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

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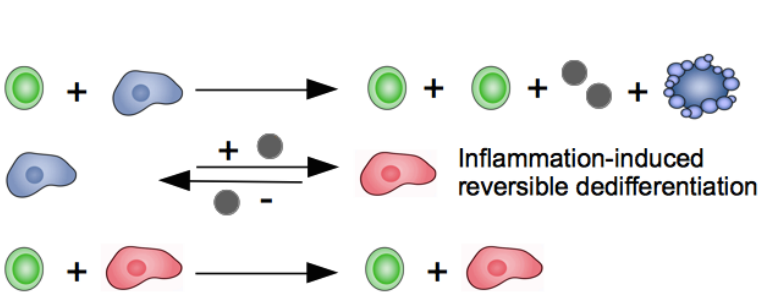
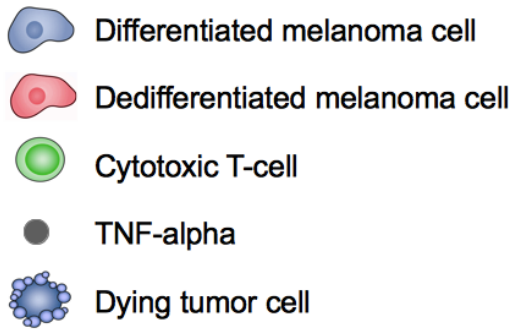
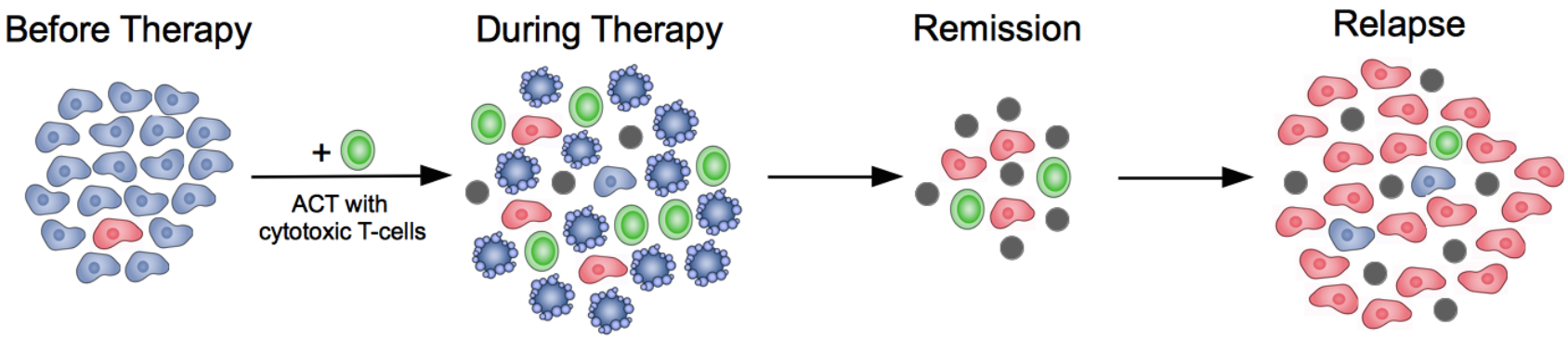
Experiment on melanoma (UniKlinik Bonn)

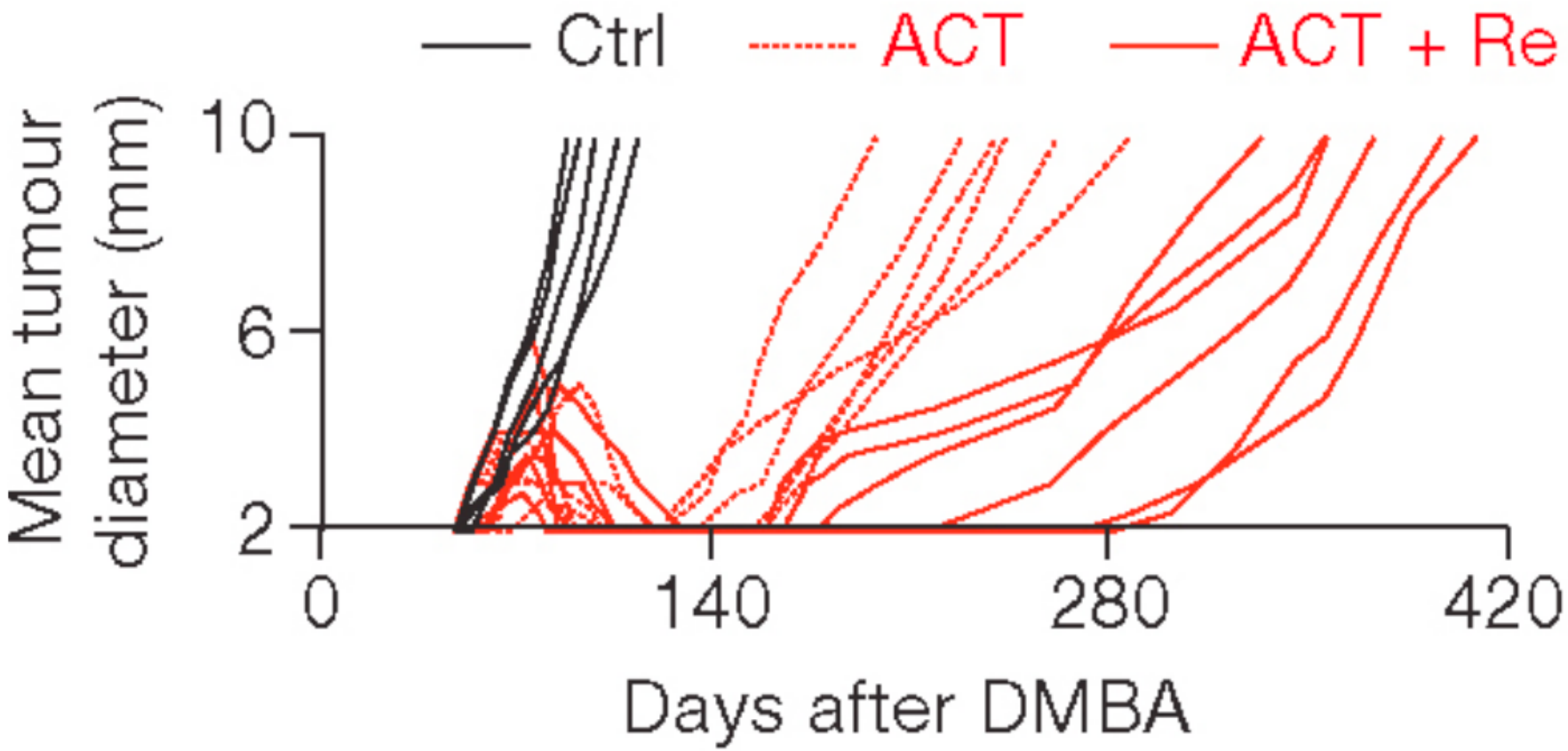
Injection of T-cells able to kill a specific type of melanoma.
The treatment induces an **inflammation**, to which the melanoma react by changing their phenotype (markers disappear on their surface, "**switch**").
The T-cells cannot kill them any more, the tumor continues to grow.







Without therapy : exponential growth of the tumor.
With therapy : relapse after 140 days.
With therapy and restimulation : late relapse.



Plan

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$-\alpha$):** 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 :

$$\mathcal{X} = \mathcal{G} \times \mathcal{P} \sqcup \mathcal{Z} \sqcup \mathcal{W} = \{g_1, \dots, g_{|\mathcal{G}|}\} \times \{p_1, \dots, p_{|\mathcal{P}|}\} \sqcup \{z_1, \dots, z_{|\mathcal{Z}|}\} \sqcup w$$

$$n = (n_{(g_1,p_1)}, \dots, n_{(g_{|\mathcal{G}|},p_{|\mathcal{P}|})}, n_{z_1}, \dots, n_{z_{|\mathcal{Z}|}}, n_w)$$

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**:

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

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

Deterministically, a number ℓ_w of TNF-α particles are produced when z_x 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

$$K \to \infty$$

$$\mu \to 0$$

Scalings and time scales

- $K \to \infty$, μ fixed, $T < \infty$:
  Law of large numbers, deterministic limit
  [Fournier, Méléard, 2004]
- $K \to \infty$, $\mu \to 0$, $T < \infty$:
  Law of large numbers, deterministic limit without mutations.
- $K \to \infty$, $\mu \to 0$, $T \sim \log(1/\mu)$:
  Deterministic jump process
  [Bovier, Wang, 2012]
- $(K, \mu) \to (\infty, 0)$ 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

- $K \to \infty$, μ fixed, $T < \infty$:
  Law of large numbers, deterministic limit
  [Fournier, Méléard, 2004]
  limit dynamical systems (with switch) are not classified
- $K \to \infty$, $\mu \to 0$, $T < \infty$:
  Law of large numbers, deterministic limit without mutations.
- $K \to \infty$, $\mu \to 0$, $T \sim \log(1/\mu)$:
  Deterministic jump process
  [Bovier, Wang, 2012]
- $(K, \mu) \to (\infty, 0)$ 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
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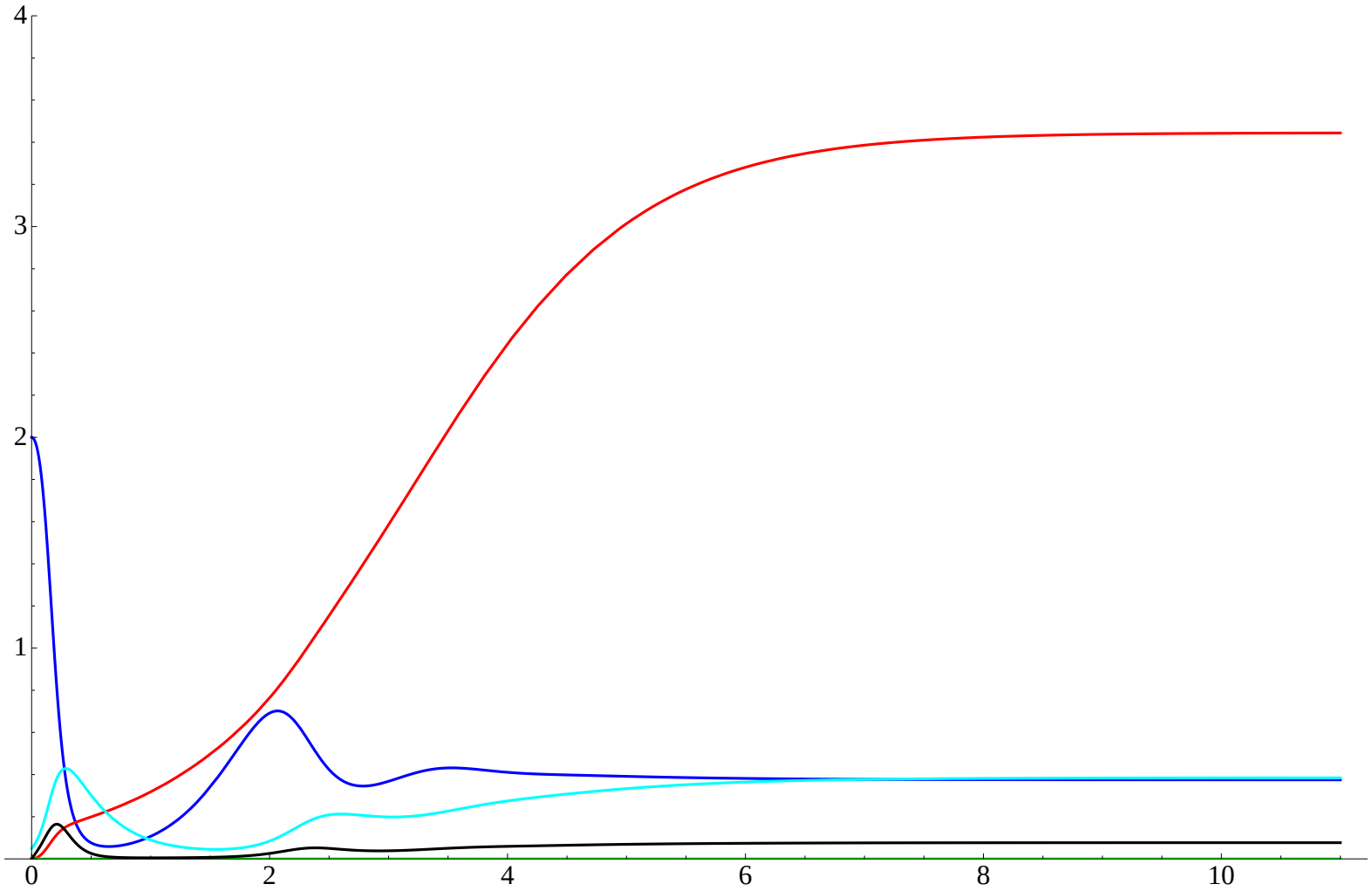
Plan

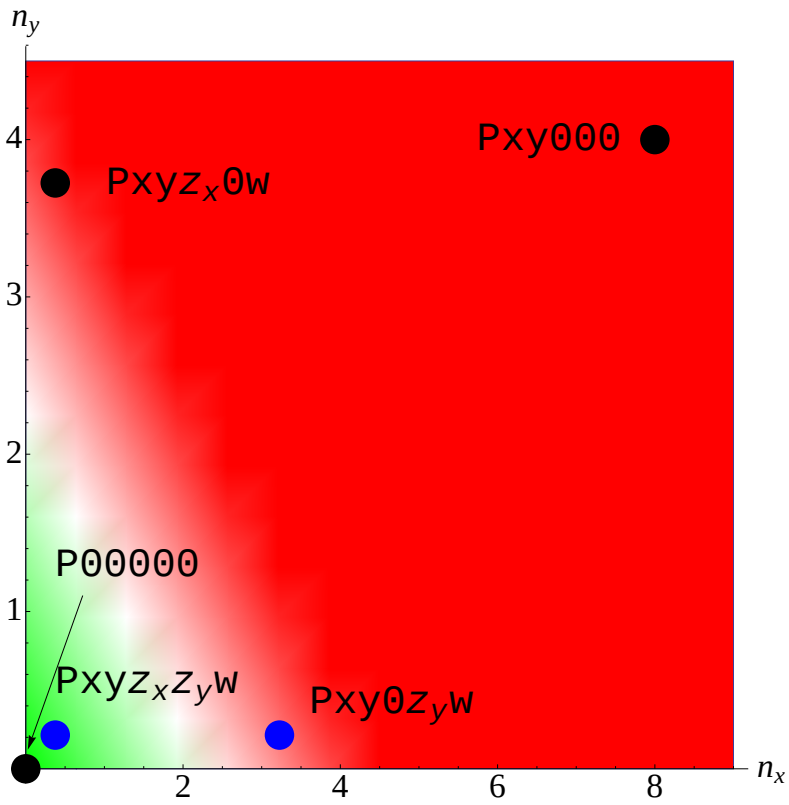
Solution of the determinisitic system

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



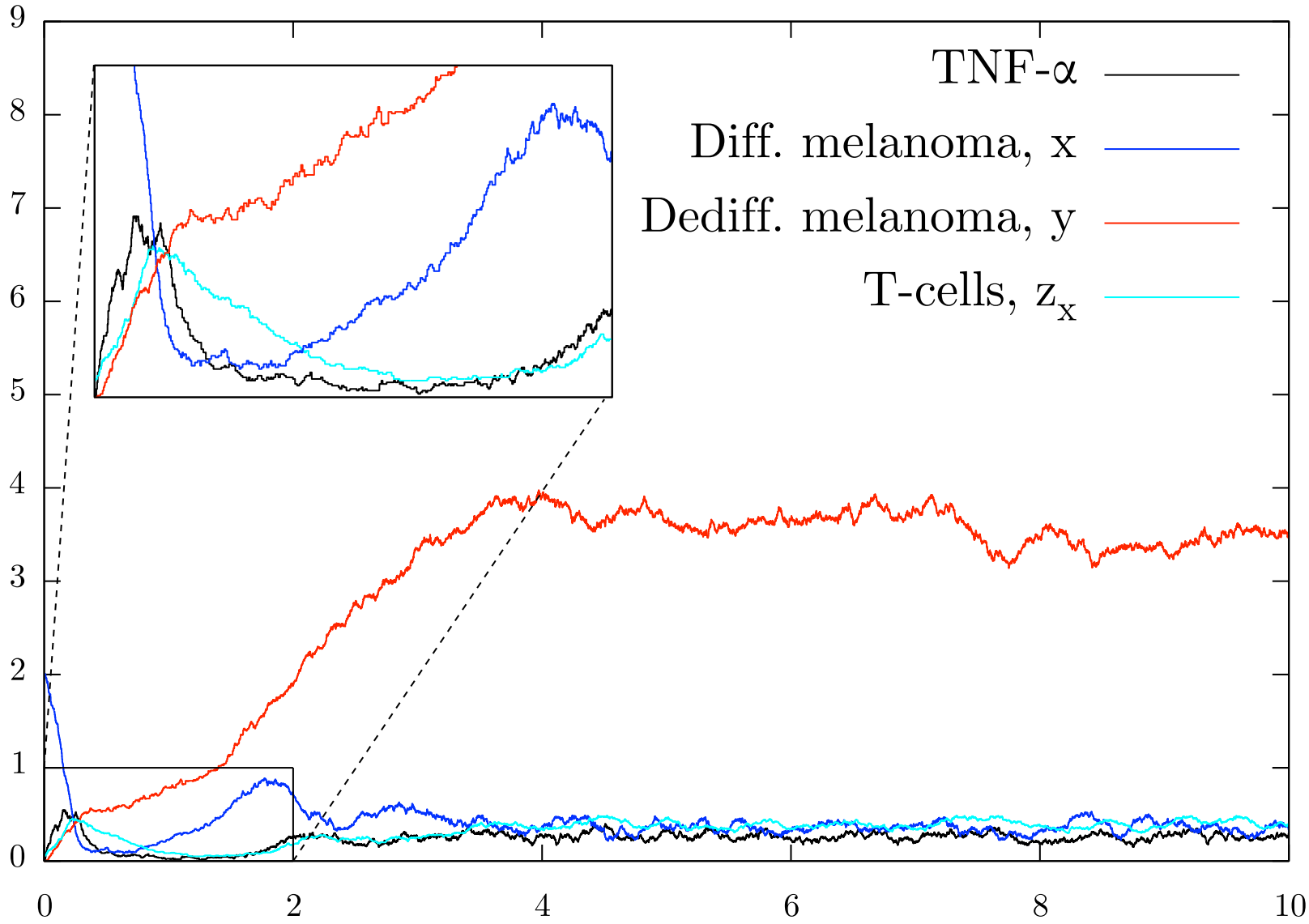
3 fixed points

With reasonable parameters we have :

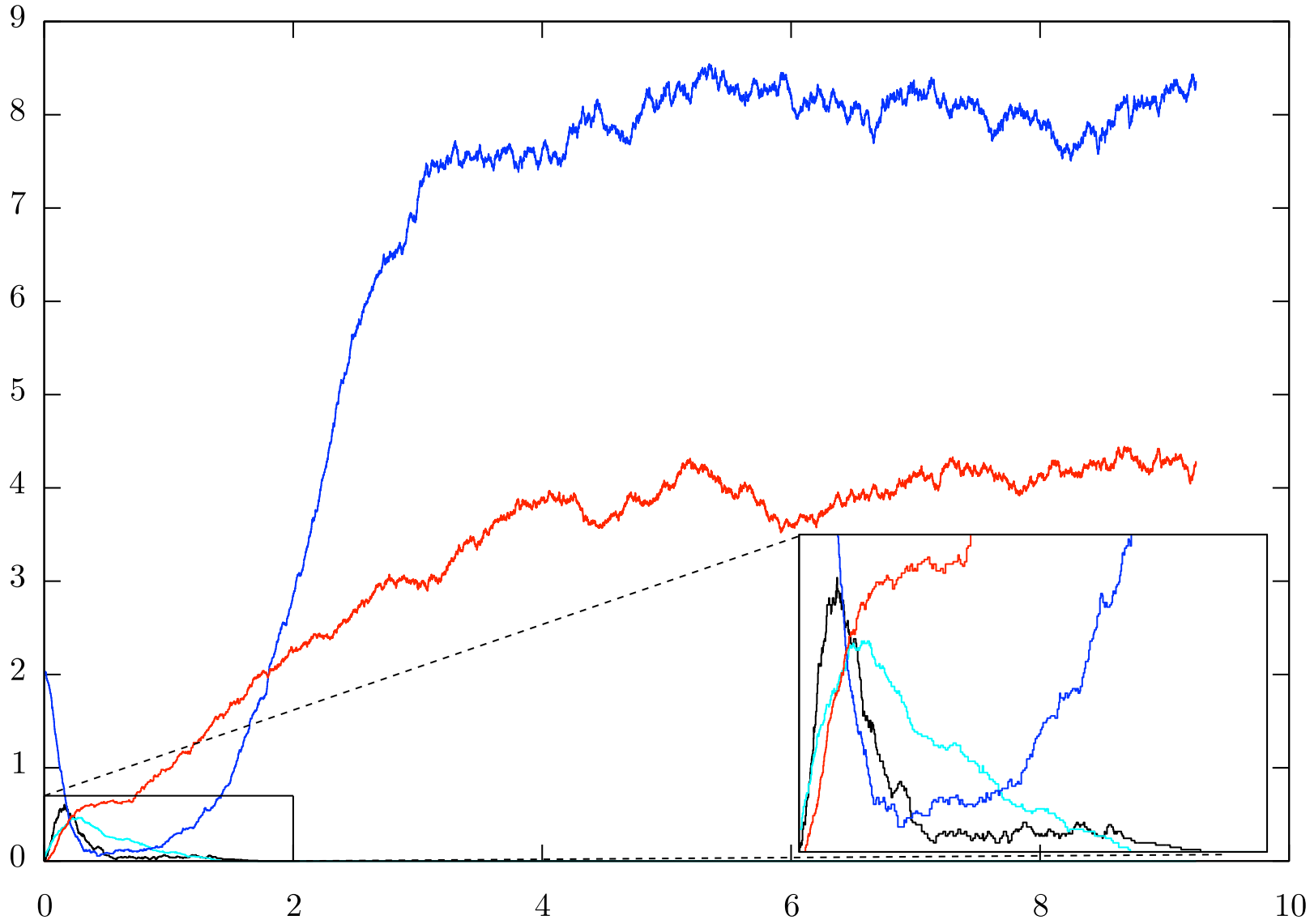


Pxyz is stable.
*Pxy*0 is stable on the invariant sub-space $\{n_{z_x} = 0\}$.

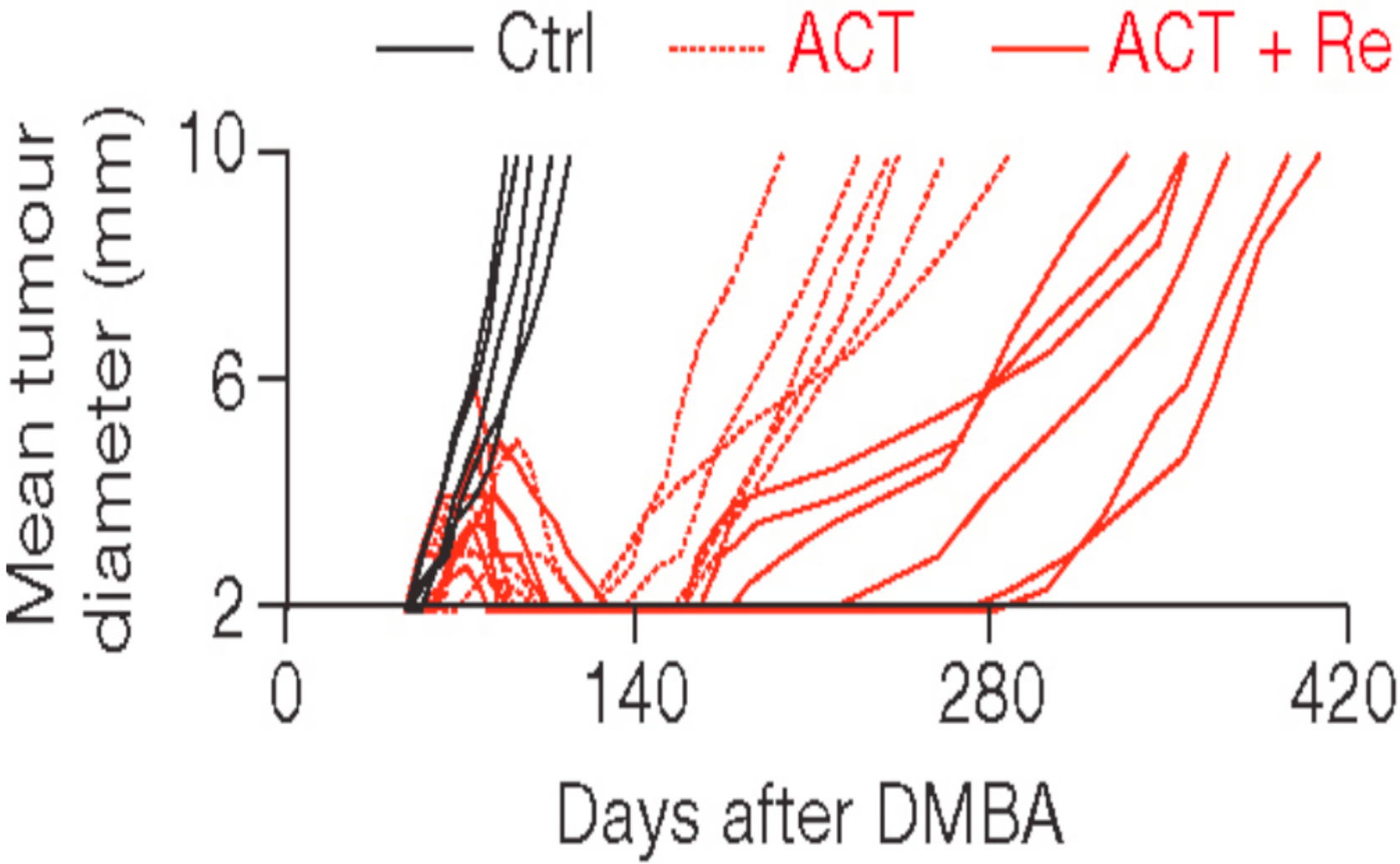
Relapse towards *Pxyz*, ($K = 200$)



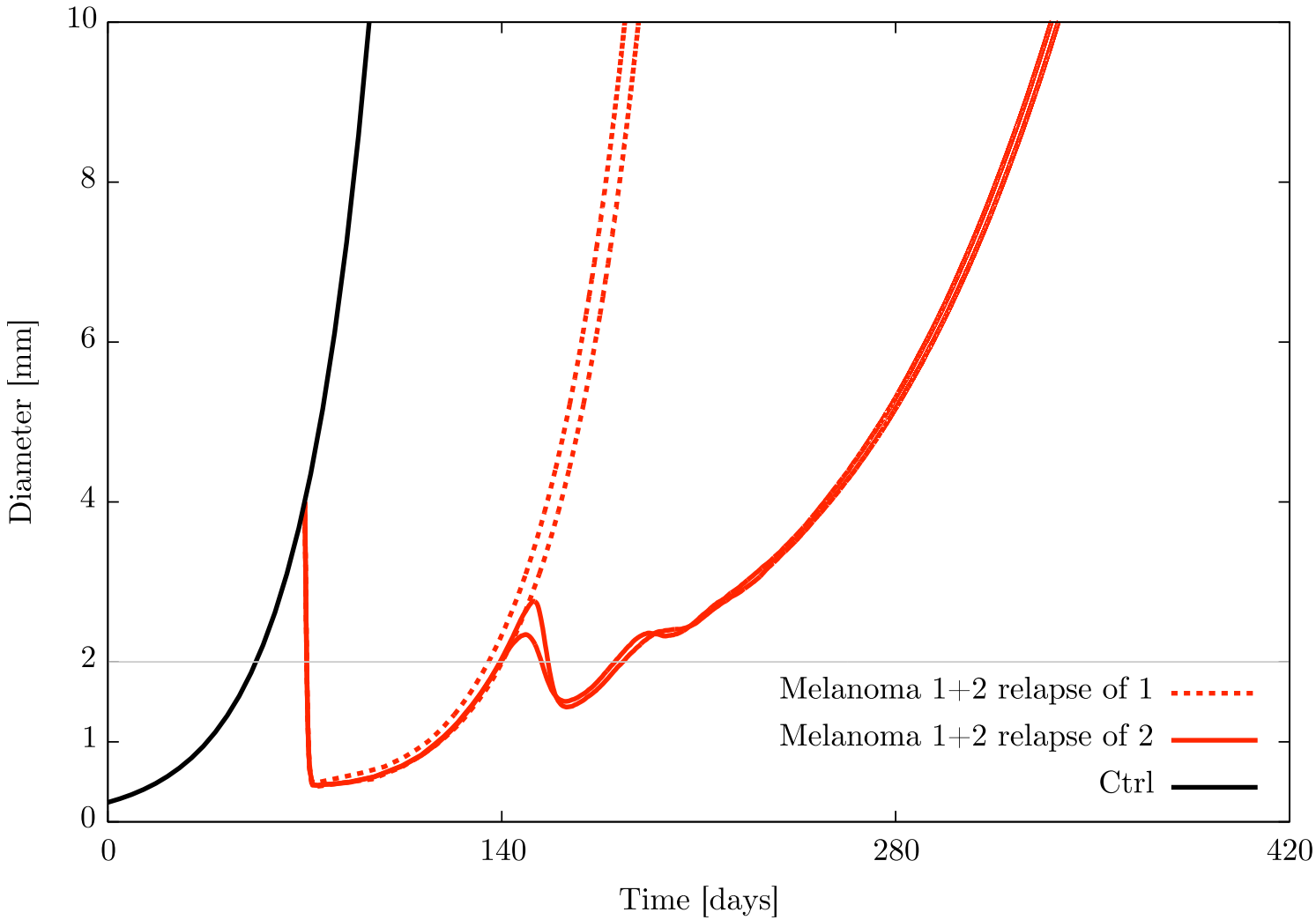
Relapse towards $Pxy0$ due to the death of z_x



Adjustment of parameters : data



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



Therapy with 1 types of T-cells

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

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

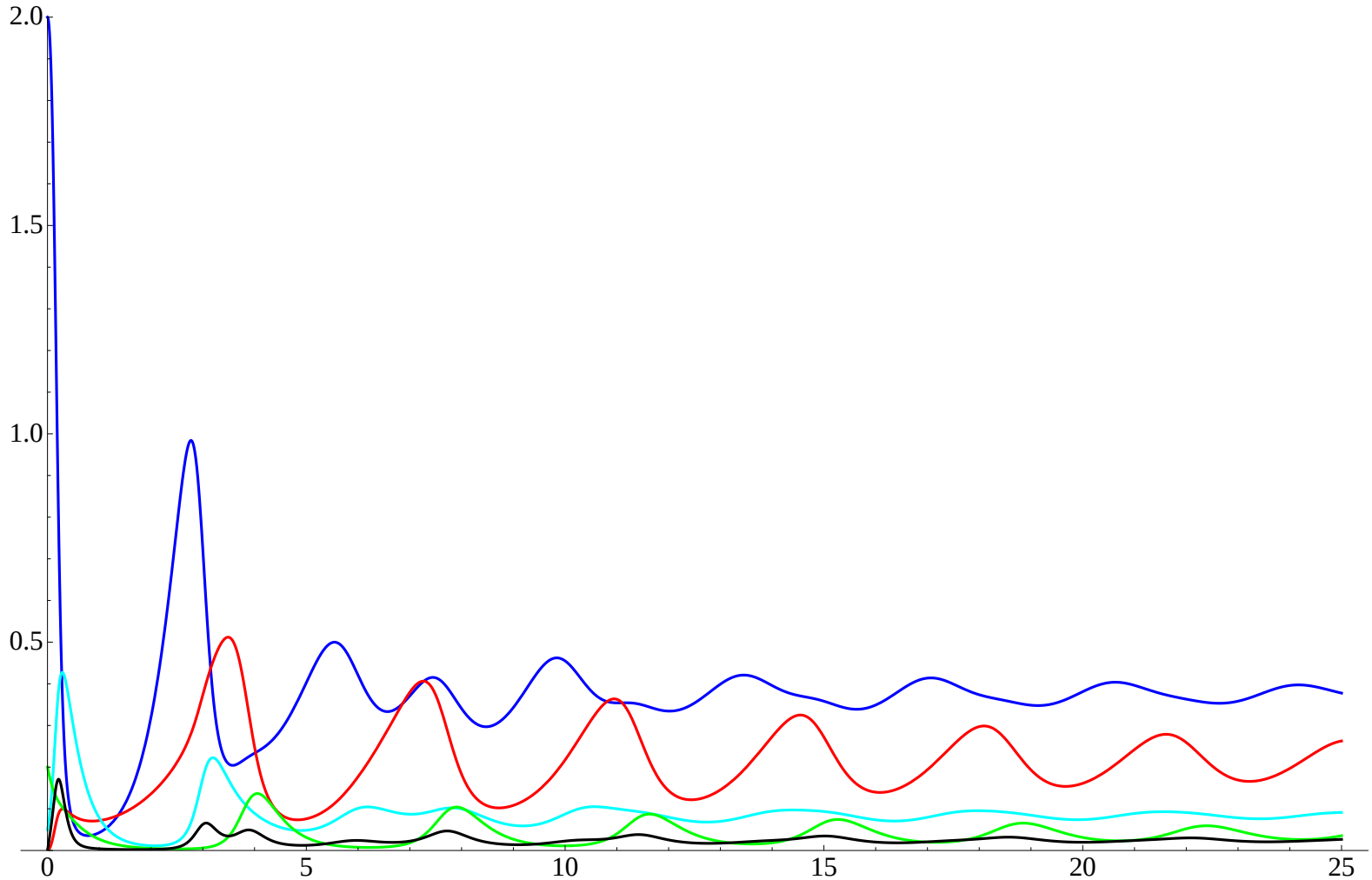
Therapy with 2 types of T-cells

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

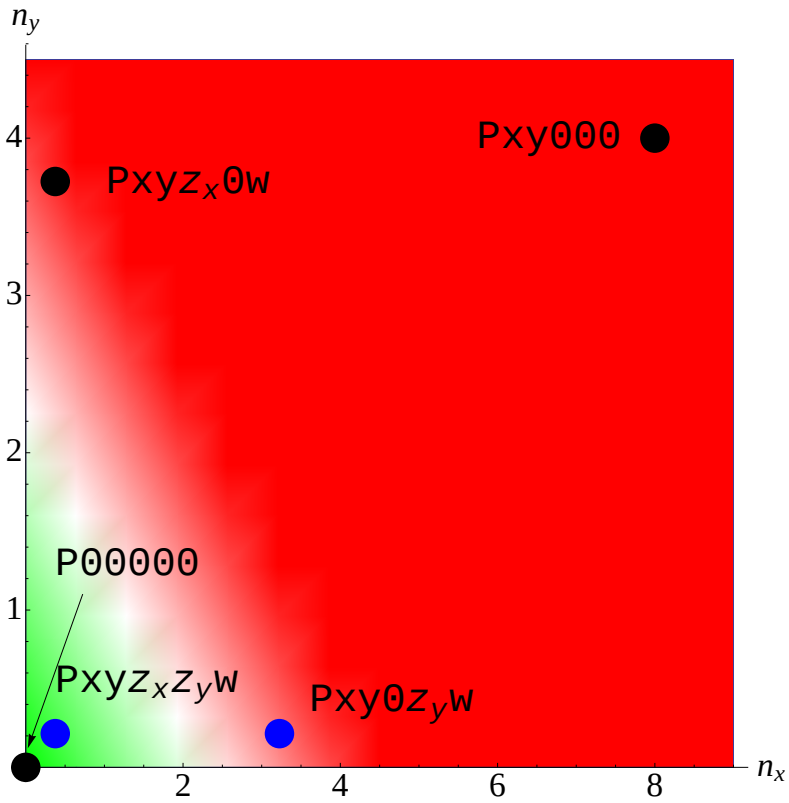
Event	Rates for x	Rates for y
Reproduction	b_x	b_y
Natural death	$d_x + c_{xx}n_x + c_{xy}n_y$	$d_y + c_{yy}n_x + c_{yx}n_y$
Death due to therapy	$t_{xz}n_{z_x}$	$t_{yz}n_{z_y}$
Switch	$s_w n_w$	s

Solution of the deterministic limit

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

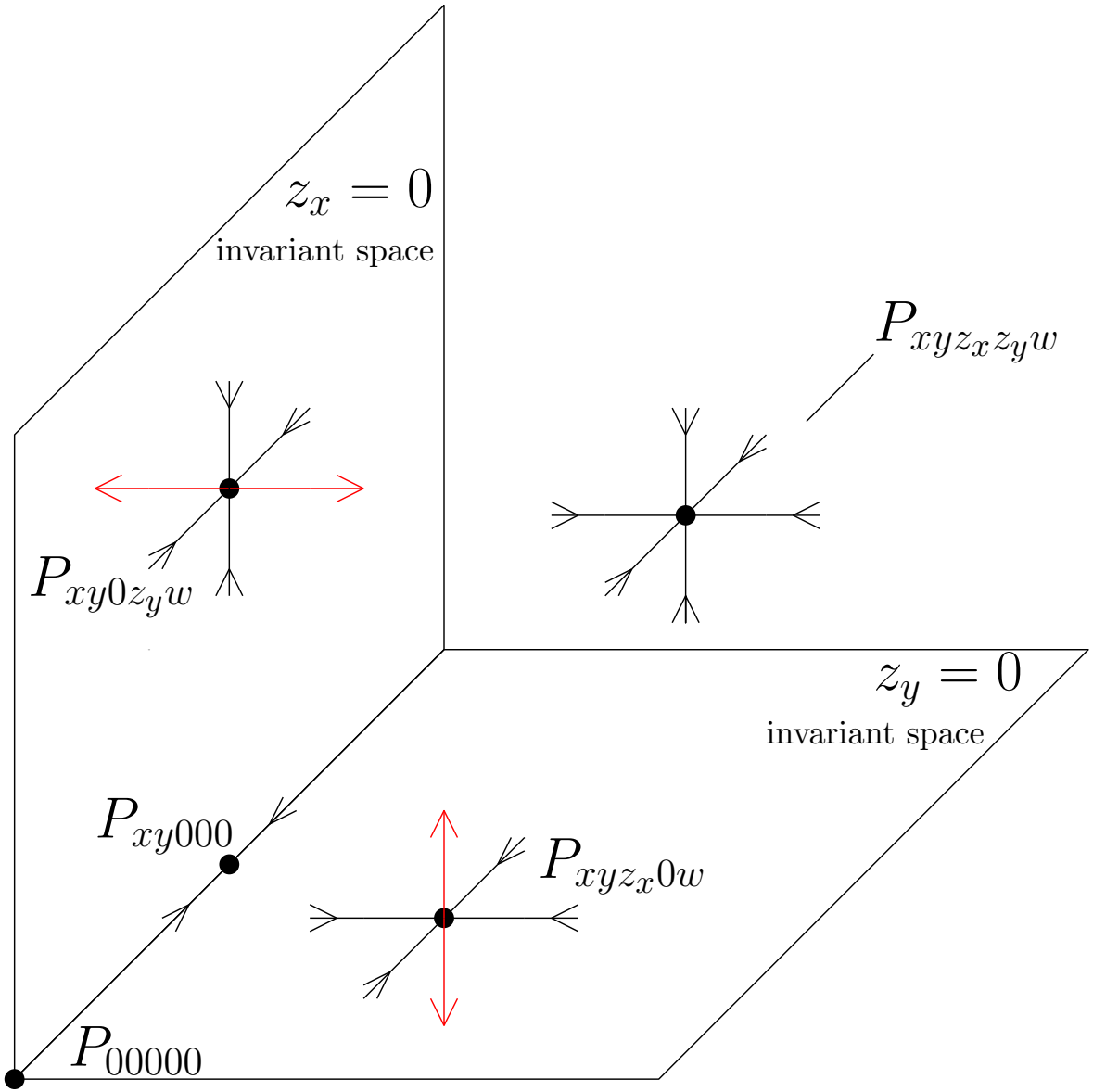


5 fixed points

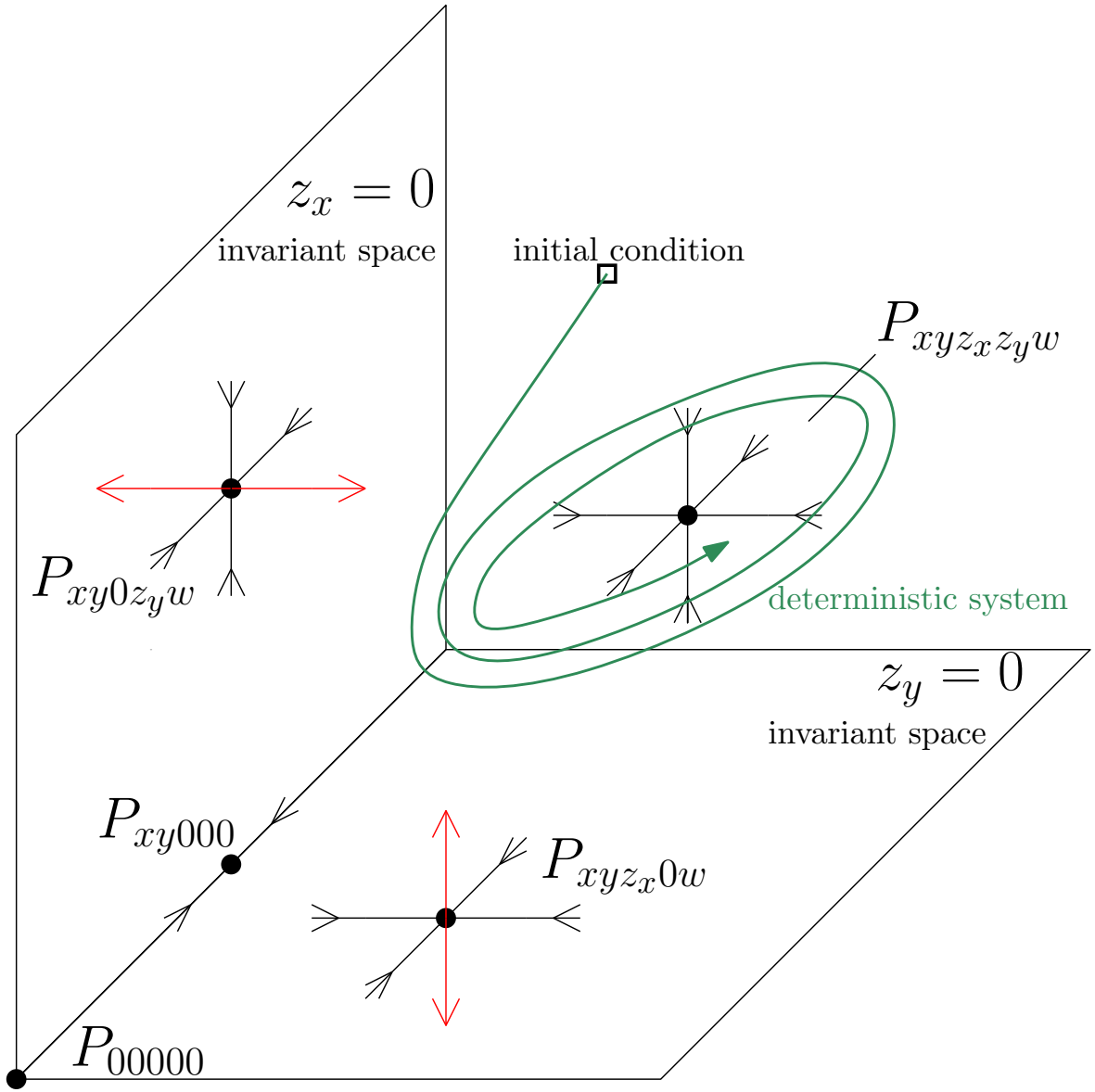


$Pxyz_xz_y$ is stable.
$Pxyz_x0$ is stable in the invariant subspace $\{n_{z_y} = 0\}$
$Pxy0z_y$ is stable in the invariant subspace $\{n_{z_x} = 0\}$
$Pxy00$ is stable in the invariant subspace $\{n_{z_x} = 0\} \cap \{n_{z_y} = 0\}$

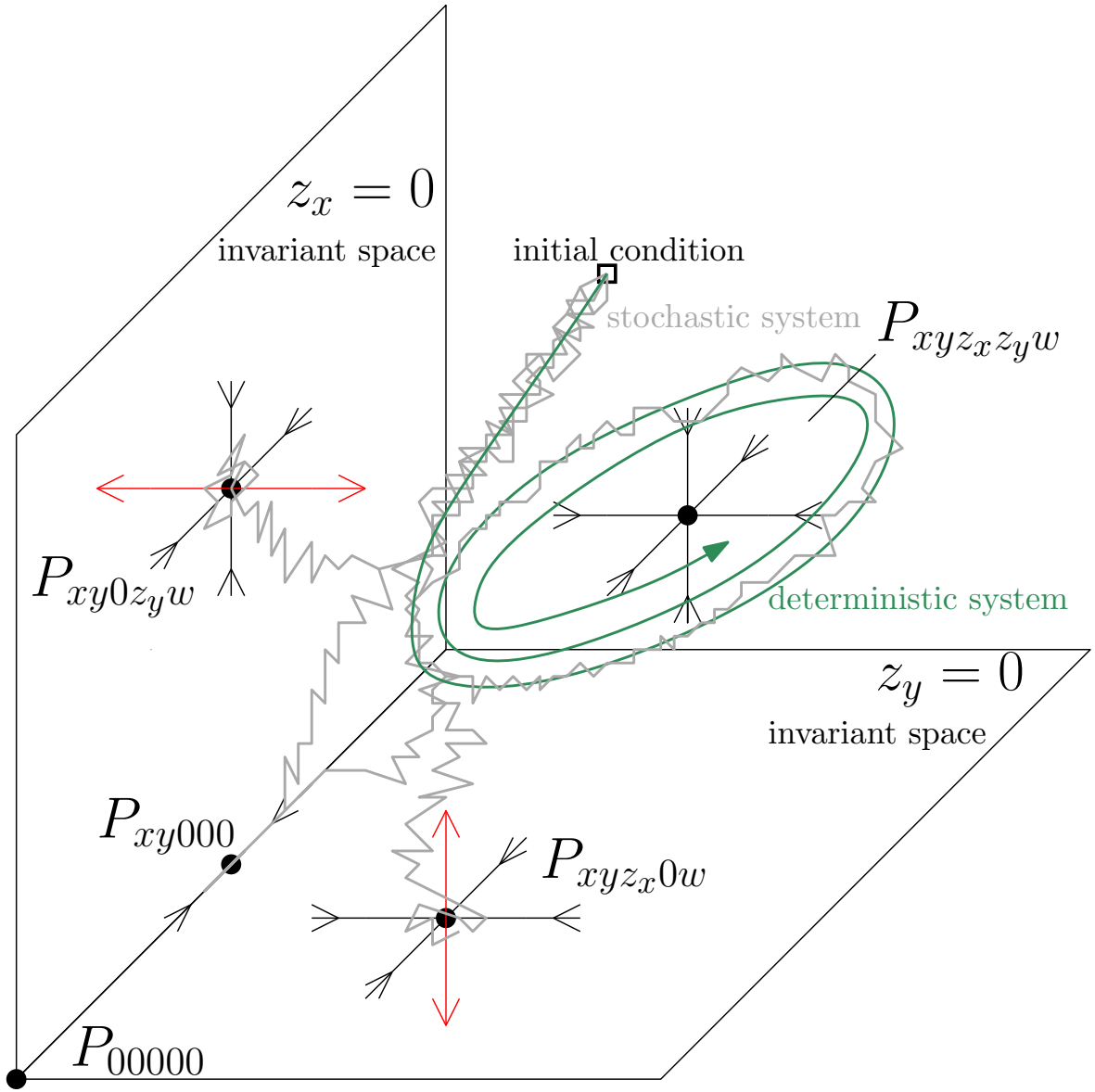
Metastable transitions between several possible relapses



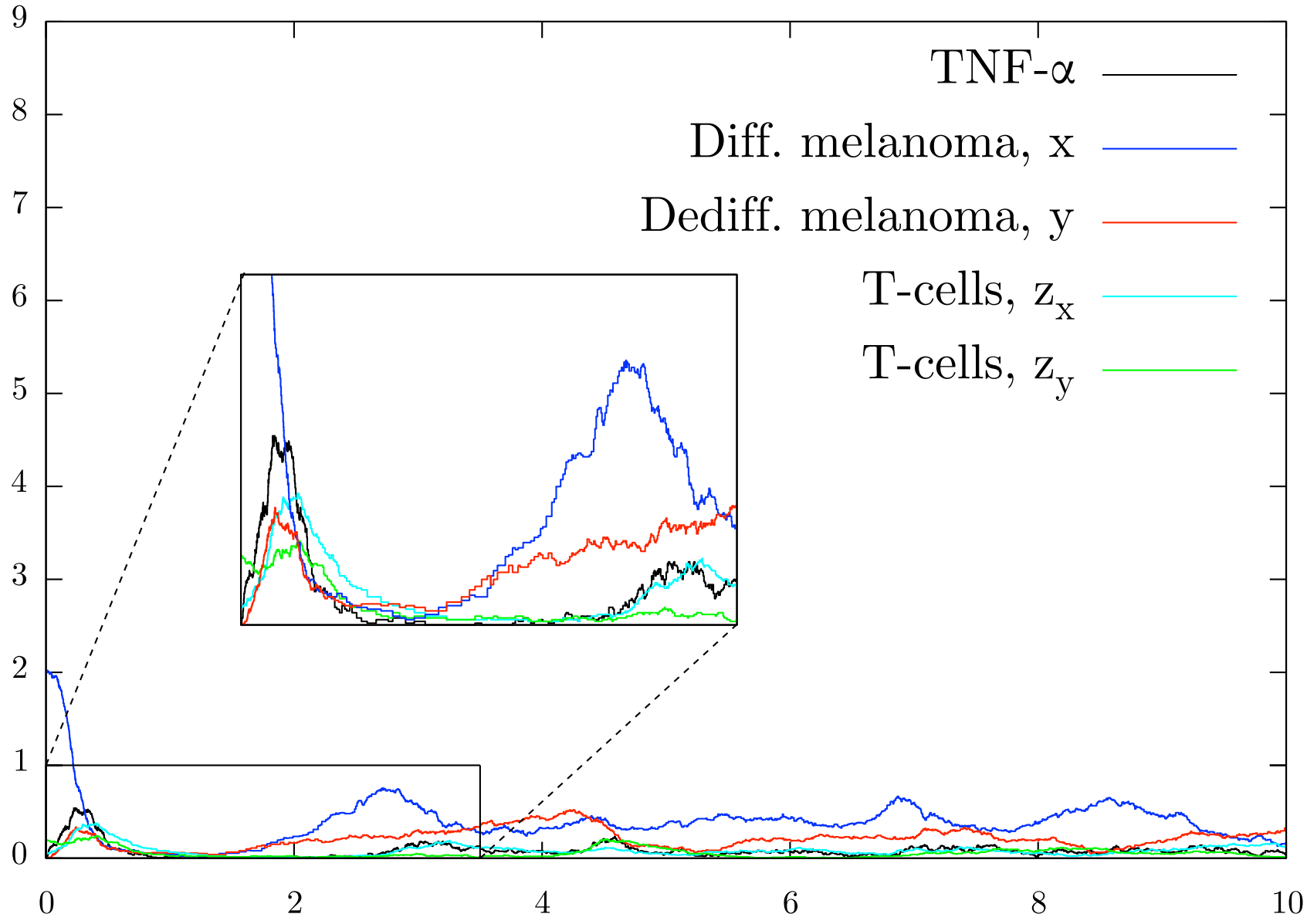
Metastable transitions between several possible relapses



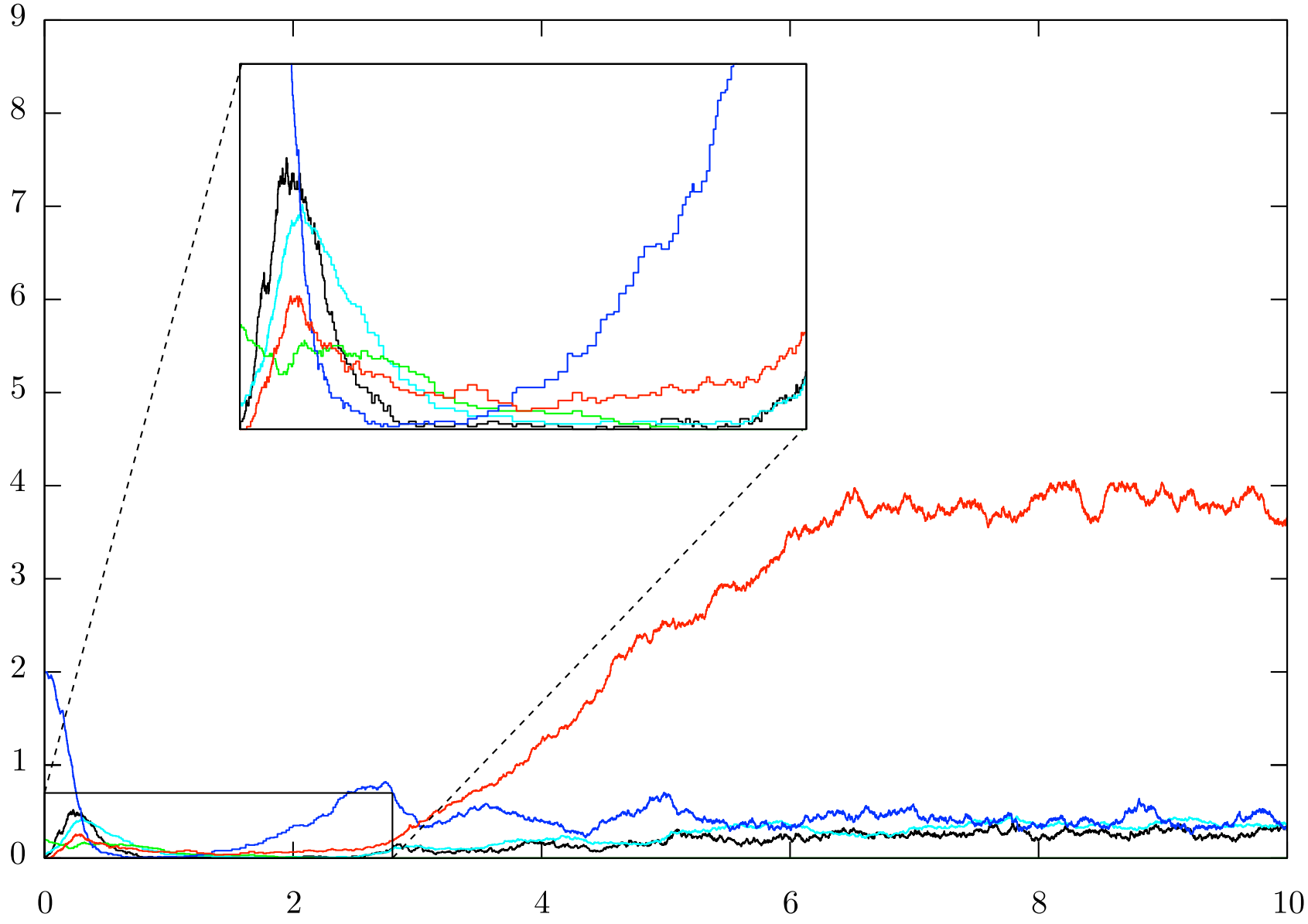
Metastable transitions between several possible relapses



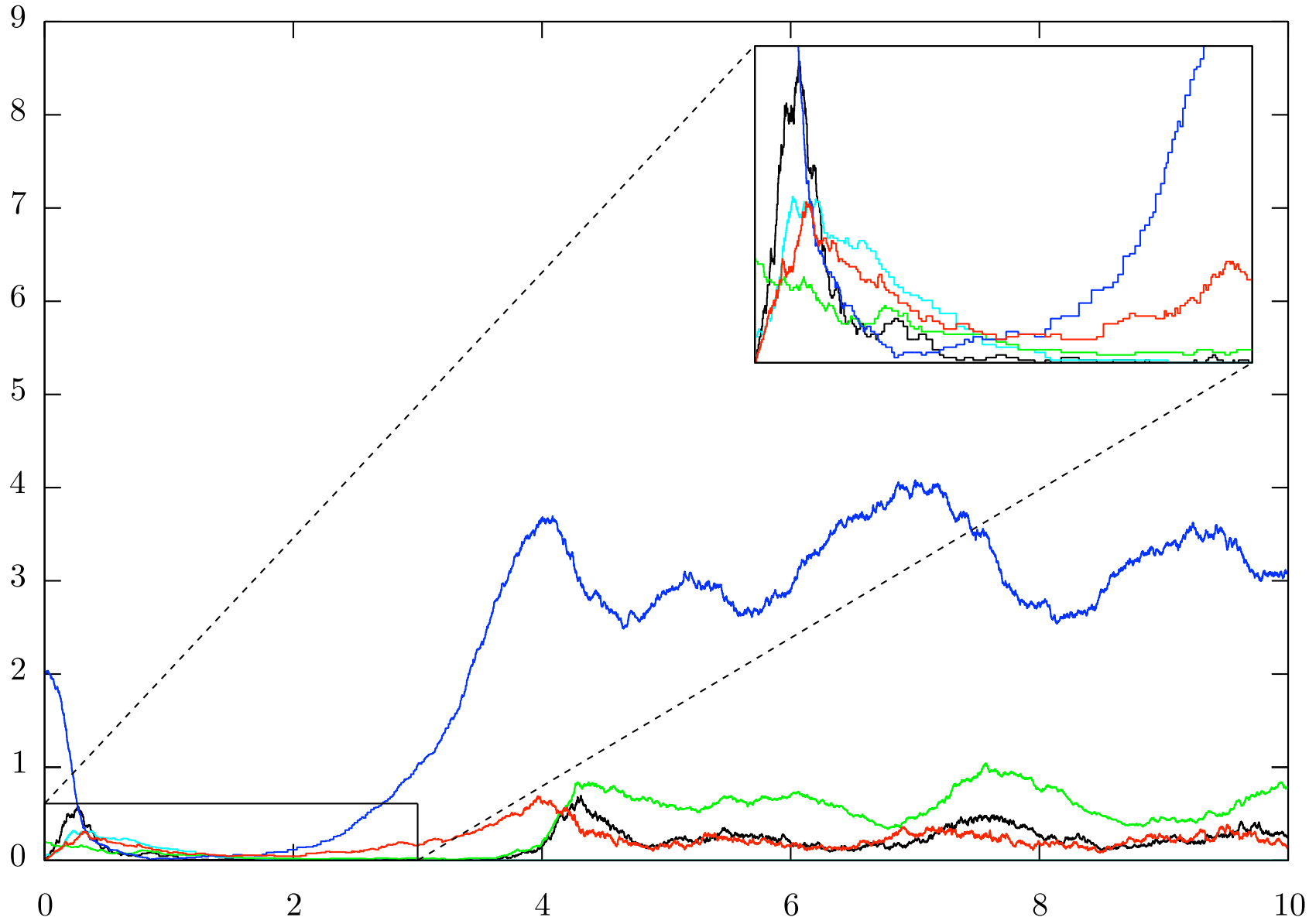
Stochastic system close to the deterministic system



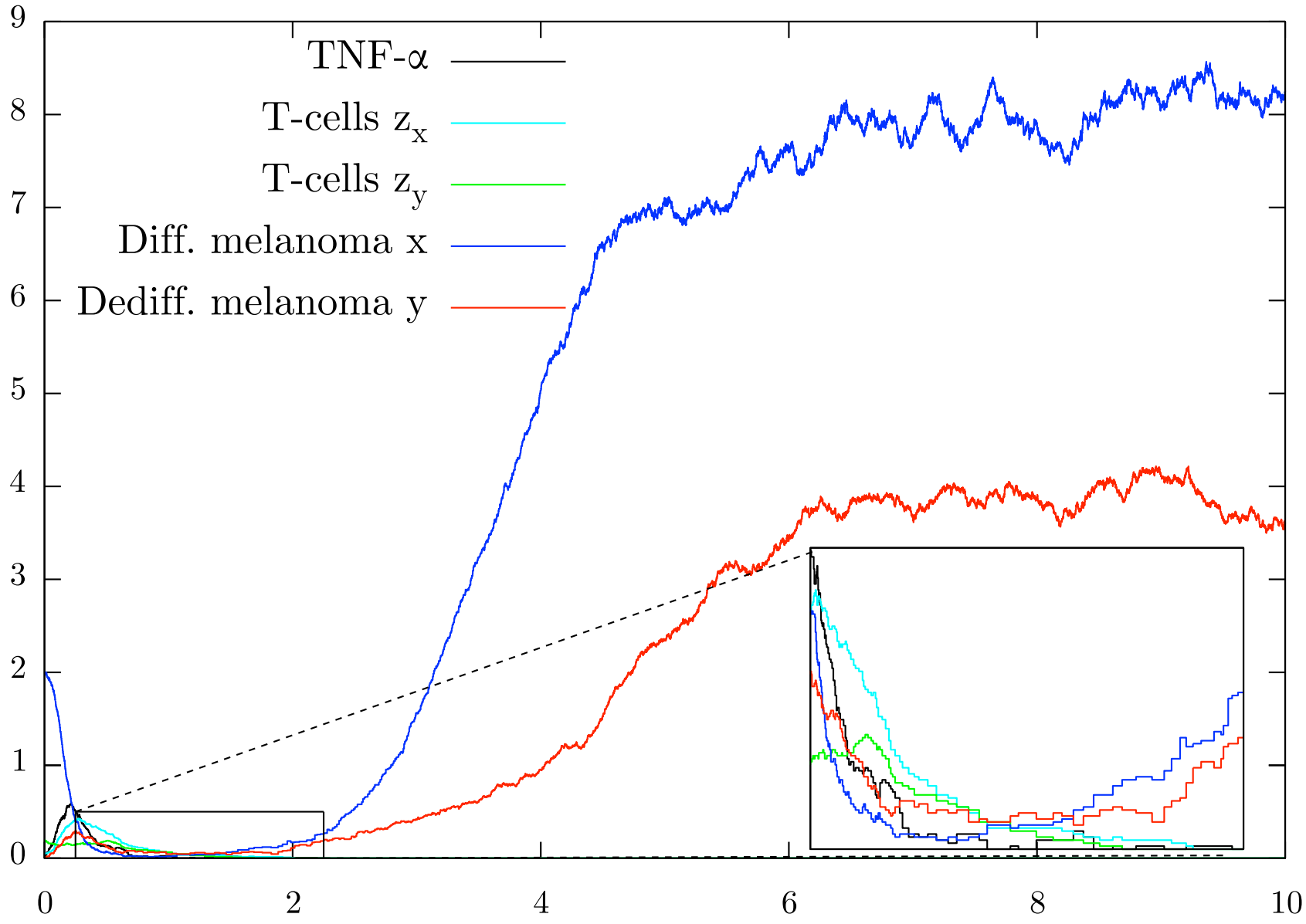
Relapse towards $Pxyz_x0$ caused by the death of z_y



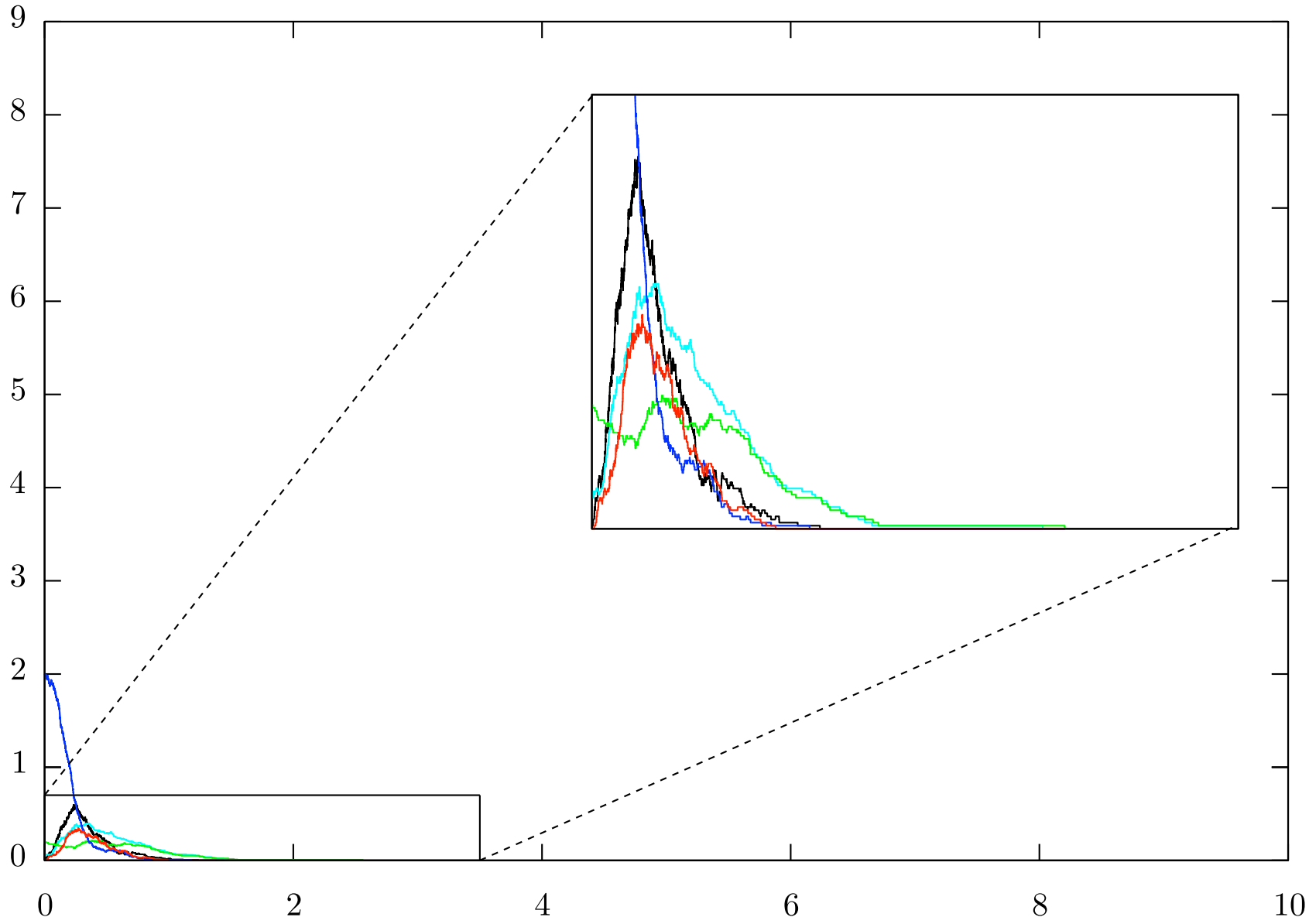
Relapse towards $Pxy0z_y$ caused by the death of z_x



Relapse towards *Pxy*00 caused by the death of z_x and z_y



Cure ! ($P0000$)



Plan

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	μb_x
Natural death	$d_x + c_{xx}n_x + c_{xy}n_y$
Death due to therapy	$t_{zx}n_z$

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

BPDL + therapy with birth-reducing competition

Event	**Rates for x**
Clonal reproduction	$(1-\mu)\lfloor b_x - c_{xx} n_x - c_{xy} n_y \rfloor_+$
Mutation towards y	$\mu \lfloor b_x - c_{xx} n_x - c_{xy} n_y \rfloor_+$
Natural death	$d_x + \lfloor b_x - c_{xx} n_x - c_{xy} n_y \rfloor_-$
Death due to therapy	$t_{zx} n_z$

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

BPDL + therapy with birth-reducing competition

Event	**Rates for y**
Clonal reproduction	$\lfloor b_y - c_{yy} n_y - c_{yx} n_x \rfloor_+$
Mutation towards x	0
Natural death	$d_y + \lfloor b_y - c_{yy} n_y - c_{yx} n_x \rfloor_-$
Death due to therapy	0

Event	**Rates for z**
Reproduction	$b_{zx} n_x$
Death	d_z

No switch $\Rightarrow$ The chemical messenger (TNF-α) has a trivial role : $\dot{n}_w = 0$

Limiting determinisitic system

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

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

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 $O(\log(K)) \to \infty$ to become macroscopic).

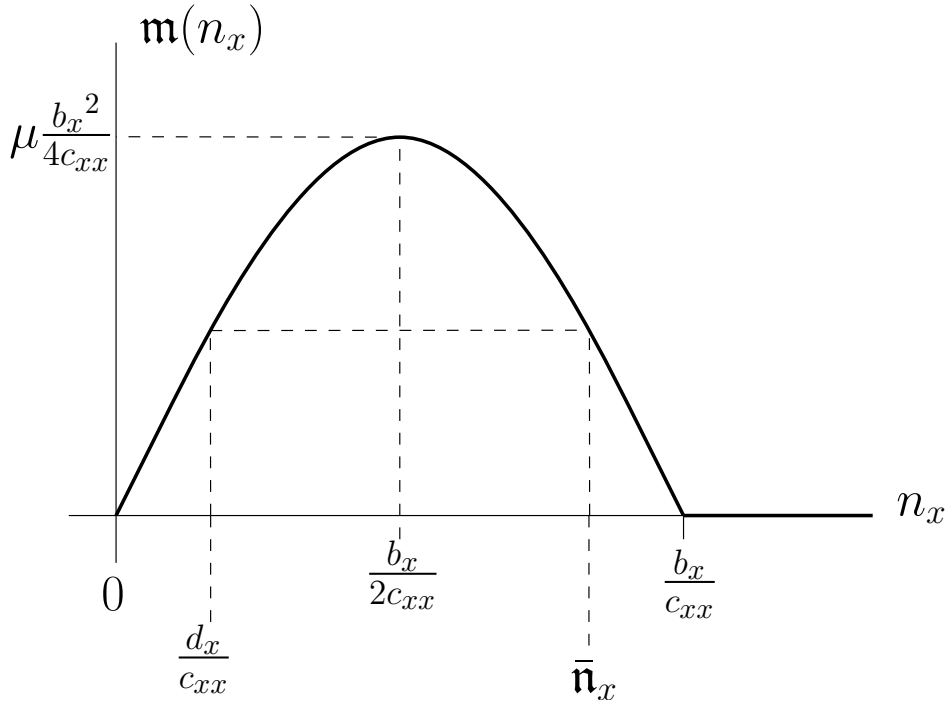
$$\begin{cases} \dot{n}_x &= n_x \Big(b_x - d_x - c_{xx} \cdot n_x - c_{xy} \cdot n_y \Big) - t_{xz} \cdot n_{z_x} n_x \\ \dot{n}_y &= n_y \Big(b_y - d_y - c_{yy} \cdot n_y - c_{yx} \cdot n_x \Big) \\ \dot{n}_{z_x} &= -d_{zx} \cdot n_{z_x} + b_{zx} \cdot n_{z_x} n_x \end{cases}$$

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

With *birth-reducing* competition

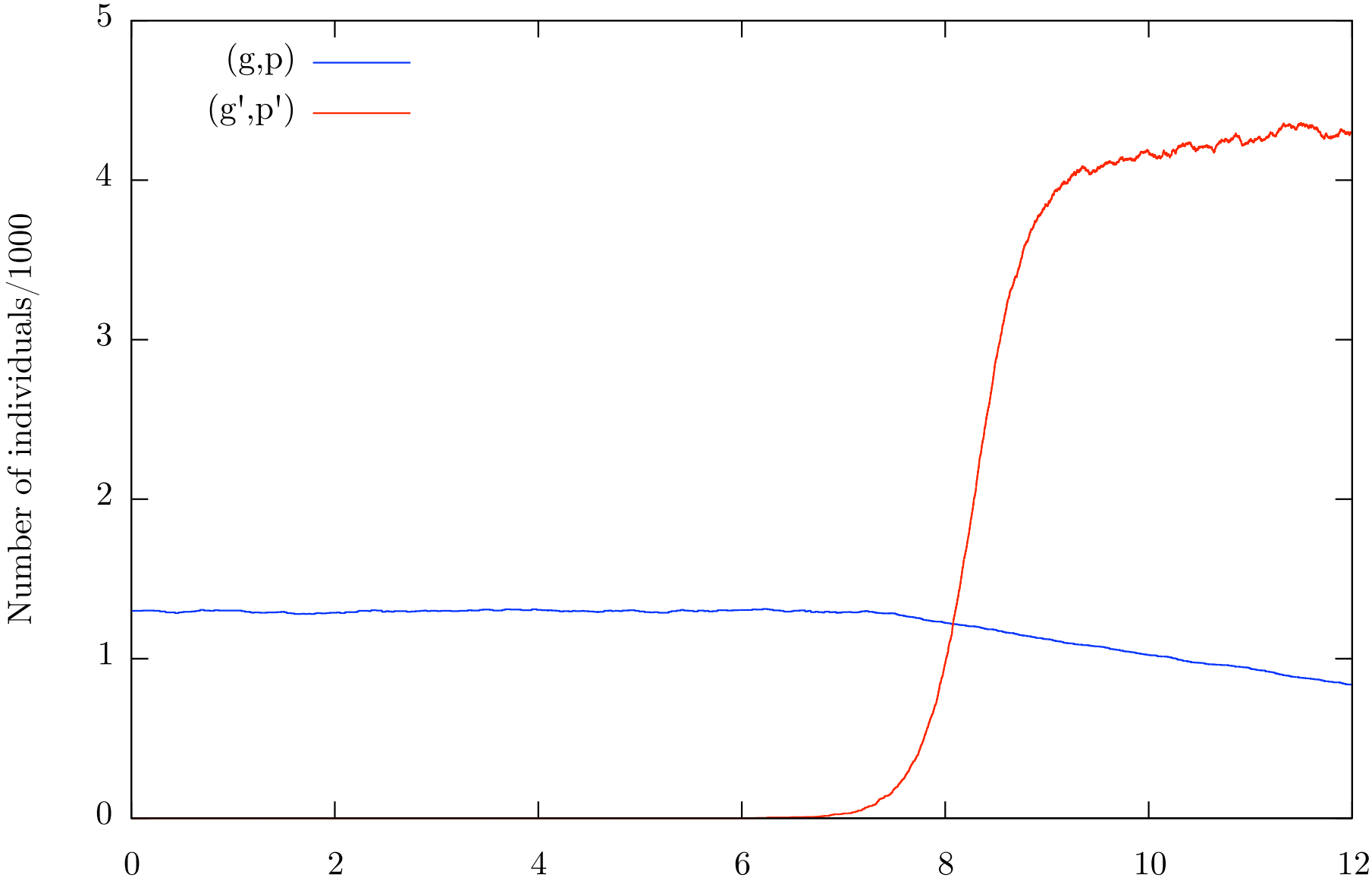
Let $n(0) = (n_x(0), 0, 0)$,
then the initial mutation rate is quadratic in the population n_x :

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

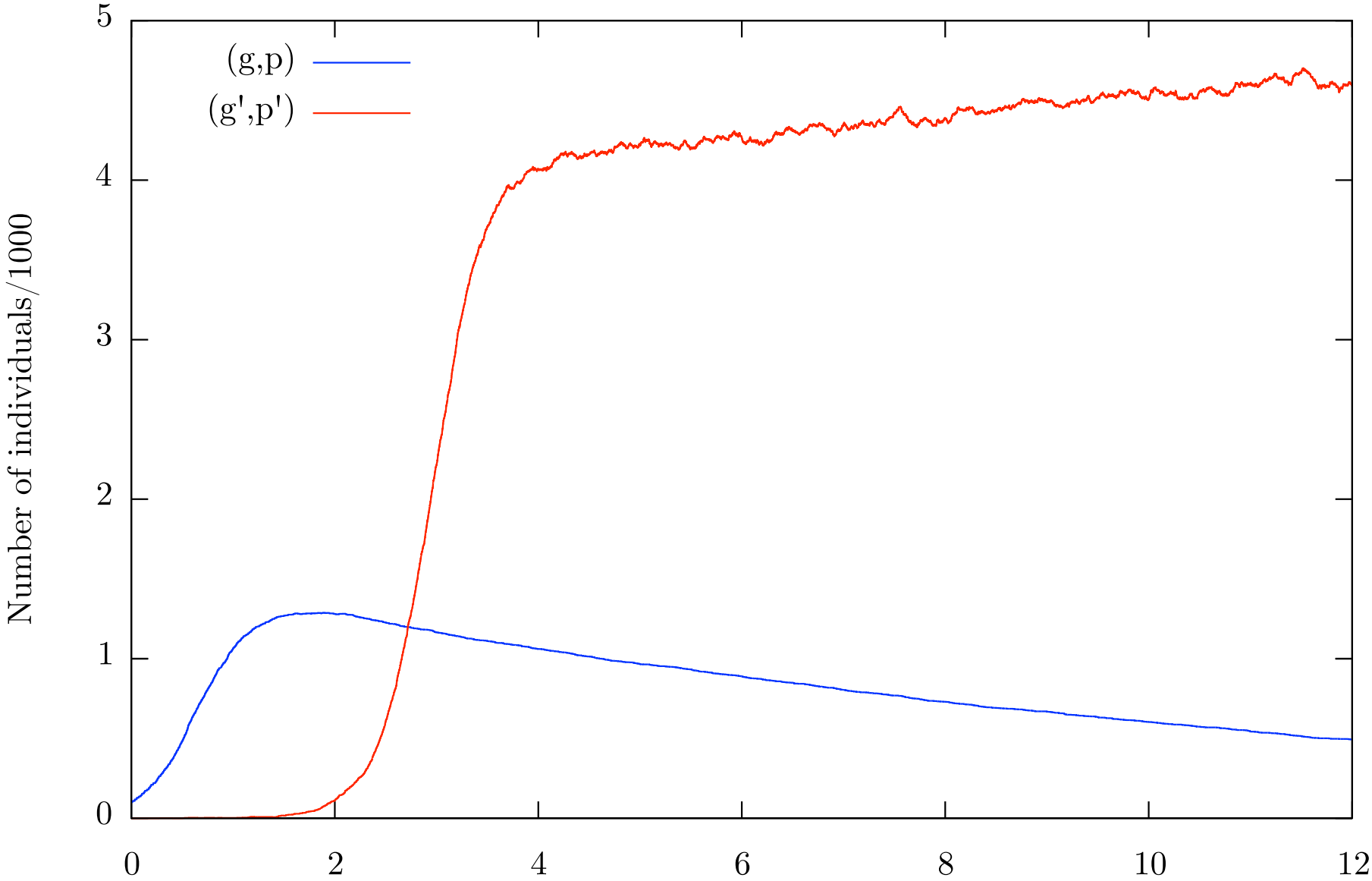


$\bar{\mathfrak{n}}_x := \frac{b_x - d_x}{c_{xx}}$ is the equilibrium of the initial x population.
A smaller population can have a higher mutation rate.
Note $\mathfrak{m}(n_x) = O(\mu K) = O(1)$.

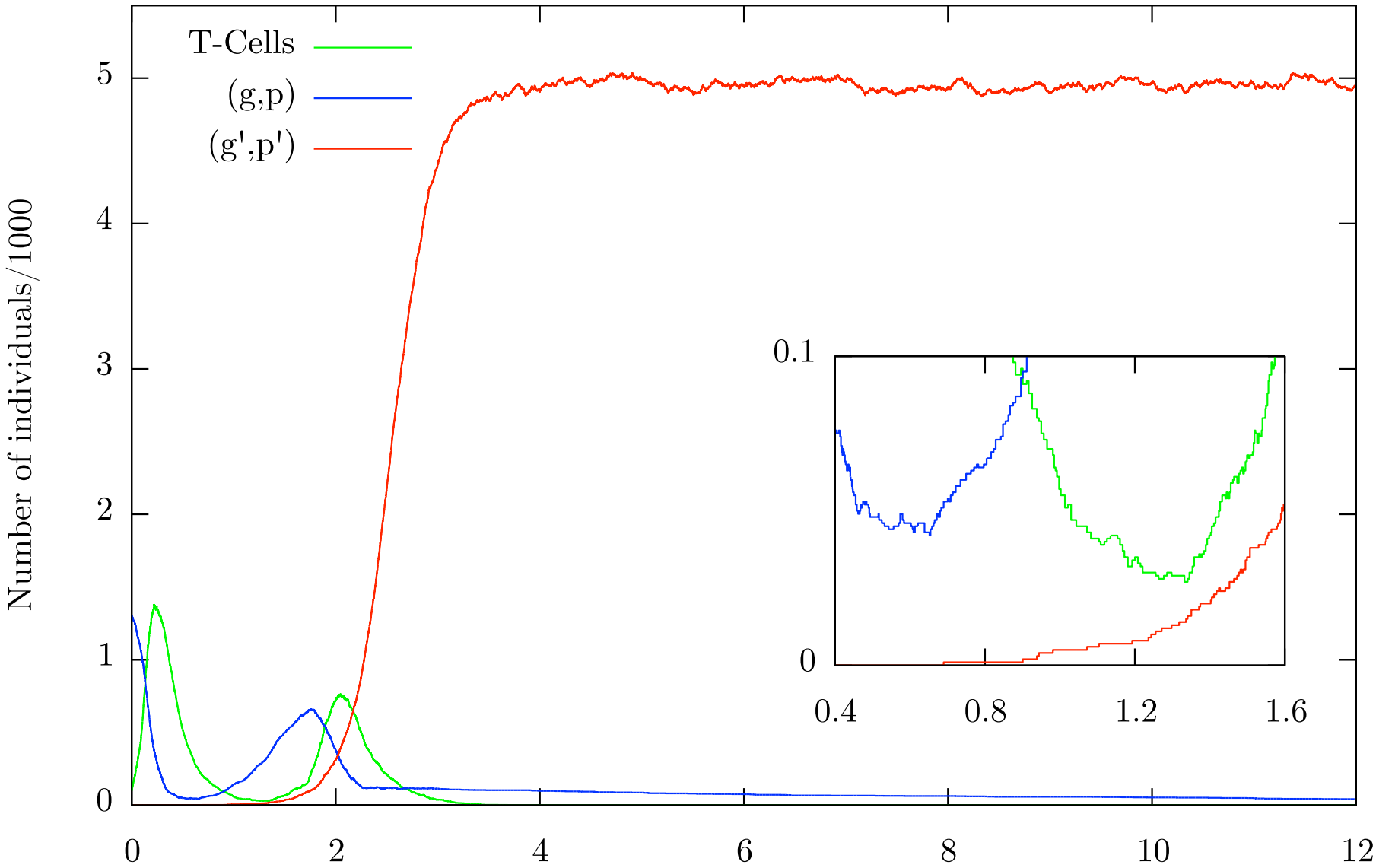
Without treatment and $n_x(0) \simeq \bar{\mathbf{n}}_x$



Without treatment and $n_x(0)$ small



With treatment

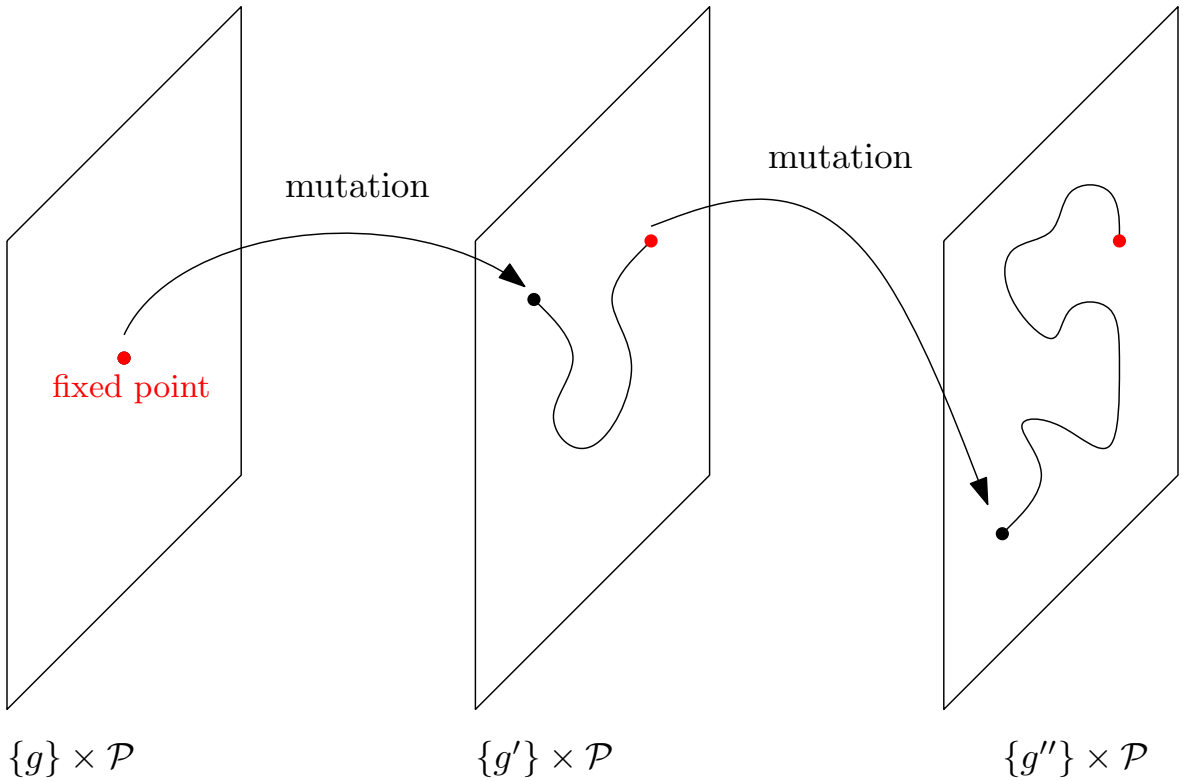


Plan

Two time scales

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

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



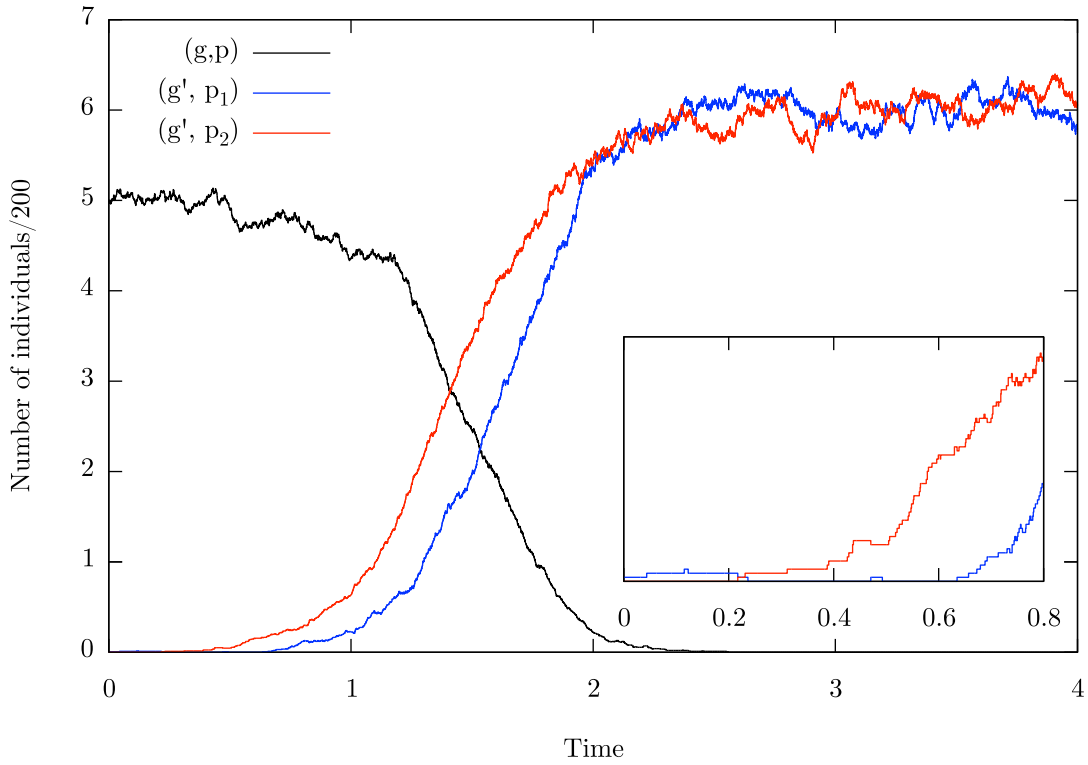
No therapy (only melanoma)

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

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

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

Study of one step (example with $\ell = 1, k = 2$)



<—1—><—2—><———3———>

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) :

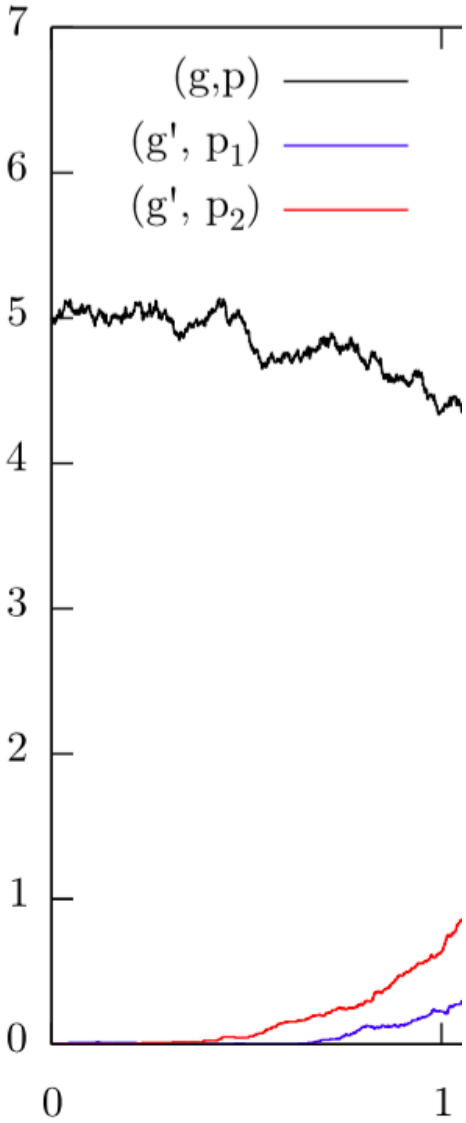
$$f(x, M) = b_x - d_x - \sum_{y \in M} c_{xy} \bar{n}_y .$$

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 $K \to \infty$) before this happens.

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

Phase 1



As long as

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

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

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

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

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

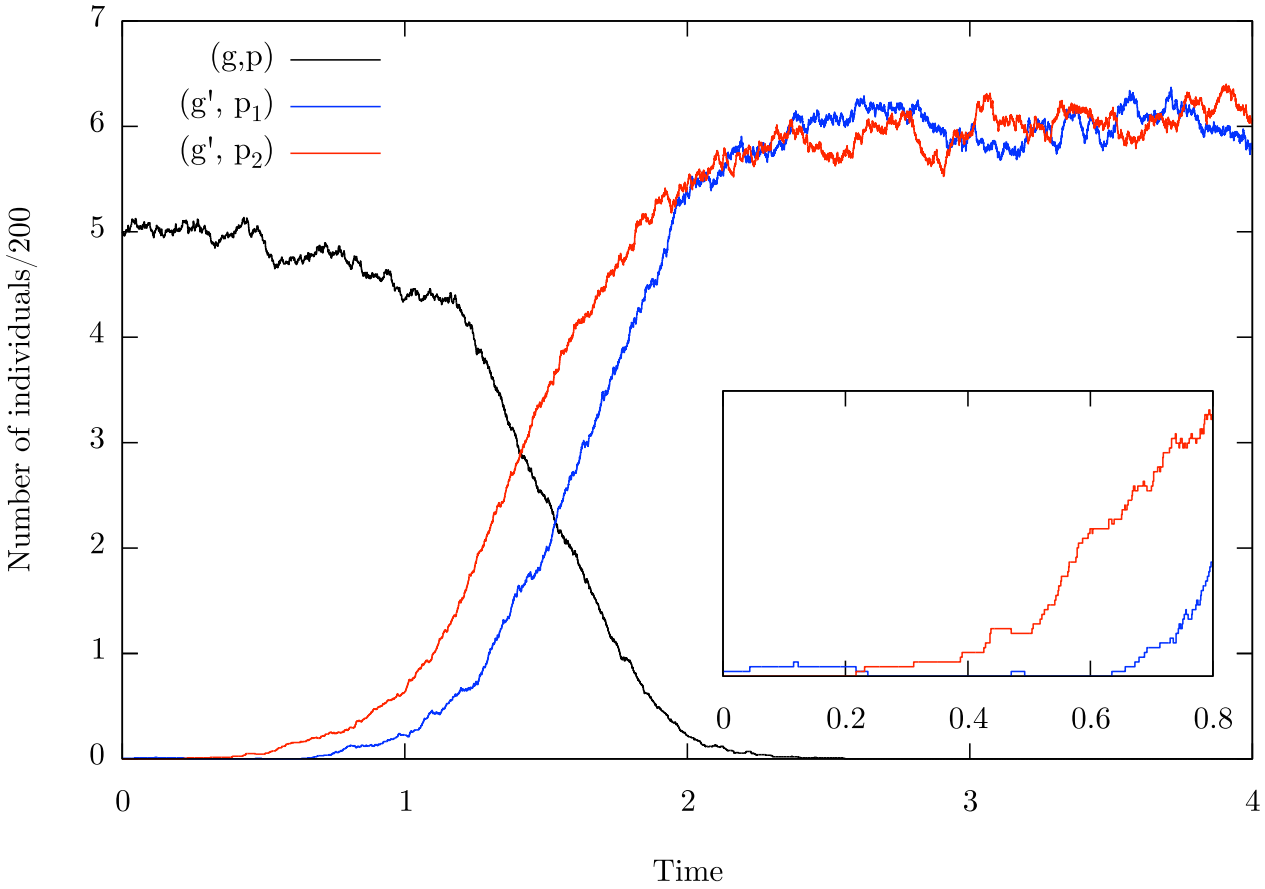
where

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

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



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

Plan

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 !