $(\rho_H^\infty, \rho_C^\infty)$, defined as follows. Let $I_H^\infty \geq 0$ be the smallest nonnegative real number such that*

$$\frac{r_H(x)}{1+\alpha_H \bar{u}_2} - \bar{u}_1 \mu_H(x) \leq d_H(x) I_H^\infty, \tag{2}$$

*and let $I_C^\infty \geq 0$ be the smallest nonnegative real number such that*

$$\frac{r_C(x)}{1+\alpha_C \bar{u}_2} - \bar{u}_1 \mu_C(x) \leq d_C(x) I_C^\infty. \tag{3}$$

*Then $(\rho_H^\infty, \rho_C^\infty)$ is the unique solution of the (invertible) system*

$$\begin{aligned} a_{HH}\rho_H^\infty + a_{HC}\rho_C^\infty &= I_H^\infty, \\ a_{CH}\rho_H^\infty + a_{CC}\rho_C^\infty &= I_C^\infty. \end{aligned} \tag{4}$$

# Idea of proof for constant controls

*Idea of proof*

Let

$$A_H := \left\{ x \in [0,1],\ \frac{r_H(x)}{1+\alpha_H \bar{u}_2} - \bar{u}_1 \mu_H(x) - d_H(x) I_H^\infty = 0 \right\}$$

$$A_C := \left\{ x \in [0,1],\ \frac{r_C(x)}{1+\alpha_C \bar{u}_2} - \bar{u}_1 \mu_C(x) - d_C(x) I_C^\infty = 0 \right\}$$

Choose **any** tuple of measures $(n_H^\infty, n_C^\infty)$ in $\mathcal{M}^1(0,1)$ satisfying $\int_0^1 n_{H,C}^\infty(x)\,dx = \rho_{H,C}^\infty$, with $\mathrm{supp}(n_H^\infty) \subset A_H$ and $\mathrm{supp}(n_C^\infty) \subset A_C$.

For $m_{H,C} := \frac{1}{d_{H,C}}$, define the Lyapunov functional as $V(t) := \lambda_H V_H(t) + \lambda_C V_C(t)$ where

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

(*Jabin, Raoul*, J. Math. Bio 2011)

# Consequence

If the controls are constant

$$u_1 \equiv \bar{u}_1, \ u_2 \equiv \bar{u}_2,$$

and if

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

then we have a mapping

$$(\bar{u}_1, \bar{u}_2) \longmapsto (x_H^\infty, x_C^\infty, \rho_H^\infty, \rho_C^\infty)$$

with $\rho_H^\infty \delta_{x_H^\infty}$ and $\rho_C^\infty \delta_{x_C^\infty}$ the respective limits of $n_H(t,\cdot)$ and $n_C(t,\cdot)$ in $\mathcal{M}^1(0,1)$, as $t$ goes to $+\infty$.

In particular, if we restrict ourselves to **constant controls** and a **large time** $T$, the problem of minimising $\rho_C(T)$ is equivalent to minimising $\rho_C^\infty$ as a function of $(\bar{u}_1, \bar{u}_2)$.

# Simulations of the effect of constant doses

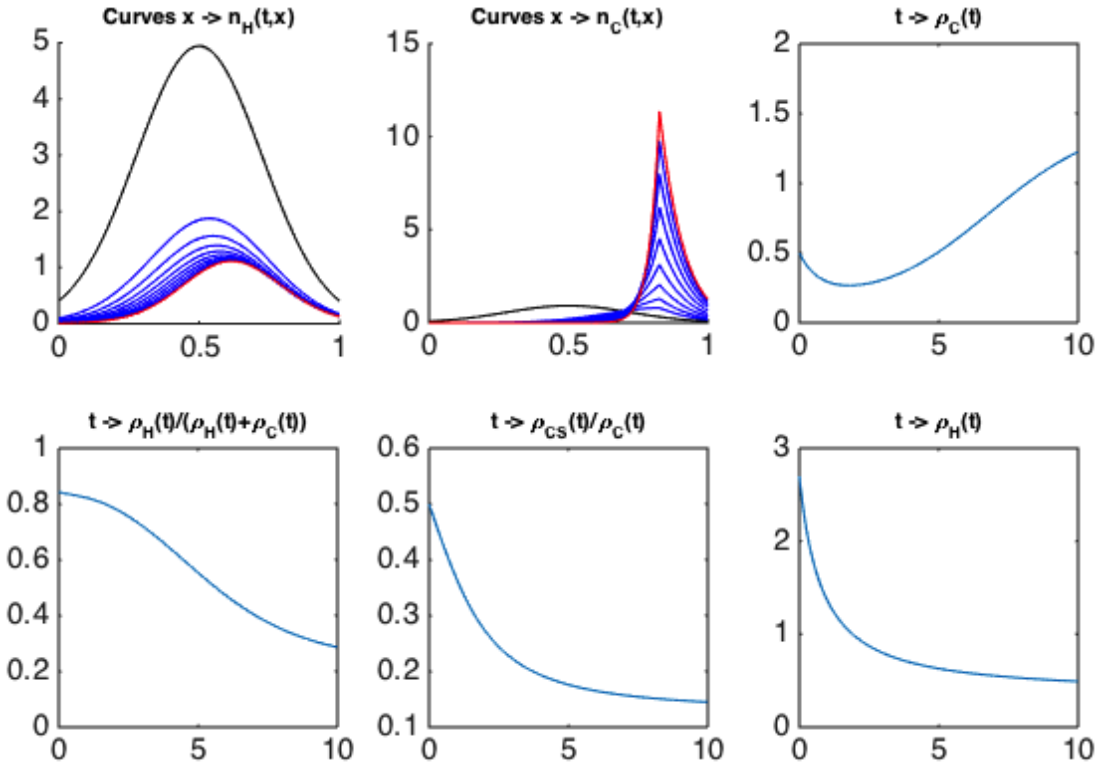


Figure : **Simulation with** $u_1 \equiv 3.5$, $u_2 \equiv 2$ **and** $T = 10$. $(\rho_{CS}(t) := \int_0^1 x\, n_C(t,x)\, dx)$

# Optimal control problem

## Definition

*Let $T > 0$ be fixed. We define the optimal problem (**OCP**)*

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

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

- $$0 \leq u_1(t) \leq u_1^{\max}, \qquad 0 \leq u_2(t) \leq u_2^{\max}.$$
- $$\frac{\rho_H(t)}{\rho_H(t) + \rho_C(t)} \geq \theta_{HC},$$
- $$\rho_H(t) \geq \theta_H \, \rho_H(0).$$

# Numerical solution for (**OCP**)

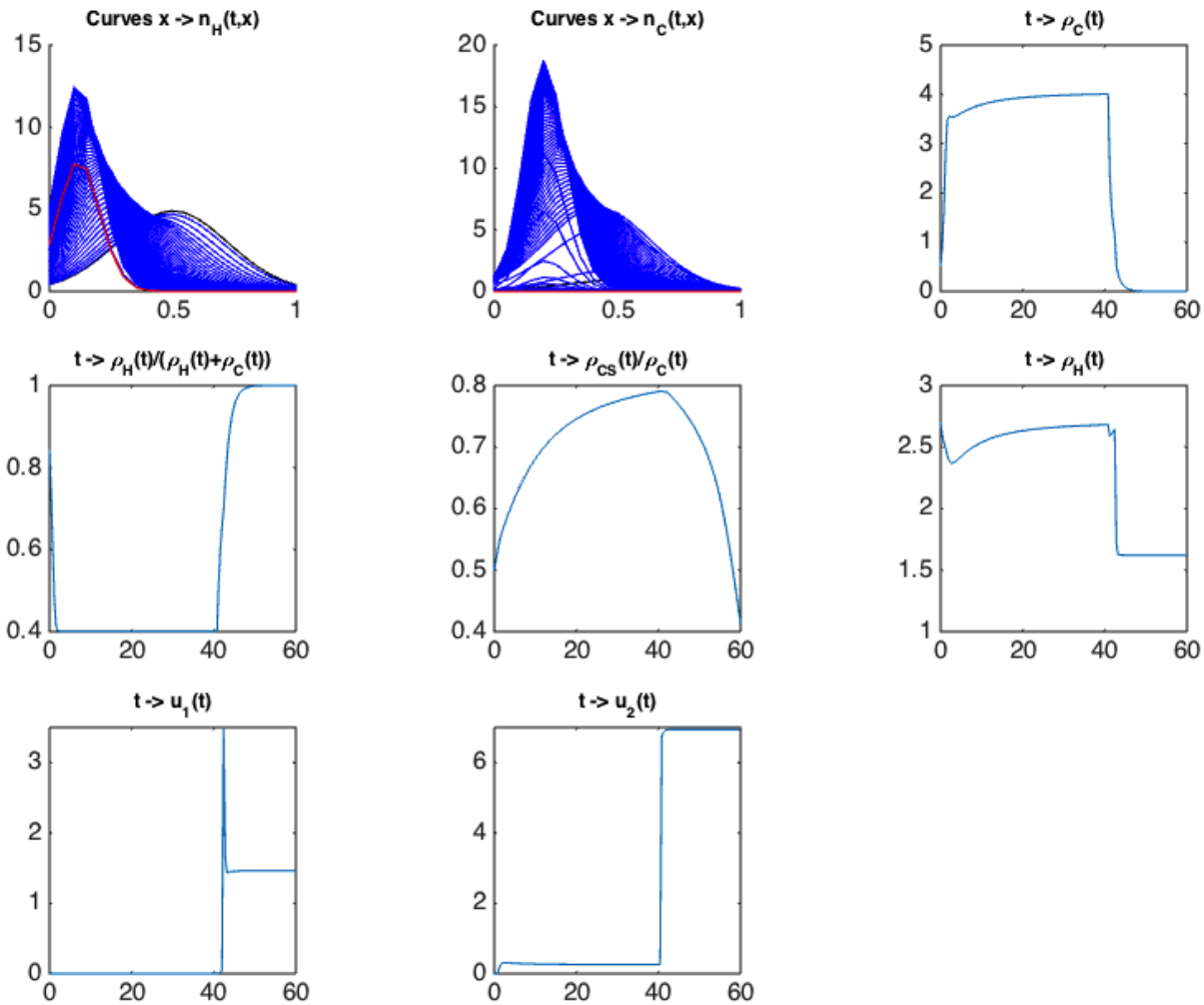


Figure : **Simulation for the solution of (OCP) for T = 60**

# Numerical simulations for (**OCP**): conclusions

Simulations suggest that the optimal strategy for **large** $T$ consists of two phases:

- A first **long** phase with **no cytotoxic drugs** and a **small constant dose of cytostatic drugs**, at the end of which the cancer cells are concentrated on a sensible phenotype.
- A second **short** phase with **maximum tolerated doses for both drugs**, in order to eradicate the maximal amount of cancer cells, and then a boundary arc on the constraint $\rho_H = \theta_H \rho_H(0)$.

# Restriction to a smaller class of controls: an asymptotic result

We consider the class of controls which are

- constant during a long first phase $(0, T_1)$
- switch to any controls on a short phase $(T_1, T)$ with $T - T_1 \leq T_2^M$.

Then, we have the following result (requiring several technical hypotheses):

## Theorem

*Asymptotically in $T_1$ and for $T_2^M$ small enough, there exists at least one solution to (**OCP**) in this class. Furthermore, on $(T_1, T)$ the trajectory obtained with $(u_1, u_2)$ is arbitrarily close to the concatenation of at most three arcs:*

- *a boundary arc along the constraint $\frac{\rho_H}{\rho_H+\rho_C} \geq \delta_H$,*
- *a free arc with controls $u_1 = u_1^{max}$ and $u_2 = u_2^{max}$,*
- *a boundary arc along the constraint $\rho_H \geq \theta_H \rho_H(0)$, with $u_2 = u_2^{max}$.*

# Idea of proof

- At the end of the first long phase, the system has concentrated,
- thus the dynamics of $(\rho_H, \rho_C)$ is arbitrarily close to being driven by an ODE system,
- then, one can use the Pontryagin Maximum Principle for an optimal control problem (ODE with state constraints); the optimal strategy has at most three identifiable arcs.

# References


- Perthame, B. Transport equations in biology, *Springer*, 2007.
- Murray, J. Mathematical biology, *Springer* , 2002.
- Jabin PE, Raoul, G. On selection dynamics in competitive interactions. *J. Math. Bio*, 2011.
- Chisholm, RH, Lorenzi, T, Lorz, A, Larsen, AK, Almeida, L, Escargueil, A, Clairambault, J. Emergence of drug tolerance in cancer cell populations: an evolutionary outcome of selection, non-genetic instability and stress-induced adaptation. *Cancer Research*, in press 2015.
- Lorz, A, Lorenzi, T, Clairambault, J, 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.
- Lorz, A, Lorenzi, T, Hochberg, ME, Clairambault, J, Perthame, B. Populational adaptive evolution, chemotherapeutic resistance and multiple anticancer therapies. *ESAIM: Mathematical Modelling and Numerical Analysis*, 47(02):377-399, 2013.
- Lorz, A, Mirrahimi, S, Perthame, B. Dirac mass dynamics in multidimensional nonlocal parabolic equations. *Comm. Part. Diff. Eqs.*, 36(6):1071-1098, 2011.
- Perthame, B, Barles, G. Dirac concentrations in Lotka-Volterra parabolic PDEs. *Indiana University Mathematics Journal*, 57(7):3275-3302, 2008.
- Clairambault, J, Lorz, A, Trélat, E, *CP*. Asymptotic analysis and optimal control of an integro-differential system modelling healthy and cancer cells exposed to chemotherapy. *In progress*, 2016.