

Une approche stochastique à la modélisation de l'immunothérapie contre le cancer

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-
Travail en collaboration avec

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Plan

- 1 Biological motivations
- 2 Adaptative dynamics
 - The model
 - State of the art
- 3 Only switches : Relapse caused by stochastic fluctuations
 - Therapy with 1 type of T-cell
 - Biological parameters
 - Therapy with 2 types of T-cells
- 4 Only mutations : Early mutation induced by the therapy
- 5 Mutations and switches : Polymorphic Evolution Sequence
- 6 Conclusion

Plan

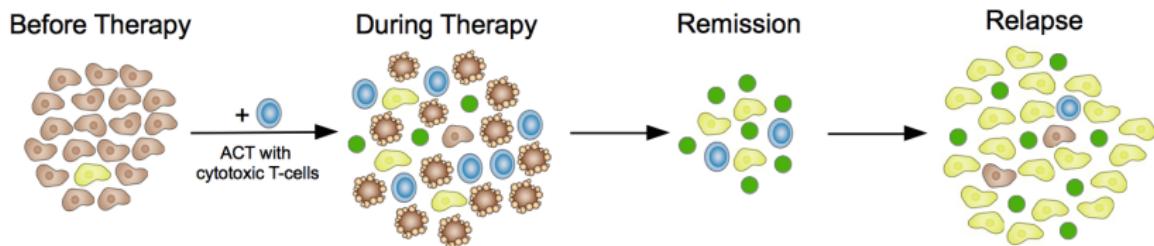
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Experiment on melanoma (UniKlinik Bonn)

Injection of T-cells able to kill a specific type of melanoma.

The treatment induces an **inflammation**, to which the melanoma react by changing their phenotype (markers disappear on their surface, "switch").

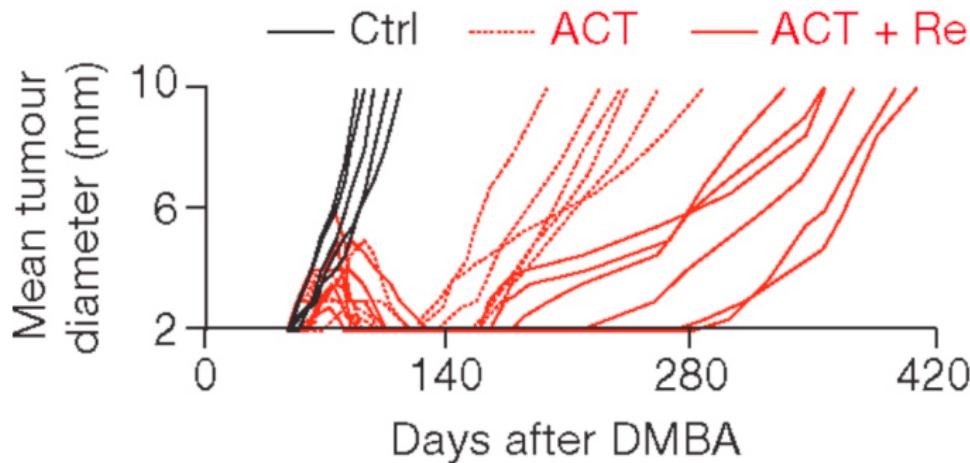
The T-cells cannot kill them any more, the tumor continues to grow.



Without therapy : exponential growth of the tumor.

With therapy : relapse after 140 days.

With therapy and restimulation : late relapse.



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Individual-based model

- **Cancer cells (melanoma)**: each cell is characterized by a genotype and a phenotype. Each can **reproduce**, **die**, **mutate** (reproduction with genotypic change) or **switch** (phenotypic change, without reproduction) at prescribed rates.
- **Immune cells (T-cells)**: Each cell can **reproduce**, **die**, or **kill** a cancer cell of prescribed type (which produces a chemical messenger) at prescribed rates.
- **Chemical messenger (TNF- α)**: Each particle can **die** at a prescribed rate. Its presence influences the ability of a fixed type of cancer cell to switch.

Trait space and measure :

$$\begin{aligned}\mathcal{X} &= \mathcal{G} \times \mathcal{P} \sqcup \mathcal{Z} \sqcup \mathcal{W} = \{g_1, \dots, g_{|\mathcal{G}|}\} \times \{p_1, \dots, p_{|\mathcal{P}|}\} \sqcup \{z_1, \dots, z_{|\mathcal{Z}|}\} \sqcup w \\ n &= (n_{(g_1, p_1)}, \dots, n_{(g_{|\mathcal{G}|}, p_{|\mathcal{P}|})}, n_{z_1}, \dots, n_{z_{|\mathcal{Z}|}}, n_w)\end{aligned}$$

Example for 2 types of melanoma and 1 type of T-cell

The stochastic model converges, in the limit of large populations, towards the solution this dynamical system with **logistic**, **predator-prey**, **switch**:

$$\begin{cases} \dot{n}_x = n_x \left(b_x - d_x - c_{xx} \cdot n_x - c_{xy} \cdot n_y \right) + s \cdot n_y - s_w \cdot n_w n_x - t_{xz} \cdot n_{zx} n_x \\ \dot{n}_y = n_y \left(b_y - d_y - c_{yy} \cdot n_y - c_{yx} \cdot n_x \right) - s \cdot n_y + s_w \cdot n_w n_x \\ \dot{n}_{zx} = -d_{zx} \cdot n_{zx} + b_{zx} \cdot n_{zx} n_x \\ \dot{n}_w = -d_w \cdot n_w + \ell_x \cdot t_{xz} \cdot n_x n_{zx} \end{cases}$$

Event	Rates for x	Rates for y	for z	for w
(Re)production	b_x	b_y	$b_{zx} n_x$	
Natural death	$d_x + c_{xx} n_x + c_{xy} n_y$	$d_y + c_{yy} n_y + c_{yx} n_x$	d_{zx}	d_w
Therapy death	$t_{xz} n_{zx}$	0		
Switch	$s_w n_w$	s		

Deterministically, a number ℓ_w of TNF- α particles are produced when z kills x .

State of the art for the BPDL model

In general \mathcal{X} continuous. Measure $\nu_t = \sum_{i=1}^{N_t} \delta_{x_i}$.

Markov process on the space of positive measures.

Event	Rate
Clonal reproduction	$(1 - p(x)) \cdot b(x)$
Reproduction with mutation	$m(x, dy) \cdot p(x) \cdot b(x)$
Death	$d(x) + \int_{\mathcal{X}} c(x, y) \nu(dy)$

State of the art for the BPDL model

In general \mathcal{X} continuous. Measure $\nu_t = \frac{1}{K} \sum_{i=1}^{N_t} \delta_{x_i}$.

Markov process on the space of positive measures.

Event	Rate
Clonal reproduction	$(1 - \mu p(x)) \cdot b(x)$
Reproduction with mutation	$m(x, dy) \cdot \mu p(x) \cdot b(x)$
Death	$d(x) + \int_{\mathcal{X}} \frac{c(x,y)}{K} \nu(dy)$

Limit of large populations and rare mutations

$$K \rightarrow \infty$$

$$\mu \rightarrow 0$$

Scalings and time scales

- $K \rightarrow \infty$, μ fixed, $T < \infty$:
Law of large numbers, deterministic limit
[Fournier, Méléard, 2004]
- $K \rightarrow \infty$, $\mu \rightarrow 0$, $T < \infty$:
Law of large numbers, deterministic limit without mutations.
- $K \rightarrow \infty$, $\mu \rightarrow 0$, $T \sim \log(1/\mu)$:
Deterministic jump process
[Bovier, Wang, 2012]
- $(K, \mu) \rightarrow (\infty, 0)$ t.q. $\frac{1}{\mu K} \gg \log K$, $T \sim \frac{1}{\mu K}$:
Random jump process
[Champagnat, Méléard, 2009, 2010]
Trait Substitution Sequence
Polymorphic Evolution Sequence

Scalings and time scales

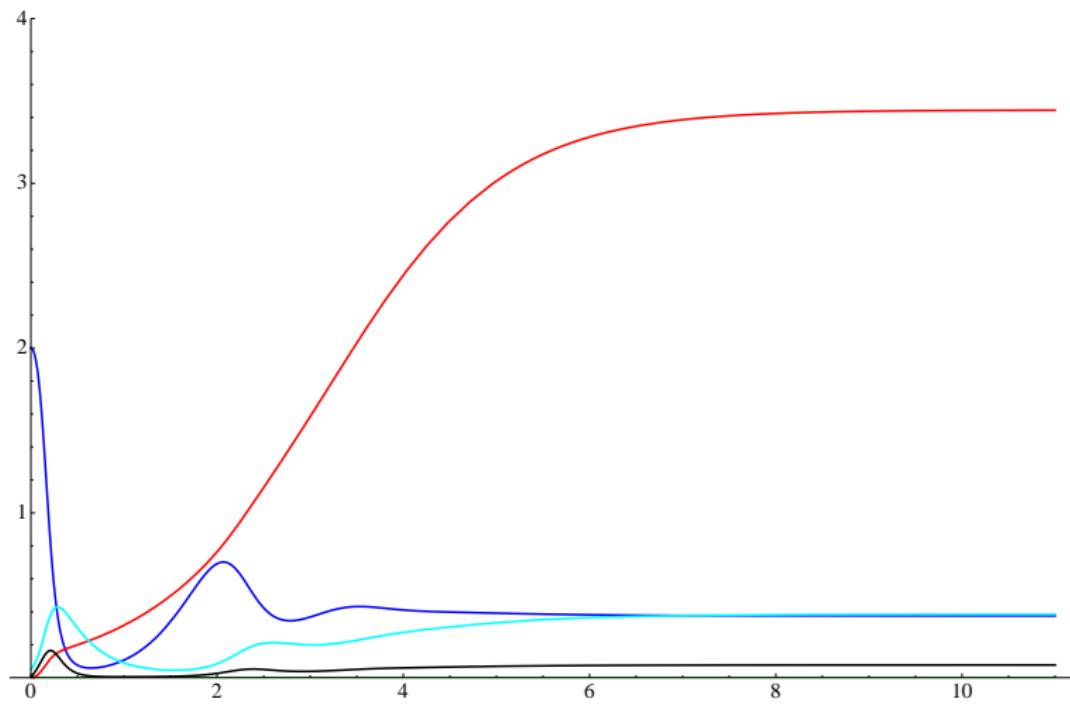
- $K \rightarrow \infty$, μ fixed, $T < \infty$:
Law of large numbers, deterministic limit
[Fournier, Méléard, 2004]
limit dynamical systems (with switch) are not classified
- $K \rightarrow \infty$, $\mu \rightarrow 0$, $T < \infty$:
Law of large numbers, deterministic limit without mutations.
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Solution of the deterministic system

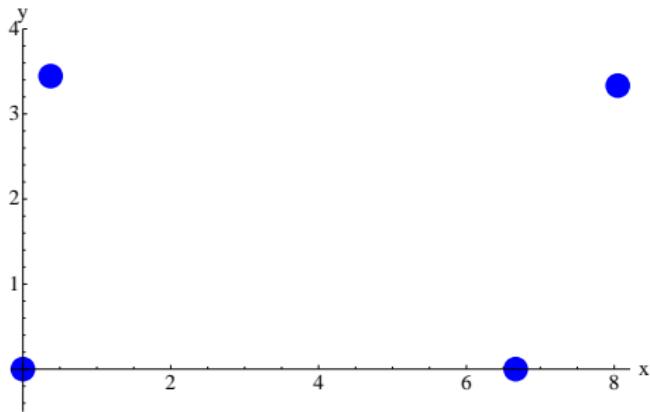
Legend : Melanoma x , melanoma y , T-cells, TNF- α



4 fixed points in the positive quadrant

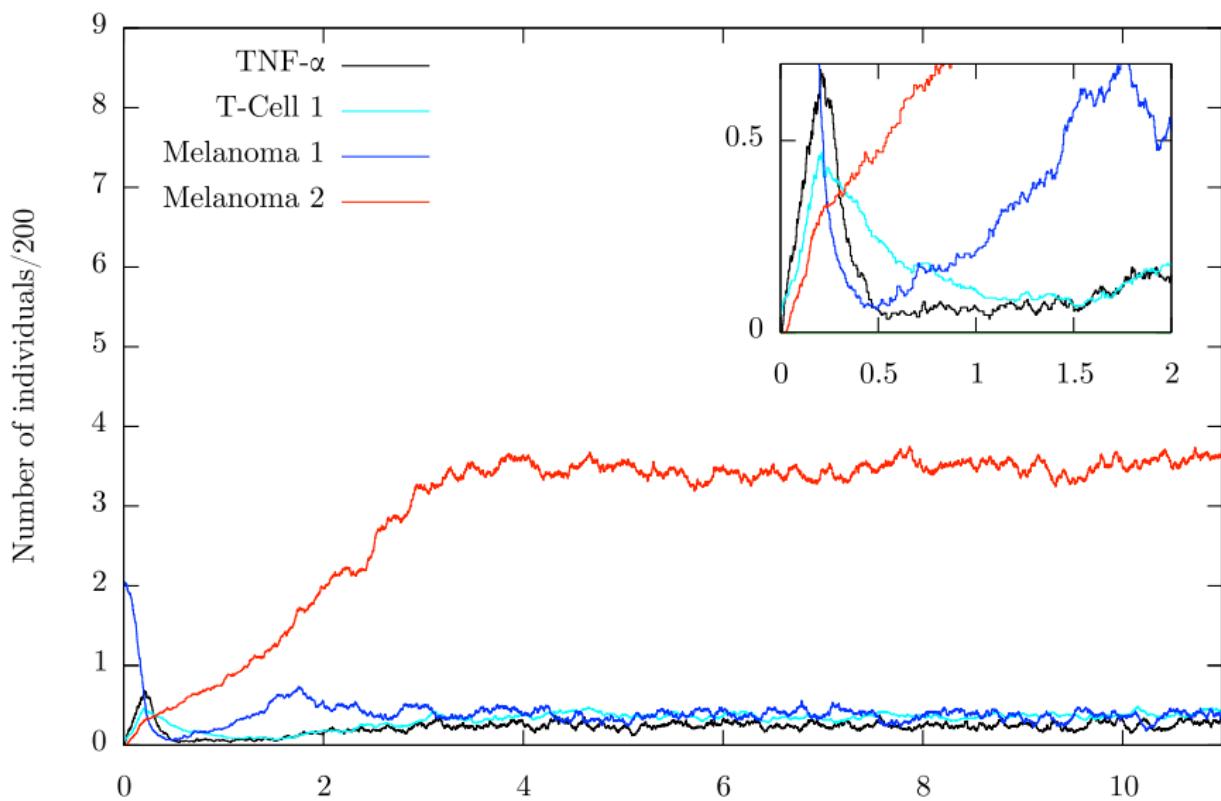
With reasonable parameters we have :

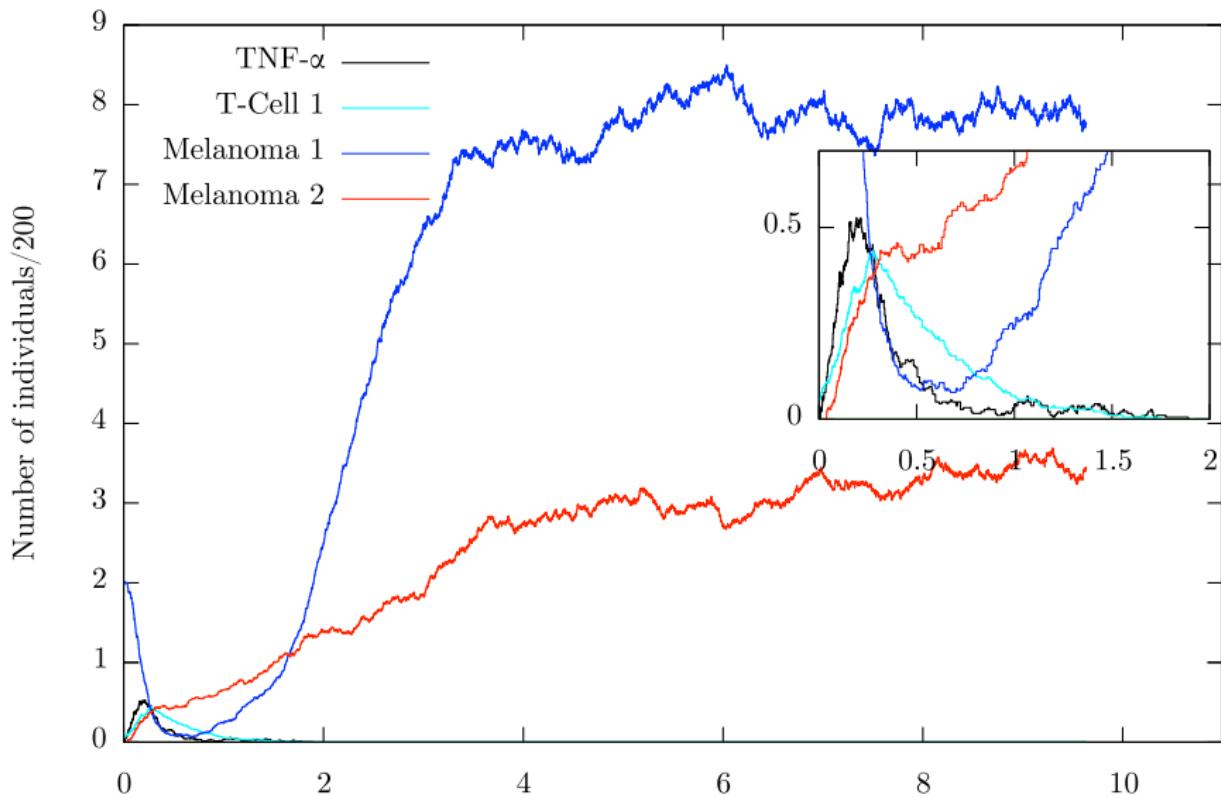
P_{xyz}	P_{xy0}
P_{000}	(P_{x00})



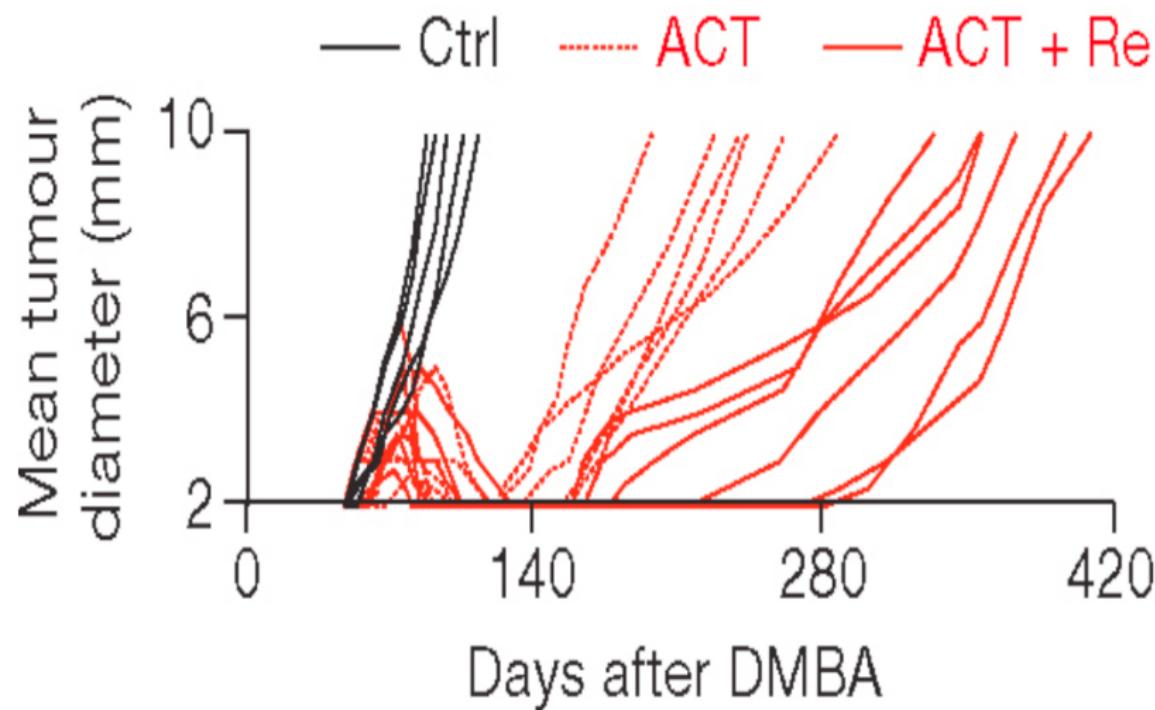
P_{xyz} is stable.

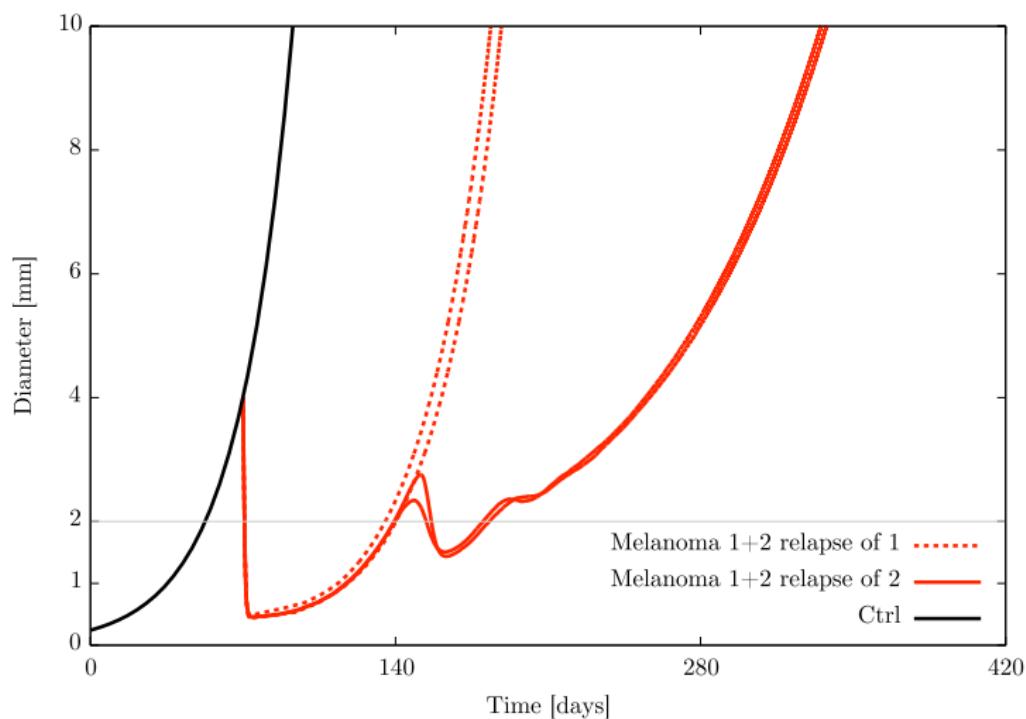
P_{xy0} is stable on the invariant sub-space $\{n_z = 0\}$.

Relapse towards P_{xyz} , ($K = 200$)

Relapse towards P_{xy0} due to the death of z 

Adjustment of parameters : data



Adjustment of parameters : simulations ($K = 10^5$)

Therapy with 1 types of T-cells

$$\begin{cases} \dot{n}_x = n_x \left(b_x - d_x - c_{xx} \cdot n_x - c_{xy} \cdot n_y \right) - t_{xz} \cdot n_{zx} n_x + s \cdot n_y - s_w \cdot n_w n_x \\ \dot{n}_y = n_y \left(b_y - d_y - c_{yy} \cdot n_y - c_{yx} \cdot n_x \right) - s \cdot n_y + s_w \cdot n_w n_x \\ \dot{n}_{zx} = - d_{zx} \cdot n_{zx} + b_{zx} \cdot n_{zx} n_x \\ \dot{n}_w = - d_w \cdot n_w + \ell_x \cdot t_{xz} \cdot n_x n_{zx} \end{cases}$$

Event	Rates for x	Rates for y
Reproduction	b_x	b_y
Natural death	$d_x + c_{xx} n_x + c_{xy} n_y$	$d_y + c_{yy} n_y + c_{yx} n_x$
Death due to therapy	$t_{xz} n_{zx}$	0
Switch	$s_w n_w$	s

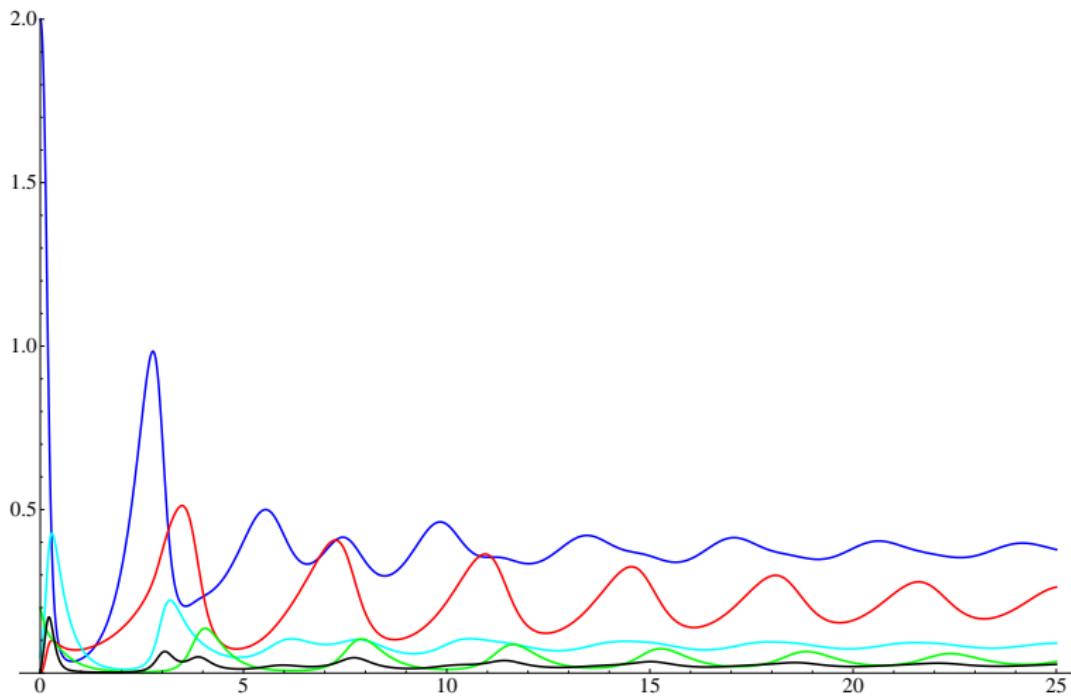
Therapy with 2 types of T-cells

$$\begin{cases} \dot{n}_x = n_x \left(b_x - d_x - c_{xx} \cdot n_x - c_{xy} \cdot n_y \right) - t_{xz} \cdot n_{zx} n_x + s \cdot n_y - s_w \cdot n_w n_x \\ \dot{n}_y = n_y \left(b_y - d_y - c_{yy} \cdot n_y - c_{yx} \cdot n_x \right) - t_{yz} \cdot n_{zy} n_y - s \cdot n_y + s_w \cdot n_w n_x \\ \dot{n}_{zx} = -d_{zx} \cdot n_{zx} + b_{zx} \cdot n_{zx} n_x \\ \dot{n}_{zy} = -d_{zy} \cdot n_{zy} + b_{zy} \cdot n_{zy} n_y \\ \dot{n}_w = -d_w \cdot n_w + \ell_x \cdot t_{xz} \cdot n_x n_{zx} + \ell_y \cdot t_{yz} \cdot n_y n_{zy} \end{cases}$$

Event	Rates for x	Rates for y
Reproduction	b_x	b_y
Natural death	$d_x + c_{xx} n_x + c_{xy} n_y$	$d_y + c_{yy} n_y + c_{yx} n_x$
Death due to therapy	$t_{xz} n_{zx}$	$t_{yz} n_{zy}$
Switch	$s_w n_w$	s

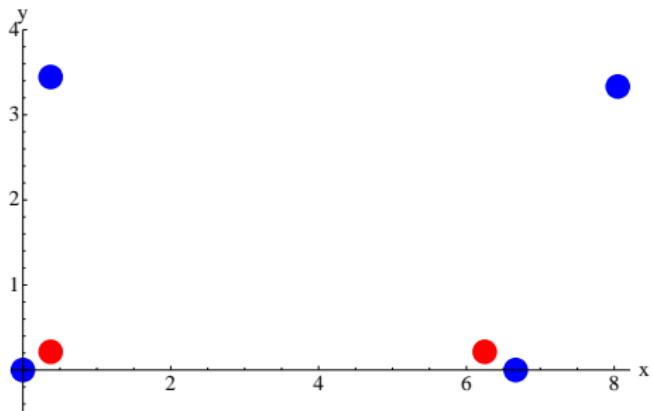
Solution of the deterministic limit

Legend : Melanoma x , melanoma y , T-cell z_x , T-cell z_y , TNF- α



6 fixed points in the positive quadrant

$Pxyz_x 0$	$Pxy00$
$Pxyz_x z_y$	$Pxy0z_y$
$P0000$	$(Px000)$



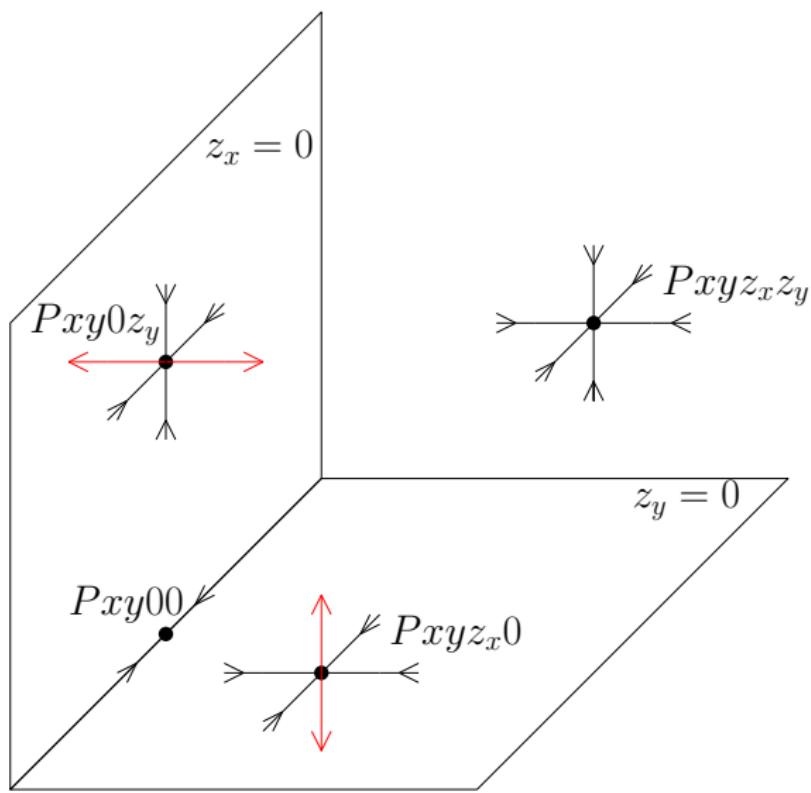
$Pxyz_x z_y$ is stable.

$Pxyz_x 0$ is stable in the invariant subspace $\{n_{z_y} = 0\}$

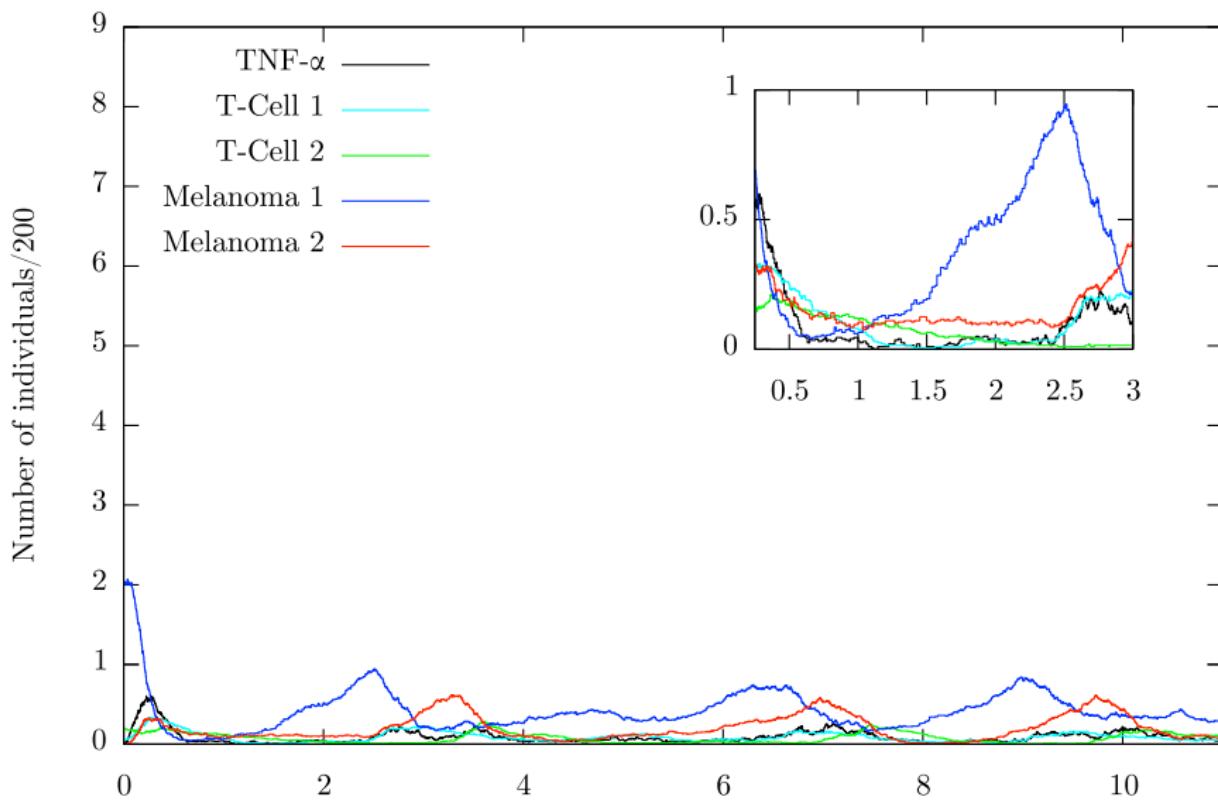
$Pxy0z_y$ is stable in the invariant subspace $\{n_{z_x} = 0\}$

$Pxy00$ is stable in the invariant subspace $\{n_{z_x} = 0\} \cap \{n_{z_y} = 0\}$

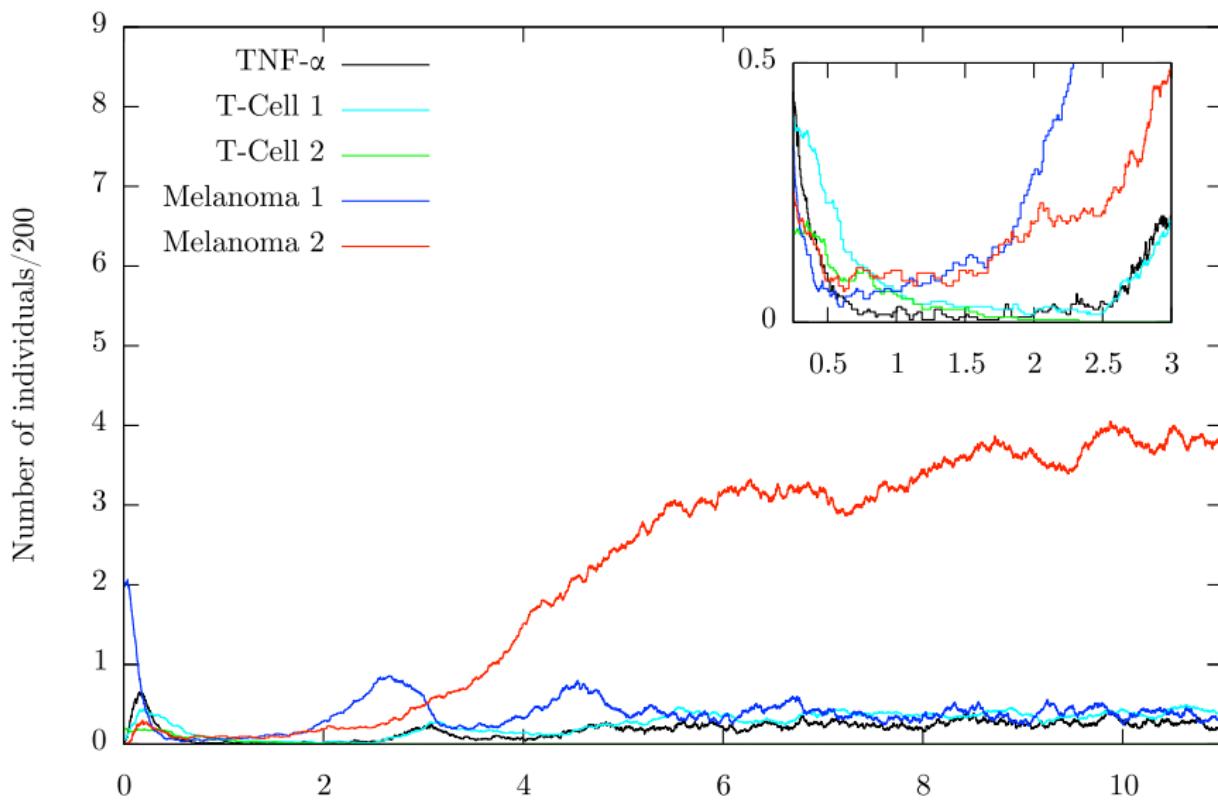
Branching between several possible relapses

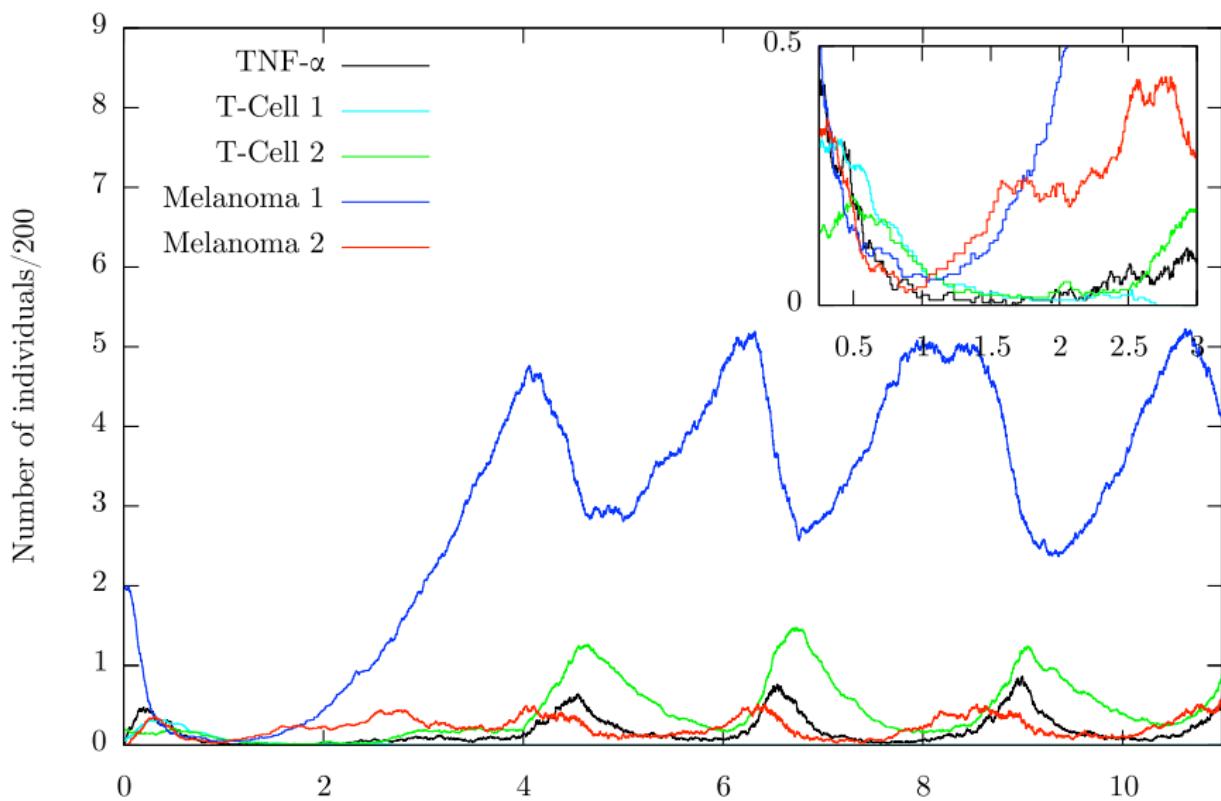


Stochastic system close to the deterministic system

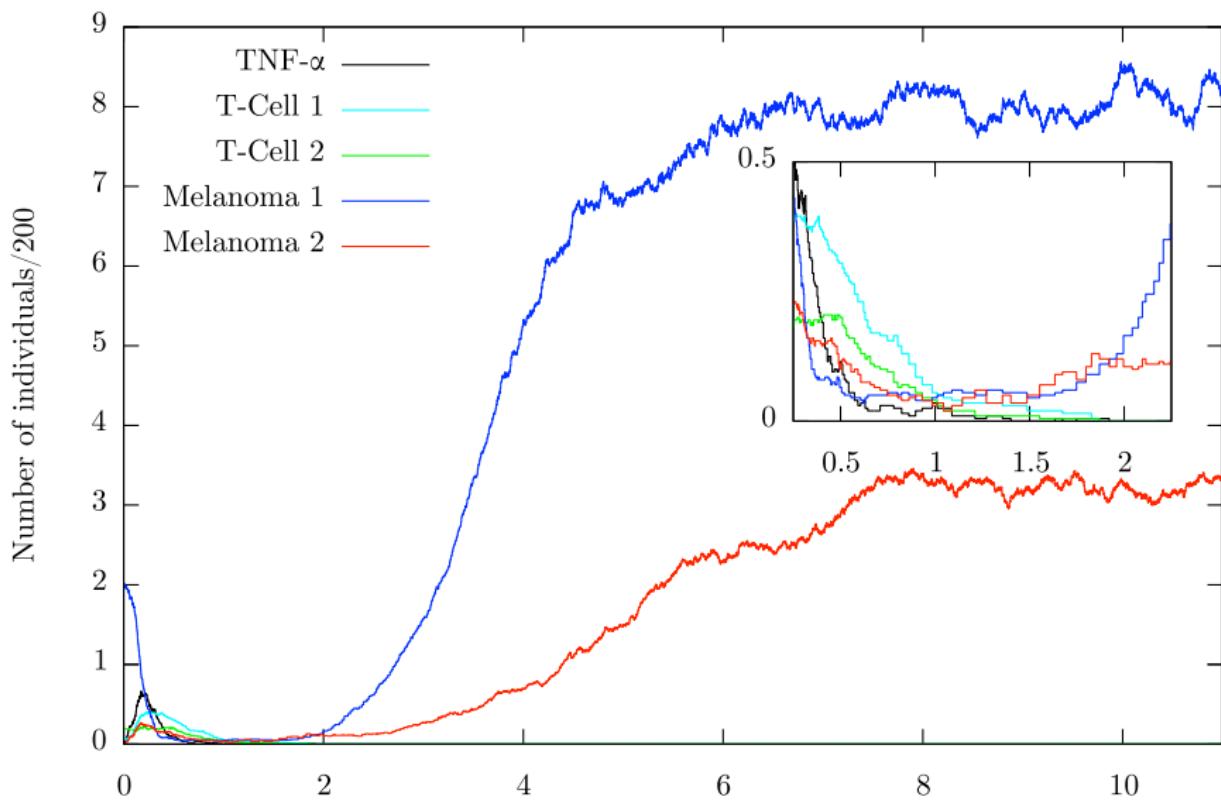


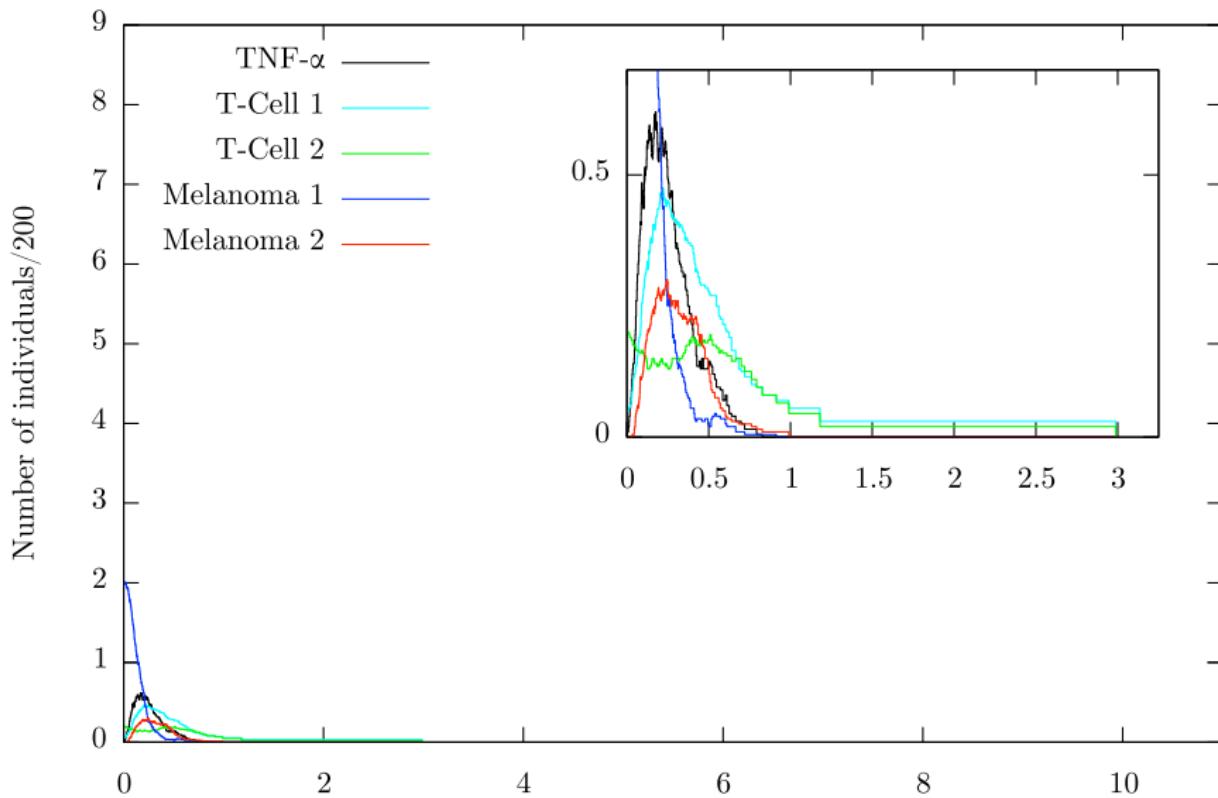
Relapse towards $Pxyz_x0$ caused by the death of z_y



Relapse towards $Pxy0z_y$ caused by the death of z_x 

Relapse towards P_{xy00} caused by the death of z_x and z_y



Cure ! ($P=0.0000$)

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Example for 2 types of melanoma and 1 type of T-cell

BPDL + therapy with usual competition

Event	Rates for x
Clonal reproduction	$(1 - \mu)b(x)$
Mutation towards y	$\mu b(x)$
Natural death	$d(x) + c(x, x)n_x + c(x, y)n_y$
Death due to therapy	$t(z, x)n_z$

Example for 2 types of melanoma and 1 type of T-cell

BPDL + therapy with birth-reducing competition

Event	Rates for x
Clonal reproduction	$(1 - \mu) \lfloor b(x) - c(x, x)n_x - c(x, y)n_y \rfloor_+$
Mutation towards y	$\mu \lfloor b(x) - c(x, x)n_x - c(x, y)n_y \rfloor_+$
Natural death	$d(x) + \lfloor b(x) - c(x, x)n_x - c(x, y)n_y \rfloor_-$
Death due to therapy	$t(z, x)n_z$

Example for 2 types of melanoma and 1 type of T-cell

BPDL + therapy with birth-reducing competition

Event	Rates for y
Clonal reproduction	$\lfloor b(y) - c(y, y)n_y - c(y, x)n_x \rfloor_+$
Mutation towards x	0
Natural death	$d(y) + \lfloor b(y) - c(y, y)n_y - c(y, x)n_x \rfloor_-$
Death due to therapy	0

Event	Rates for z
Reproduction	$b(z, x)n_x$
Death	$d(z)$

No switch \Rightarrow The chemical messenger (TNF- α) has a trivial role : $n_w = 0$

Limiting deterministic system

When $(K, \mu) \rightarrow (\infty, 0)$ such that

$$\mu \cdot K \rightarrow \alpha > 0$$

then μ disappears from the deterministic system on the time scale $T < \infty$
 (mutant appear after a time $O(1/\mu K) = O(1)$ but need $O(\log(K)) \rightarrow \infty$
 to become macroscopic).

$$\begin{cases} \dot{n}_x = n_x(b_x - d_x - c_{xx} \cdot n_x - c_{xy} \cdot n_y) - t_{xz} \cdot n_{zx} n_x \\ \dot{n}_y = n_y(b_y - d_y - c_{yy} \cdot n_y - c_{yx} \cdot n_x) \\ \dot{n}_{zx} = -d_{zx} \cdot n_{zx} + b_{zx} \cdot n_{zx} n_x \end{cases}$$

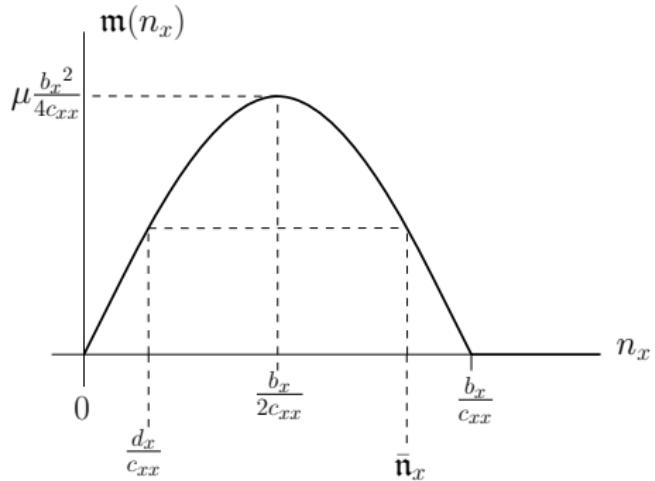
The deterministic system doesn't "see" the difference between death enhancing and birth-reducing competition.

With *birth-reducing* competition

Let $n(0) = (n_x(0), 0, 0)$,

then the initial **mutation rate** is **quadratic** in the population n_x :

$$\mathfrak{m}(n_x) := \mu \lfloor b_x - c_{xx} n_x \rfloor_+ n_x$$

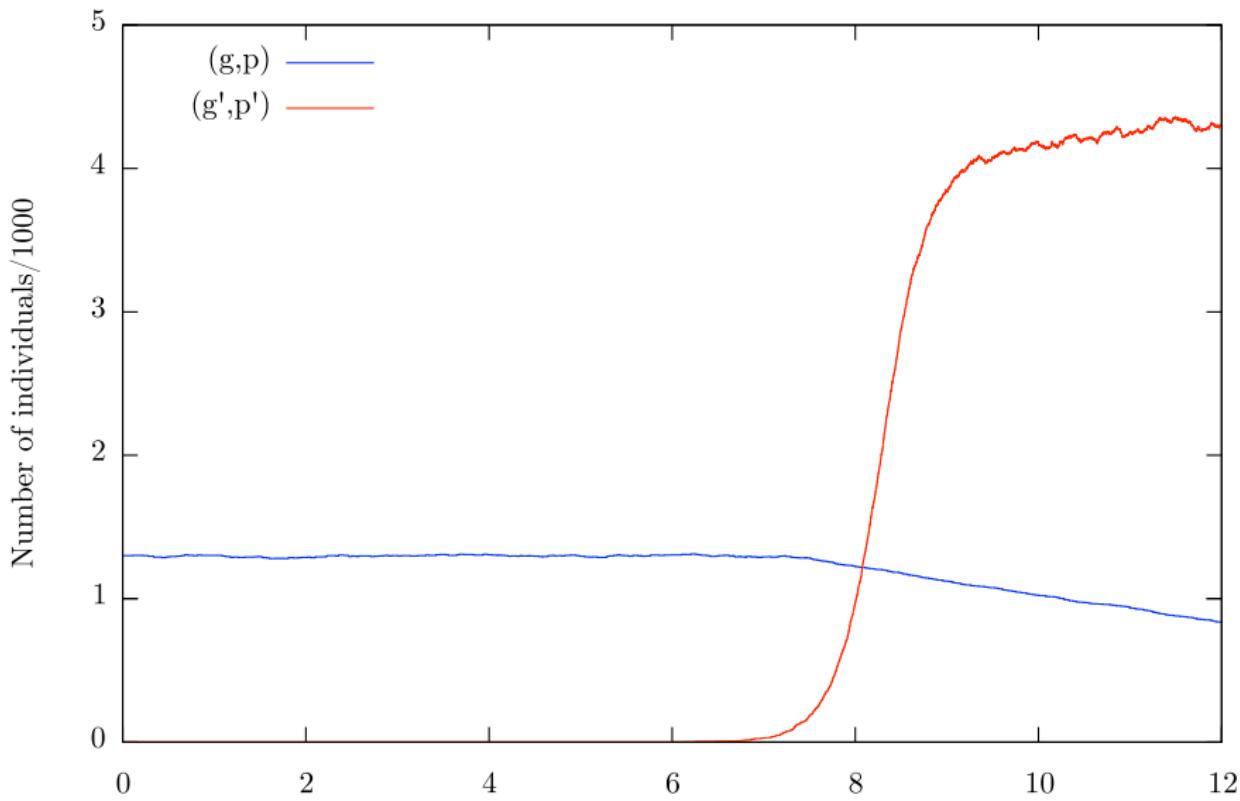


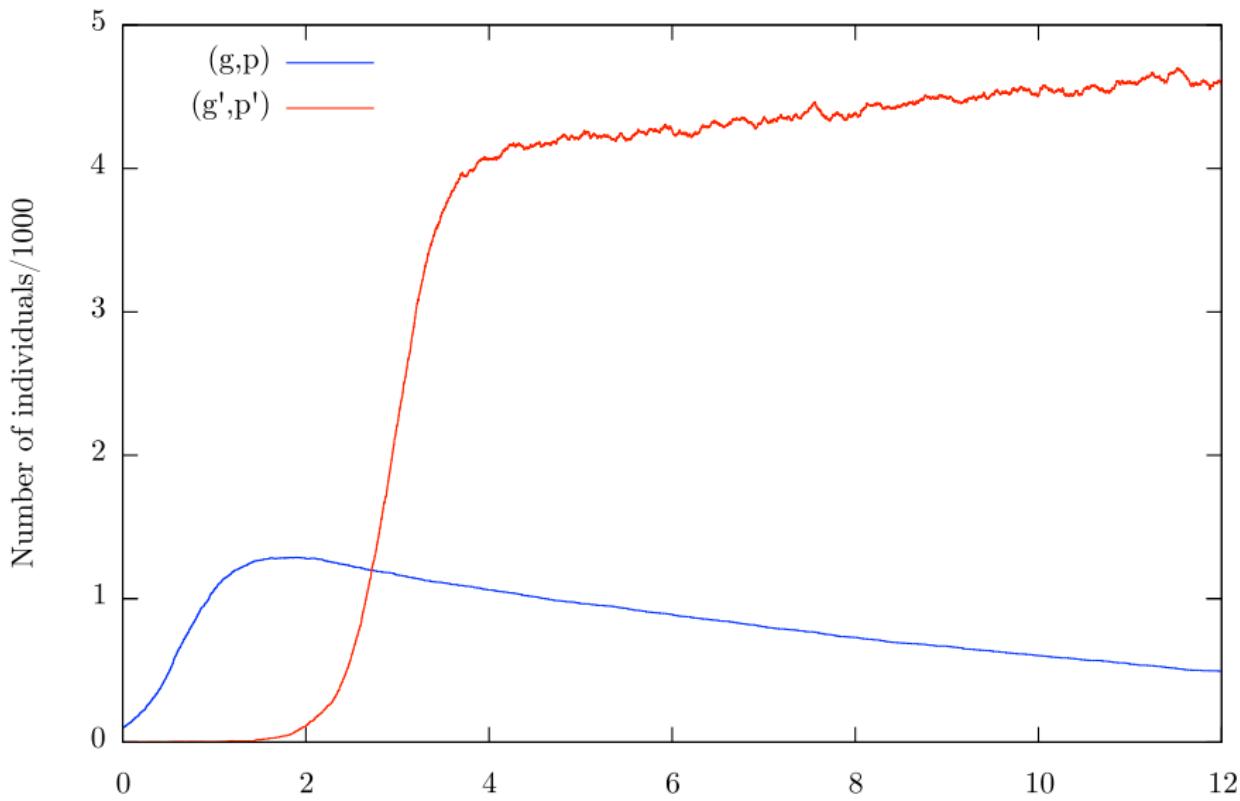
$\bar{n}_x := \frac{b_x - d_x}{c_{xx}}$ is the equilibrium of the initial x population.

A **smaller population** can have a **higher mutation rate**.

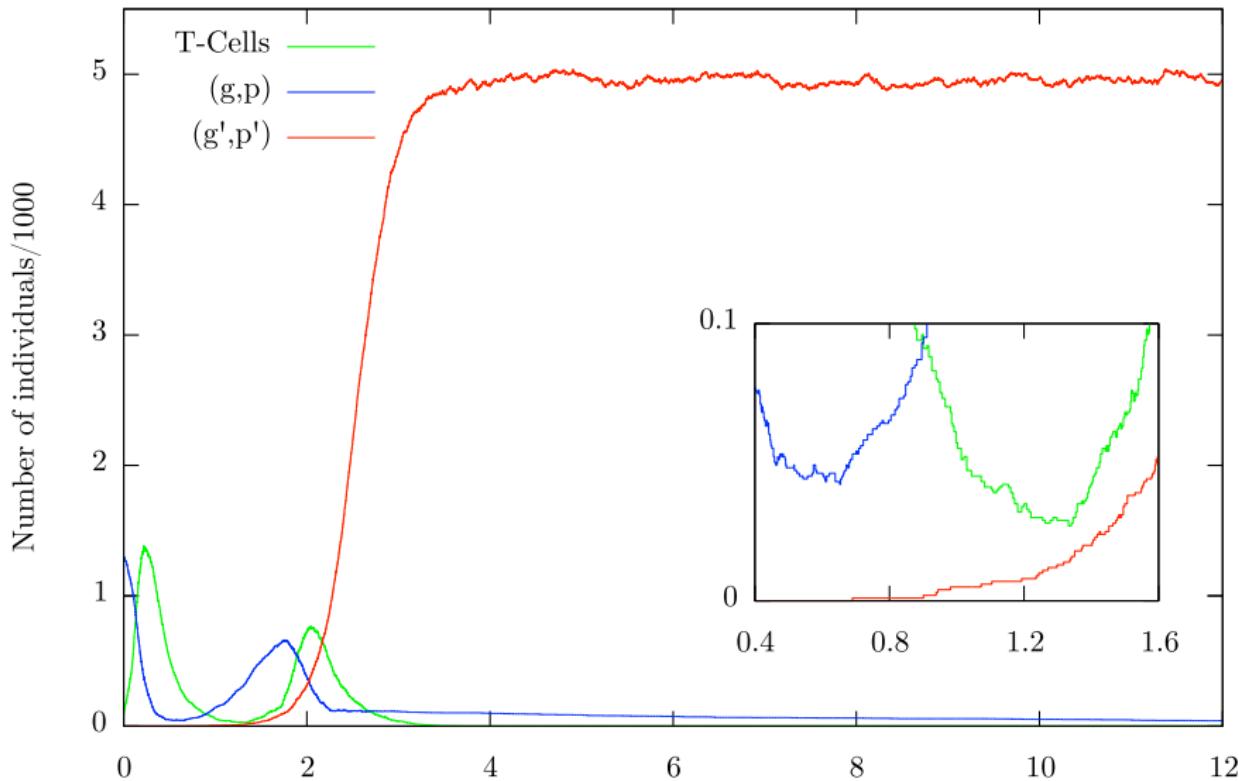
Note $\mathfrak{m}(n_x) = O(\mu K) = O(1)$.

Without treatment and $n_x(0) \simeq \bar{n}_x$



Without treatment and $n_x(0)$ small

With treatment



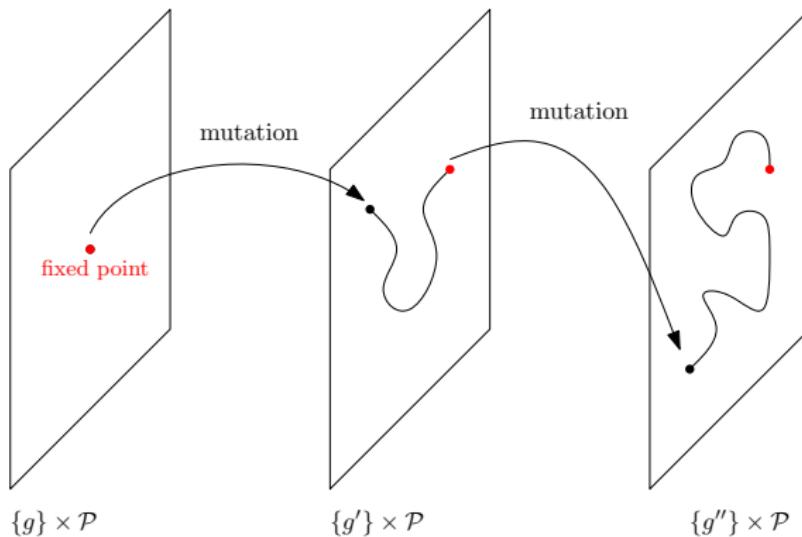
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Two time scales

Rares mutations in \mathcal{G} : $(K, \mu) \rightarrow (\infty, 0)$ s.t. $\mu \ll 1/K \log K$

Fast switches in \mathcal{P} : $\forall p, p' \in \mathcal{P} \quad s_{(g,p),(g,p')} = O(1)$



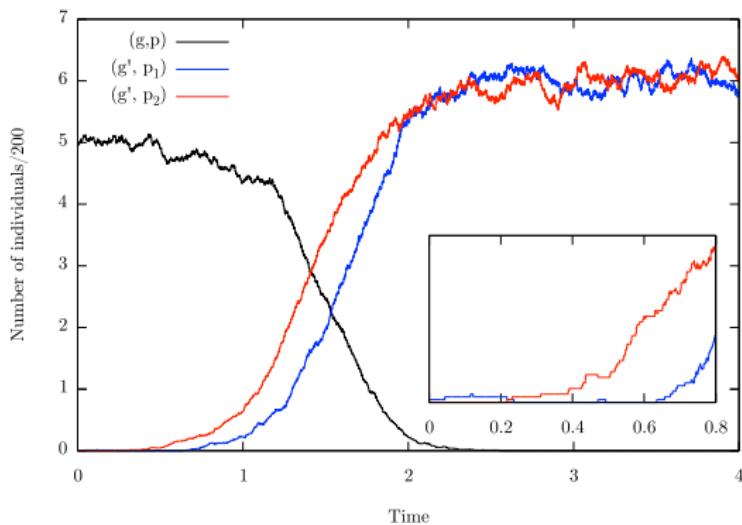
No therapy (only melanoma)

Consider an initial population of genotype g (associated with ℓ different phenotypes p_1, \dots, p_ℓ) which is able to mutate at rate μ to another genotype g' , associated with k different phenotypes p'_1, \dots, p'_k .

Consider as initial condition $n(0) = (n_{(g,p_1)}(0), \dots, n_{(g,p_\ell)}(0))$ a stable fixed point, \bar{n} , of the following system:

$$\dot{n}_{(g,p_i)} = n_{(g,p_i)} \left(b_i - d_i - \sum_{j=1}^{\ell} c_{ij} n_{(g,p_j)} - \sum_{j=1}^{\ell} s_{ij} \right) + \sum_{j=1}^{\ell} s_{ji} n_{(g,p_j)}.$$

Study of one step



$\leftarrow 1 \rightarrow \leftarrow 2 \rightarrow \leftarrow 3 \rightarrow$

Phase 1 : approximation with supercritical multi-type branching, $O(\log(K))$

Phase 2 : approximation with the deterministic system, $O(1)$

Phase 3 : approximation with subcritical multi-type branching, $O(\log(K))$

Invasion fitness ?

For the BPDL model (without switches) :

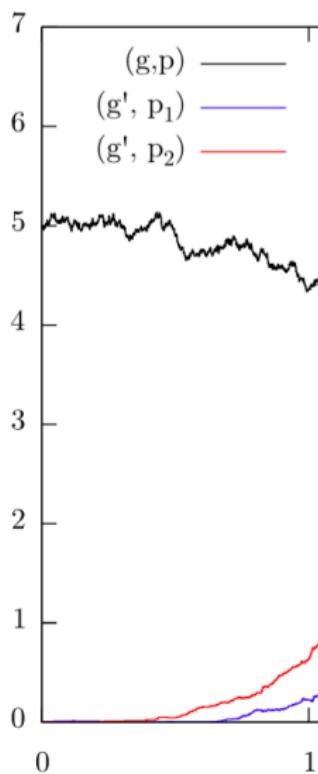
$$f(x, M) = b(x) - d(x) - \sum_{y \in M} c_{xy} \bar{n}_y.$$

is the growth rate of a single individual with trait $x \notin M$ in the presence of the equilibrium population \bar{n} on M .

- $f(x, M) > 0$: positive probability for the mutant (uniformly in K) to **grow** to a population of size $O(K)$;
- $f(x, M) < 0$: the mutant population **dies out** with probability tending to one (as $K \rightarrow \infty$) before this happens.

We need to generalize this notion to the case when fast phenotypic switches are present.

Phase 1



As long as

- $n_{(g, p_i)} \geq \bar{n}_{(g, p_i)} - \varepsilon \quad \forall i = 1, \dots, \ell$
- $\sum_{i=1}^k n_{(g', p'_i)} \leq \varepsilon K$

the mutant population $(g', p'_1), \dots, (g', p'_k)$ is well approximated by a **k -type branching process** with rates:

$$\left. \begin{array}{lll} p'_i \rightarrow p'_i p'_i & \text{with rate} & b'_i \\ p'_i \rightarrow \emptyset & \text{with rate} & d'_i + \sum_{l=1}^{\ell} c_{il} \bar{n}_l \\ p'_i \rightarrow p'_j & \text{with rate} & s'_{ij} \end{array} \right\}$$

Multi-type branching processes have been analysed by Kesten/Stigum and Atreya/Ney. Their behavior are classified in terms of the matrix A , given by

$$A = \begin{pmatrix} f_1 & s'_{12} & \dots & s'_{1k} \\ s'_{21} & f_2 & & \vdots \\ \vdots & & \ddots & \\ s'_{k1} & \dots & & f_k \end{pmatrix}$$

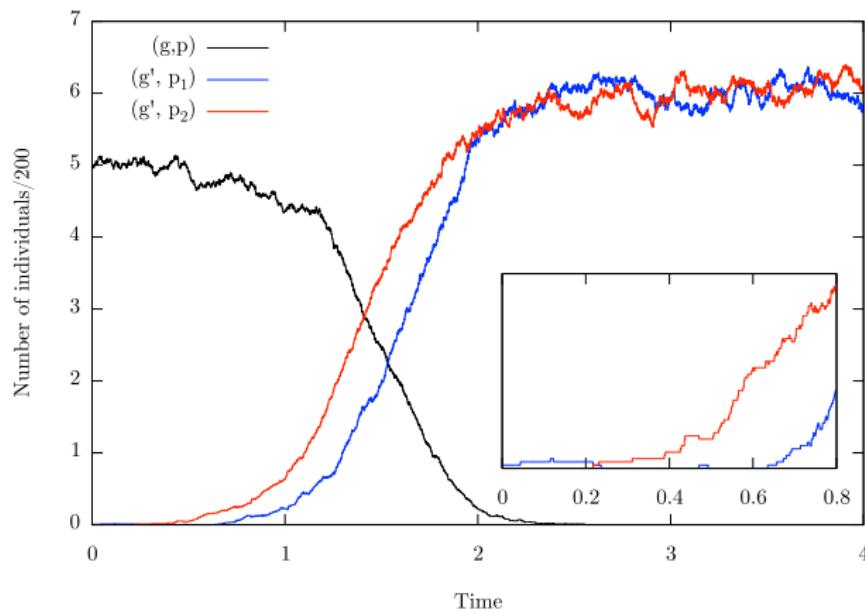
where

$$f_i := b'_i - d'_i - \sum_{l=1}^{\ell} c_{il} \cdot \bar{n}_l - \sum_{j=1}^k s'_{ij}.$$

The multi-type process is super-critical, if and only if the largest eigenvalue, $\lambda_1 = \lambda_1(A) > 0$. It is thus the appropriate generalization of the invasion fitness:

$$F(g', g) := \lambda_1(A).$$

Example : Resonance



$$\begin{aligned}
 s_{12} &= s_{21} = 2 \\
 f_1 &= f_2 = -1 \\
 F(g', g) &= \lambda_1 = 1 \\
 \tilde{F}(g, g') &= -1
 \end{aligned}$$

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Still a lot to understand...

Biologically :

- measure precise parameters appearing in the model
- check predictions (e.g. therapy with 2 types of T-cells)
- etc.

Mathematically :

- How do the transition probabilities between different relapses scale with K ?
- What happens if the deterministic system has limit cycles ?
- How does the birth-reducing competition affect the mutation probability in presence of treatment?
- etc.

Merci !