Stochastic individual-based models of adaptive dynamics

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Content

1. Motivation
2. Definition of the model
3. Some notation and a summary of the relevant known results
4. Our result and the main idea of the proof
5. Outlook and Application

Adaptive dynamics aim to study the interplay between ecology and evolution.

Darwinian evolution of a quantitative trait is the consequence of:

heredity **mutation** and **selection**.

The first papers in this context appeared during 1990s. They incorporate the three basic mechanism to describes the evolutionary dynamics.

J. Hofbauer and K. Sigmund. Adaptive dynamics and evolutionary stability. *Appl. Math. Lett.*, 3(4): 75-79, 1990.

P. Marrow, R. Law and C. Cannings. The coevolution of predator-prey interactions: ESSs and Red Queen dynamics. *Proc. R. Soc. Lond. B* 250 : 133-141, 1992.

J.A.J. Metz, R.M. Nisbet and S.A.H. Geritz. How should we define 'fitness' for general ecological scenarios? *Trends Ecol. Evolut.* 7: 198-202, 1992.

Important advance was the canonical equation of adaptive dynamics

ODE that describes the change of the expected trait value for a population with asexual reproduction, introduced by

U. Dieckmann and R. Law. The dynamical theory of coevolution: a derivation from stochastic ecological processes. *J. Math. Biol.*, 34: 579-612, 1996.

As described in

N. Champagnat, R. Ferrière and G. Ben Arous. The Canonical Equation of Adaptive Dynamics: A Mathematical View. *Selection*, 2: 73-83, 2001.

The critical assumptions in this context are:

1. ecological and evolutionary timescales are separated: the population of the wild type is at its ecological equilibrium, when a mutation occurs.
2. exclusion principle: a mutant either replaces the wild type or it is eliminated - no long coexistence is allowed

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Then, CEAD stems from three hierarchical scalings.

1. large population size
2. very small mutation probability
   (justifies that the ecological and evolutionary timescales are separated)
3. very small mutation step

The challenging problems of mathematics are:

1. to define an exact "individual-based" model, including the three basis mechanisms and to prove that the involved processes well defined

   N. Fournier and S. Méléard. A microscopic probabilistic description of a locally regulated population and macroscopic approximations. *Ann. Appl. Probab.*, 14(4): 1880-1919, 2004.

2. to identify in which sense the "real" process converge toward the CEAD. More precisely, to identify the limits that can applied to the "individual-based" model to recover the CEAD.

The individual-based model

We consider a population with asexual reproduction. Each individual is characterized by a phenotypic trait. The trait space is called $\mathcal{X} \subset \mathbb{R}$ compact. For any two individuals with traits x_1, x_2,

- $b(x_1)$ rate of birth
- $d(x_1)$ rate of natural death
- $c(x_1, x_2)$ competition kernel
- $m(x_1)$ probability of mutation in a birth
- $M(x_1, dh)$ mutation law of a mutant trait $x_1 + h \in \mathcal{X}$, born from an individual with trait x_1

At any time t, we consider a finite number N_t of individuals and denote their traits by $x_1(t), ..., x_{N_t}(t)$.

population state at time t: $\tilde{\nu}_t = \sum_{i=1}^{N_t} \delta_{x_i(t)}$

We want to study the limits of

large population, rare mutations and small mutational effects.

Therefore, we introduce:

- K (large) scaling parameter for population size
  $\Rightarrow \tilde{\nu}_t \to \nu_t = \frac{1}{K}\tilde{\nu}_t$ and $c(x,y) \to \frac{c(x,y)}{K}$
- μ (small) scaling parameter for mutation probability
  $\Rightarrow m(x) \to \mu\, m(x)$
- σ (small) scaling parameter for mutation size
  $\Rightarrow$ mutant trait $x + h \to x + \sigma h$, where $h \sim M(x, dh)$.

density of x at time t: $\langle \nu_t^{K,\mu,\sigma}, \mathbb{1}_{\{x\}} \rangle$, where $\langle \nu, f \rangle := \int_{\mathcal{X}} f d\nu$ and $\langle \nu_t, \mathbb{1} \rangle = \frac{N_t}{K}$.

The dynamics of the population can be summarized as follows:

1. At $t = 0$, we have a (possibly random) distribution $\nu_0^{K,\mu,\sigma}$.
2. Each individual (with trait x) has three independent exponential clocks:
   - a birth clock with parameter $b(x)$,
   - a natural death clock with parameter $d(x)$,
   - a competition death clock with parameter $\sum_{i=1}^{N_t} \frac{c(x,x_i(t))}{K}$.
3. If one of the two death clocks of an individuals rings, then this one disappears.
4. If the birth clock (of an ind. with trait x) rings, then it produces an offspring. Its trait is
   - x with prob. $1 - \mu m(x)$ and
   - $y = x + \sigma h$ with prob. $\mu m(x)$, where $h \sim M(x, dh)$.

Thus, the process $(\nu_t^{K,\mu,\sigma})_{t\geq 0}$ is a measure-valued Markov process with state space

$$\mathcal{M}^K(\mathcal{X}) := \left\{ \frac{1}{K}\sum_{i=1}^{n} \delta_{x_i} \ : \ n \geq 0, \ x_1, ..., x_n \in \mathcal{X} \right\}$$

and with infinitesimal generator

$$L^{K,\mu,\sigma} f(\nu) = \int_{\mathcal{X}} \left(f\left(\nu + \frac{\delta_x}{K}\right) - f(\nu) \right) (1 - \mu m(x)) b(x) \, K\nu(dx)$$

birth without mutation (linear in ν)

$$+ \int_{\mathcal{X}} \int_{\mathbb{R}} \left(f\left(\nu + \frac{\delta_{x+\sigma h}}{K}\right) - f(\nu) \right) \mu m(x) b(x) \, M(x, dh) \, K\nu(dx)$$

birth with mutation (linear in ν)

$$+ \int_{\mathcal{X}} \left(f\left(\nu - \frac{\delta_x}{K}\right) - f(\nu) \right) \left(d(x) + \int_{\mathcal{X}} c(x,y)\nu(dy) \right) K\nu(dx)$$

death due to age and competition (non-linear in ν)

The process ν is usually called BPDL-Process after Bolker, Pacala, Dieckmann and Law.

Some notation and three limit results

We have to admit always suitable smoothness and boundedness conditions on $b(.), d(.), c(.,.)$ and $M(., dh)$ and a convergence condition for $\nu_0^{K,\mu,\sigma}$ obtain these results.

Theorem 1: μ, σ fixed and $K \to \infty$ *Fournier and Méléard, 2004*

Fix μ and σ. Then, $(\nu_t^K)_{0 \le t \le T}$ converges for $K \to \infty$ to a deterministic, continuous function ξ_t. The measure-valued function ξ is the unique solution of an integrodifferential equation.

Corollary: (The special case $\mu = 0$ and ξ_0 is n-morphic)

If $\xi_0 = \sum_{i=1}^n z_i(0)\delta_{x_i}$, then ξ_t is given by $\xi_t = \sum_{i=1}^n z_i(t)\delta_{x_i}$, where z_i is the solution of the competitive system of Lotka-Volterra equations defined by

$$\dot{z}_i = z_i\left(b(x_i) - d(x_i) - \sum_{j=1}^{n} c(x_i, x_j)z_j\right), \qquad 1 \le i \le n.$$

and denoted by $LV(n, (x_1, ..., x_n))$.

Coexistence and **Invasion Fitness:**

We say that the traits x and y coexist if the system $LV(2,(x,y))$ admits a unique, strictly stable equilibrium $\overline{z}(x,y)$ with $\overline{z}_1(x,y) > 0$ and $\overline{z}_2(x,y) > 0$.

Strictly stable: Eigenvalues of Jacobian matrix of $LV(2,(x,y))$ at $\overline{z}(x,y)$ are all strictly negative.

We define the invasion fitness by $f(y;x) = b(y) - d(y) - c(y,x)\overline{z}(x)$, where $\overline{z}(x) = \frac{b(x)-d(x)}{c(x,x)}$ is equilibrium of $LV(1,x)$.

Asymmetrically: Initial growth rate of one individual with trait y which appears in a population of with trait x, which is close to its equilibrium.

Proposition: Criterion for coexistence.

There is coexistence in the system $LV(2,(x,y))$ if and only if

$$f(y,x) > 0 \quad \text{and} \quad f(x,y) > 0.$$

Theorem 2: σ fixed and $(K, \mu) \to (\infty, 0)$ *Champagnat, 2006*

Fix σ and let $\nu_0^{K,\mu}$ consist only of individuals with trait x. Let τ be the first time where two individuals in the population have traits that coexist.

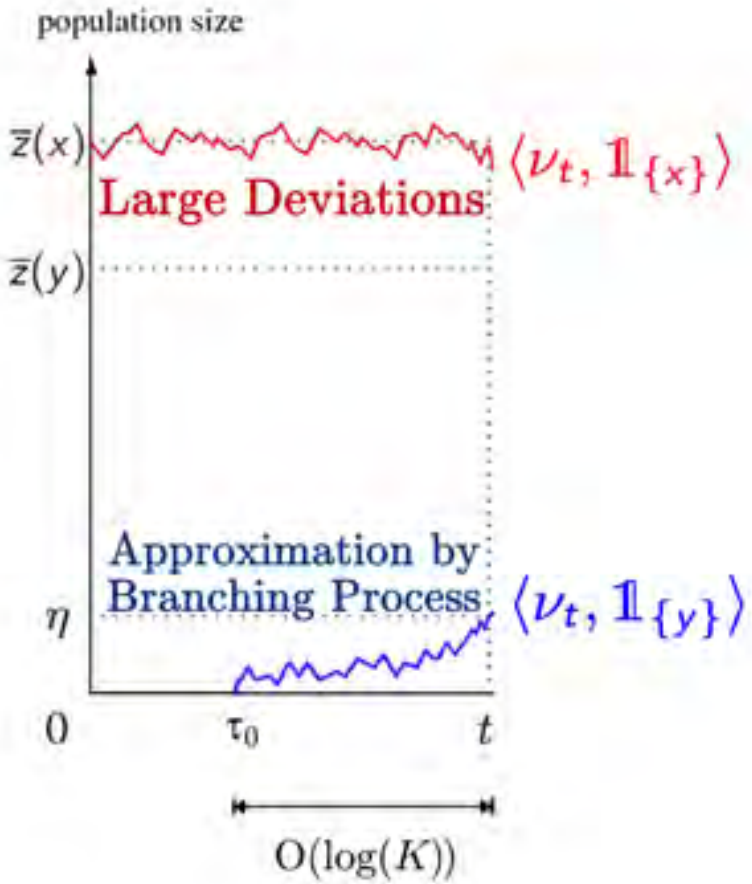
If $(K, \mu) \to (\infty, 0)$ in such a way that

$$\forall V > 0, \qquad \exp(-VK) \ll \mu \ll \frac{1}{K \log(K)}.$$

Then, $(\nu^{K,\mu}_{t/\mu K})_{0 \le t \le \tau}$ converges to the measure-valued process $\overline{z}(X_t^\sigma)\delta_{X_t^\sigma}$,

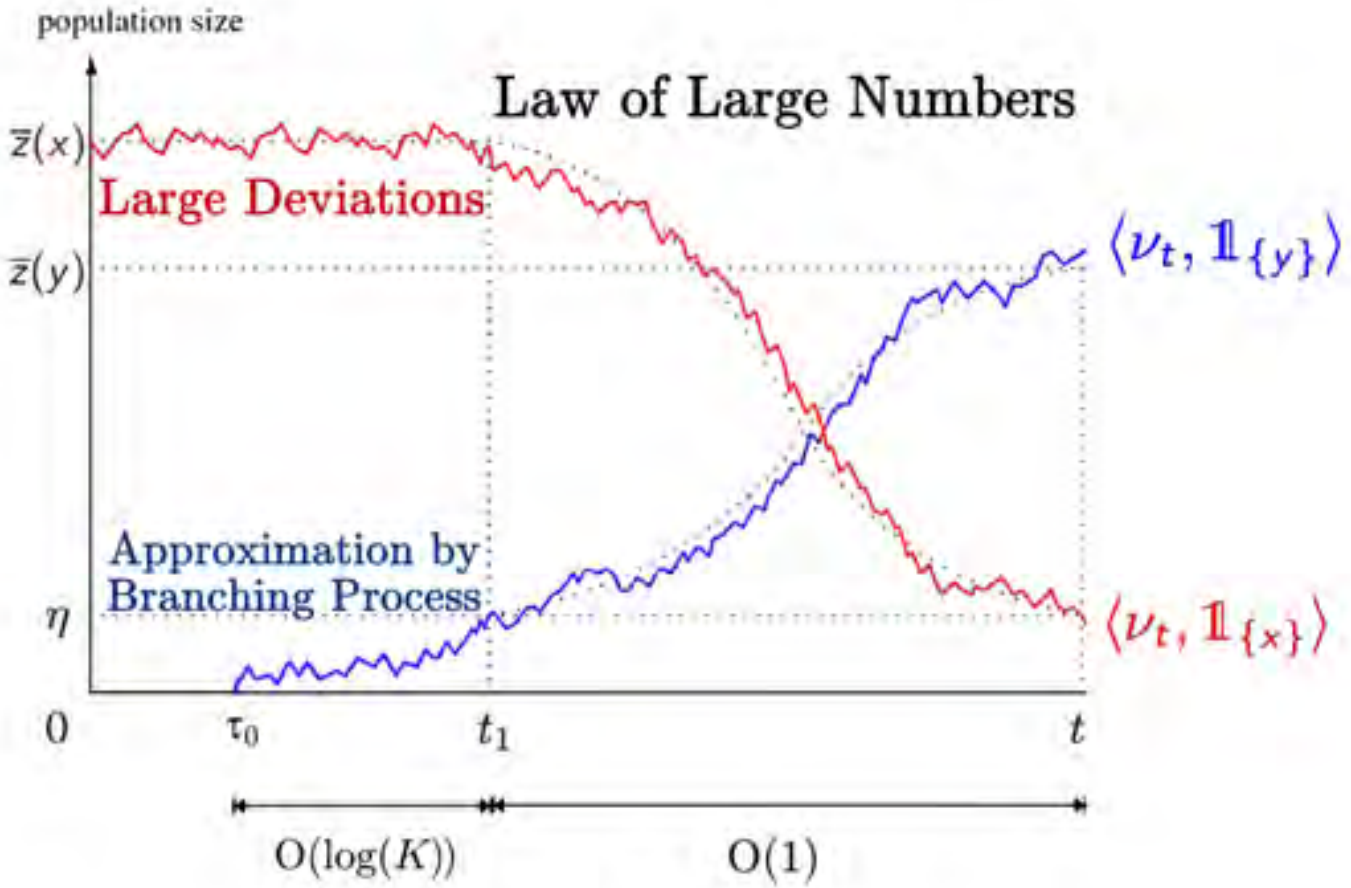
where $(X_t^\sigma)_{t \ge 0}$ is a stopped Markov jump process with $X_0^\sigma = x$ known as Trait Substitution Sequence (TSS).

Sketch of the proof: The invasion of a mutant trait.



Step 1:
- $\langle \nu_t^{K,\mu}, \mathbb{1}_{\{x\}} \rangle$ is close to $\overline{z}(x)$ as long as $\langle \nu_t^{K,\mu}, 1_{\{y\}} \rangle < \eta$.
- $\mathbb{P}[\langle \nu_t^{K,\mu}, \mathbb{1}_{\{y\}} \rangle$ reaches $\eta] \to [f(y,x)]_+ / b(y)$ (probability of non-extinction)

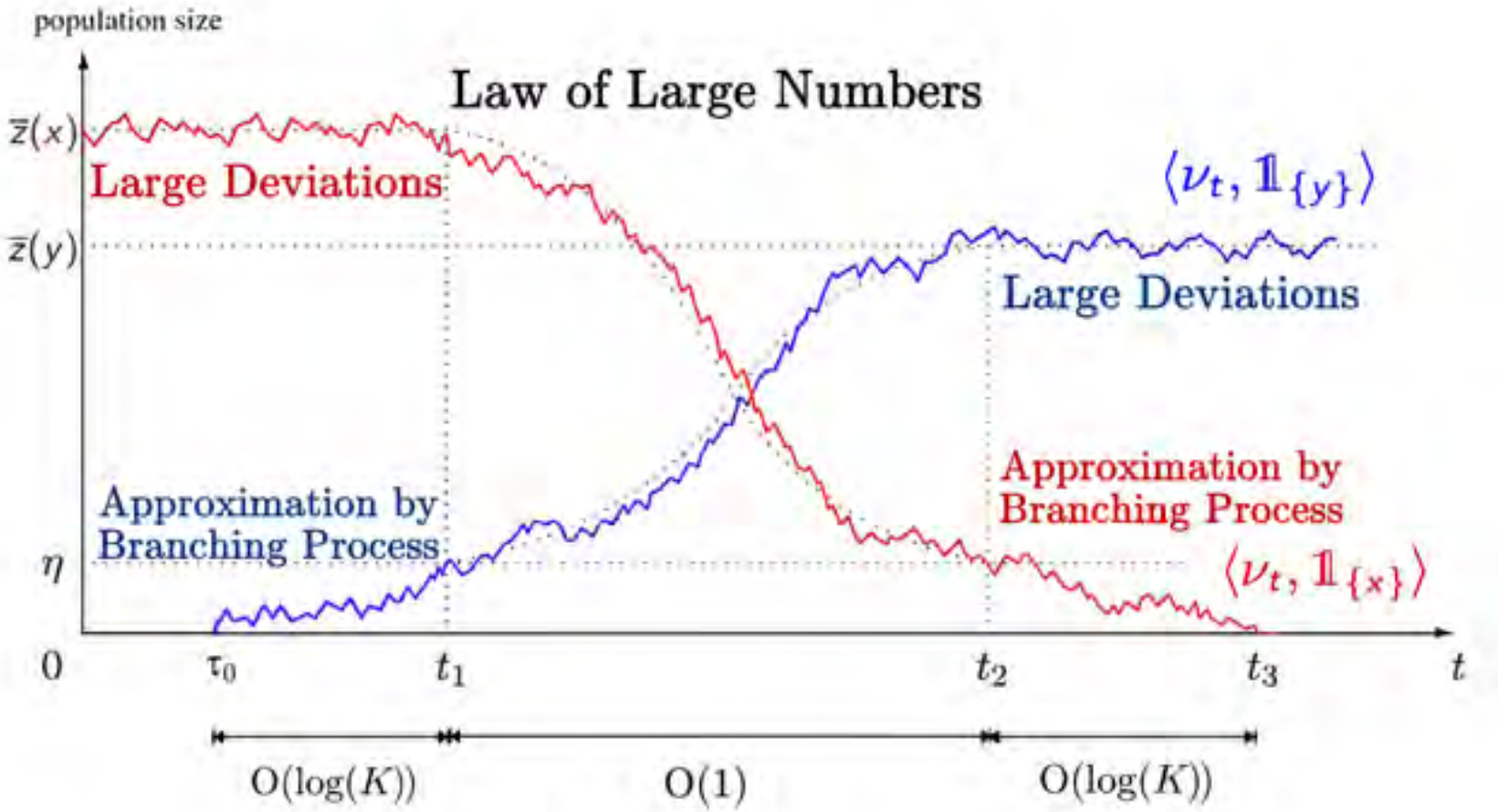
Sketch of the proof: The invasion of a mutant trait.



Step 2:

- $\nu_t^{K,\mu}$ is close to the solution of $LV(2,(x,y))$ with initial state $(\overline{z}(x),\eta)$.
- The solution reaches the $B_\eta(0,\overline{z}(y))$ in $O(1)$.
- $(0,\overline{z}(y))$ is the equilibrium (not stopped and $\langle \nu_t^{K,\mu}, \mathbb{1}_{\{y\}} \rangle > \eta$)

Sketch of the proof: The invasion of a mutant trait.



Step 3:
- $\langle \nu_t^{K,\mu}, \mathbb{1}_{\{y\}} \rangle$ stays close to $\overline{z}(y)$
- $\langle \nu_t^{K,\mu}, \mathbb{1}_{\{x\}} \rangle$ becomes extinct a.s..

Sketch of the proof: The invasion of a mutant trait.

The time between two mutations is of order $\frac{1}{\mu K} \gg \log(K)$.

Therefore, the three steps of invasion are completed, with high probability, before a new mutation occurs.

So the population process either stops or it is again monomorph, when a new mutation occurs.

Theorem 3: $\sigma \to 0$ for the TSS. *Champagnat and Méléard, 2009*

The rescaled Trait Substitution Sequence, X^{σ}_{t/σ^2}, *converges for* $\sigma \to 0$ *to the solution of the Canonical Equation of Adaptive Dynamics,* $x(t)$, *where* $x(0) = x$ *and*

$$\frac{d\,x(t)}{dt} = \int_{\mathbb{R}} h\, m(x)\overline{z}(x(t))[h\,\partial_1 f(x(t), x(t))]_+ M(x(t), h)dh. \quad (CEAD)$$

The TSS X^{σ}_t starts with $X^{\sigma}_0 = x$ and has the generator

$$A\phi(x) = \int_{\mathbb{R}} (\phi(x + \sigma h) - \phi(x))\, m(x)b(x)\overline{z}(x)\frac{[f(x + \sigma h, x)]_+}{b(x + \sigma h)} M(x, h)dh,$$

The jump sizes are of order σ and the survival probability is of order σ.

$\Rightarrow$ one has to resale the time by $1/\sigma^2$.

Remark:

Theorem 3 does not imply the convergence to the CEAD in any case, when we apply first the limit $(K, \mu) \to (\infty, 0)$ and next the limit $\sigma \to 0$.

$\to$ This is only true if the parameters of the microscopic model prevent the coexistence of any two traits.

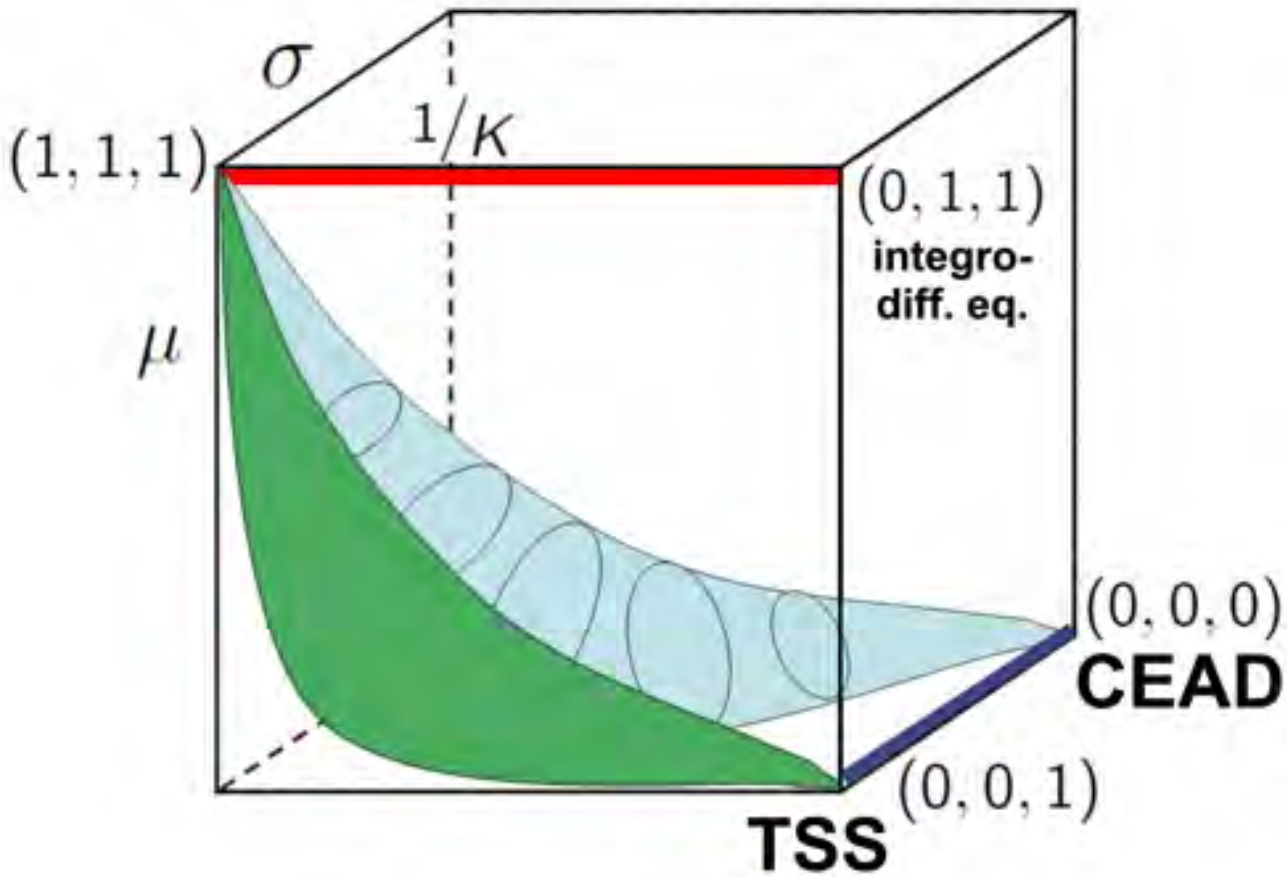
$\to$ Such a property is called "Invasion Implies Fixation Principle".

Our goal:

We want to combine the last two limits to a single step
i.e. we want to study $(K, \mu, \sigma) \to (\infty, 0, 0)$ simultaneously.

We illustrate the different convergences of the model in the following picture.

The convergence of Theorem 1, Theorem 2,Theorem 3 and of our result.



Theorem 4: $(K, \mu, \sigma) \to (\infty, 0, 0)$ *B., Bovier, Champagnat, In progress*

Let $\nu_0^{K,\mu,\sigma}$ *consist only of individuals with trait* x.
If $(K, \mu, \sigma) \to (\infty, 0, 0)$ *in such a way that*

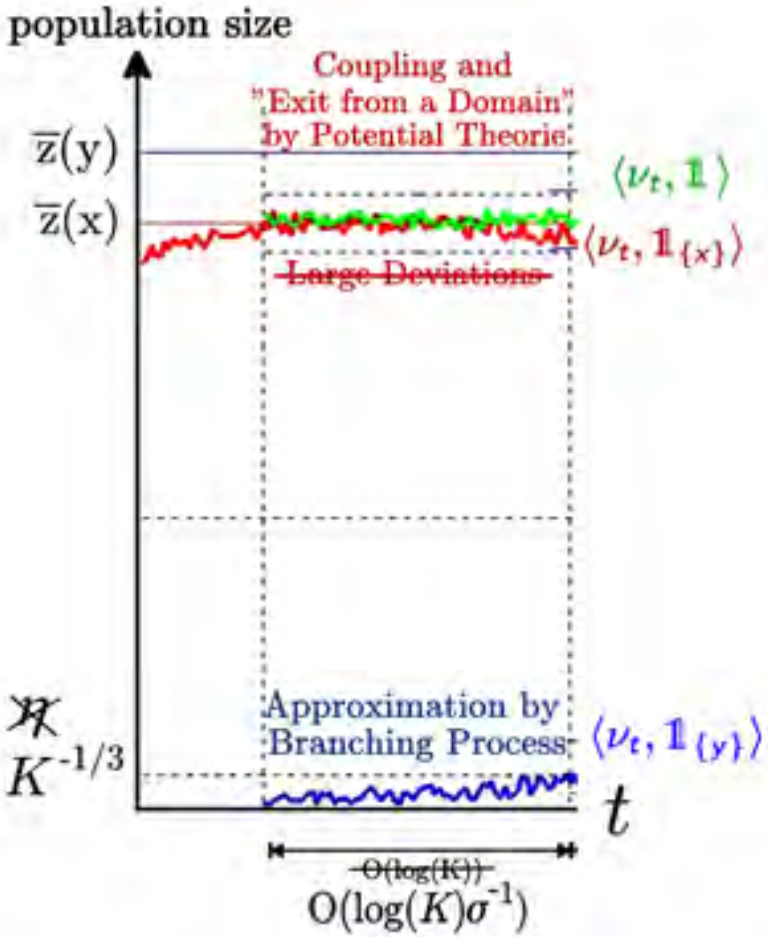
$$K^{-1/3+\alpha} \ll \sigma \ll 1 \qquad \text{for some } \alpha > 0$$

$$\text{and} \quad \exp(-CK^{1/3}) \ll \mu \ll \frac{\sigma^3}{K \log K} \qquad \text{for all } C > 0,$$

then $\nu^{K,\mu,\sigma}_{t/(\mu K \sigma^2)}$ *converges to the measure-valued function* $\overline{z}(x(t))\delta_{x(t)}$,

where $x(0) = x$ *and* $x(t)$ *is the unique solution of the Canonical Equation of Adaptive Dynamics (CEAD).*

Sketch of the proof: The three steps of invasion.



Step 1:
- $\langle \nu_t, \mathbb{1}_{\{x\}} \rangle$ is in $B_{MK^{-1/3}}(\overline{z}(x))$ while $\langle \nu_t, \mathbb{1}_{\{y\}} \rangle < K^{-1/3}$.
- $\mathbb{P}[\langle \nu_t^{K,\mu,\sigma}, \mathbb{1}_{\{x+\sigma k\}} \rangle$ reaches $K^{-1/3}] = \sigma \frac{[k\partial_1 f(x,x)]_+}{b(x)} - o(\sigma)$.

Sketch of the proof: The three steps of invasion.

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Step 2: Similar as in the Theorem 2?

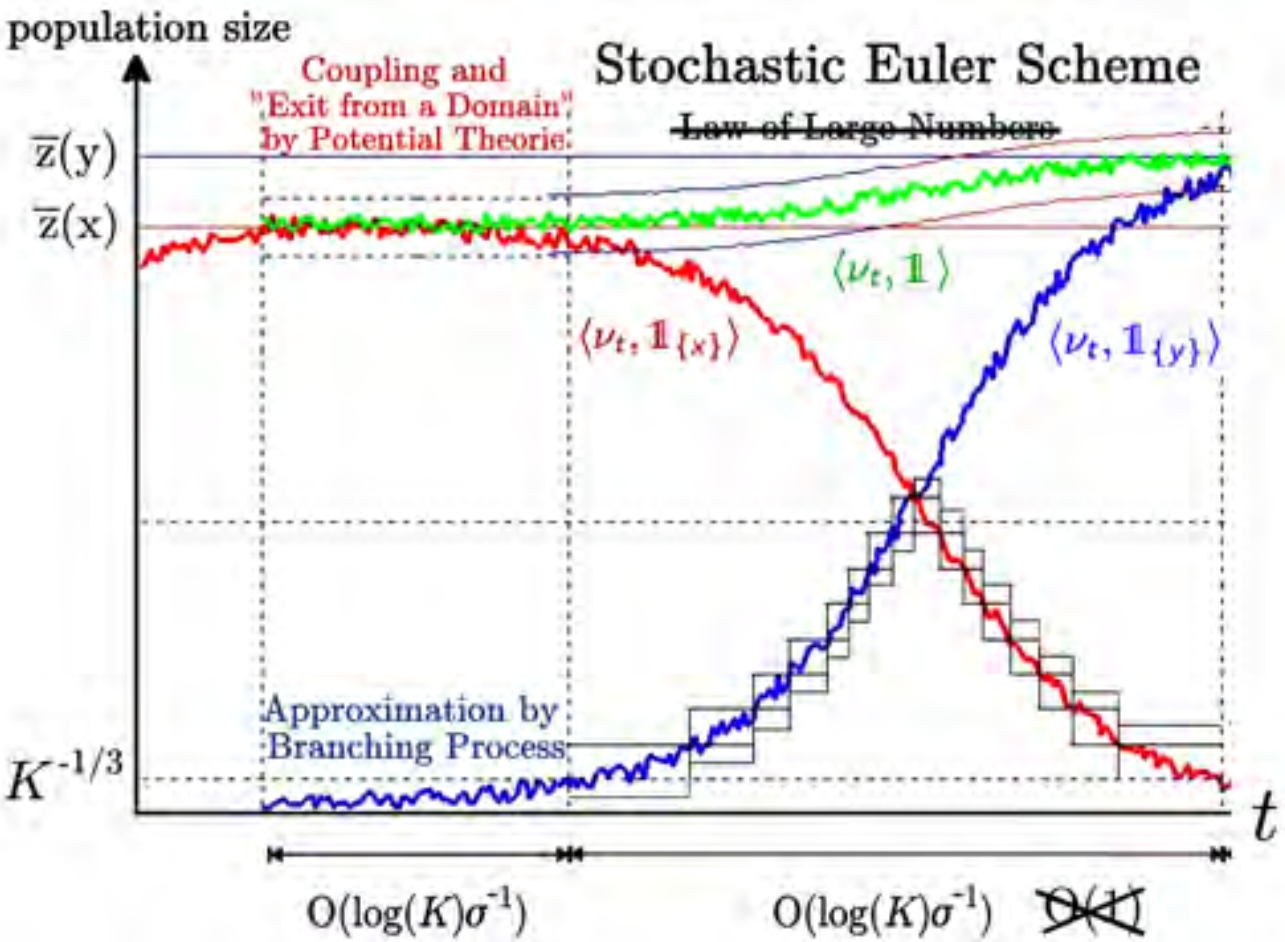
Problems:

1. $\langle \nu_{t_1}^{K,\mu,\sigma}, \mathbb{1}_{\{y\}} \rangle$ is microscopic ($=K^{-1/3}$).
2. The fitness advantage of the mutant trait, y, is only of order σ.

$\Rightarrow$ The time $LV(2,(x,y))$ needs to reach $B_\epsilon(0,\overline{z}(y))$ is not $O(1)$

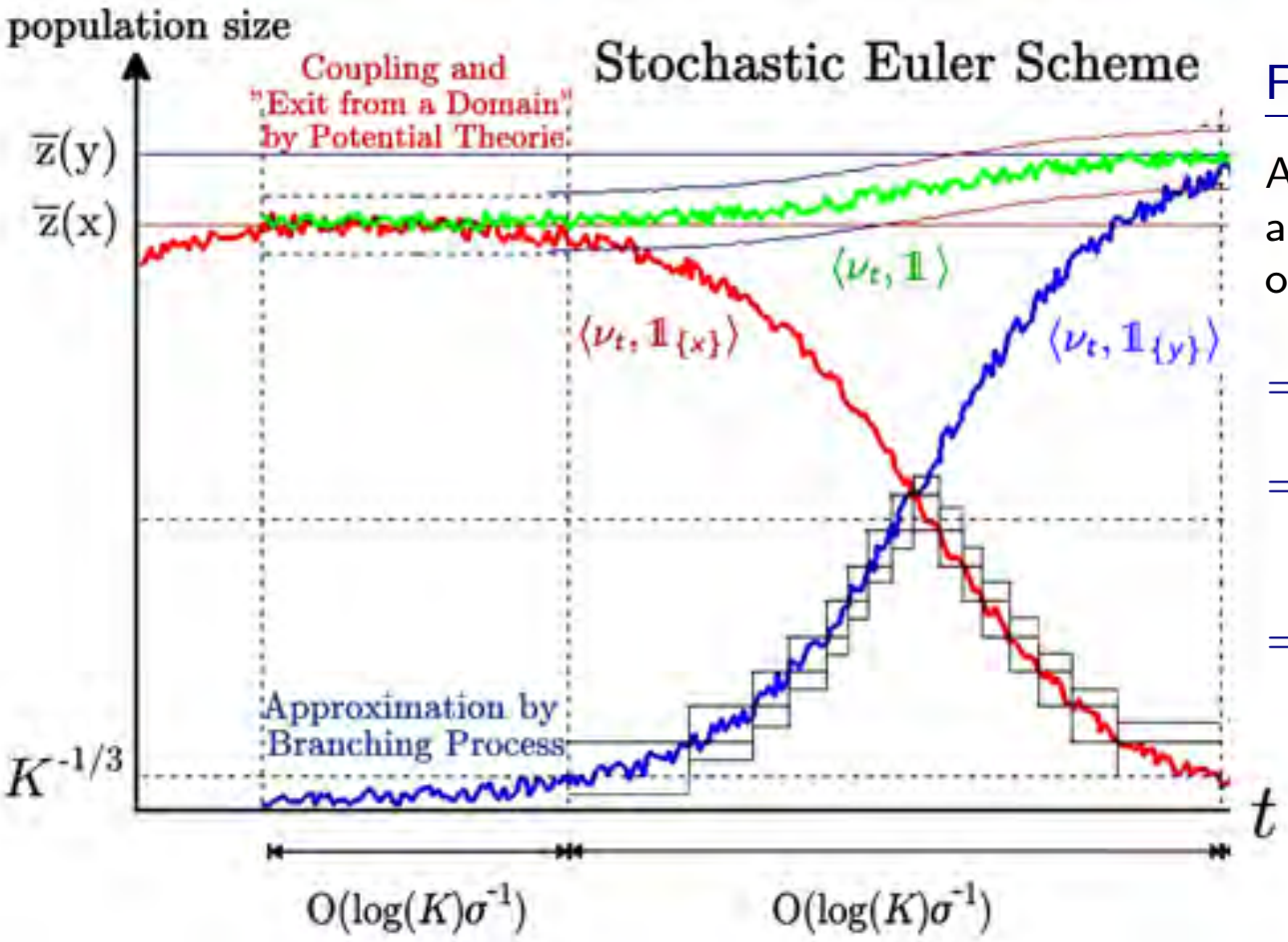
Therefore, we can not use the "Law of Large Numbers for Density Depending Population Processes" from Ethier and Kurtz.

Step 2: Stochastic Euler Scheme.



Note: If $\langle \nu^{K,\mu,\sigma}, \mathbb{1}_{\{y\}} \rangle > K^{-1/3}$, coexistence of the traits x and y is not possible.

Step 2: Stochastic Euler Scheme.



Frist part:

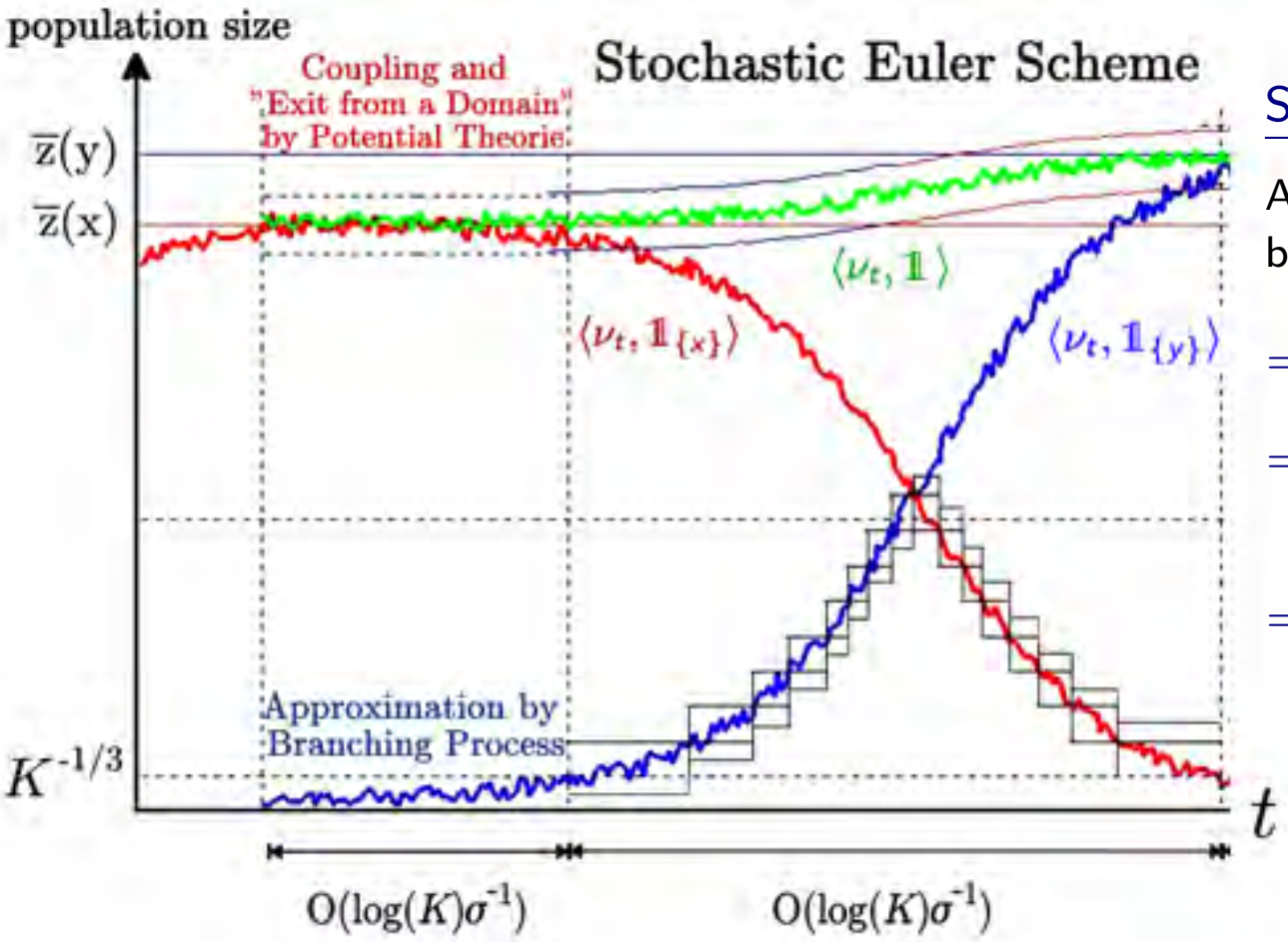
Approximate $\langle \nu^{K,\mu,\sigma}, \mathbb{1} \rangle$ by a function, which depends only on $\langle \nu^{K,\mu,\sigma}, \mathbb{1}_{\{y\}} \rangle$.

$\Rightarrow$ $\langle \nu_t, \mathbb{1}_{\{y\}} \rangle$ drift of order $+\sigma$

$\Rightarrow$ In little steps prove that $\langle \nu_t, \mathbb{1}_{\{y\}} \rangle$ increases to $\overline{z}(x)/2$.

$\Rightarrow$ Simultaneously $\langle \nu_t, \mathbb{1}_{\{x\}} \rangle$ decreases to $\overline{z}(x)/2$.

Step 2: Stochastic Euler Scheme.



Second part:

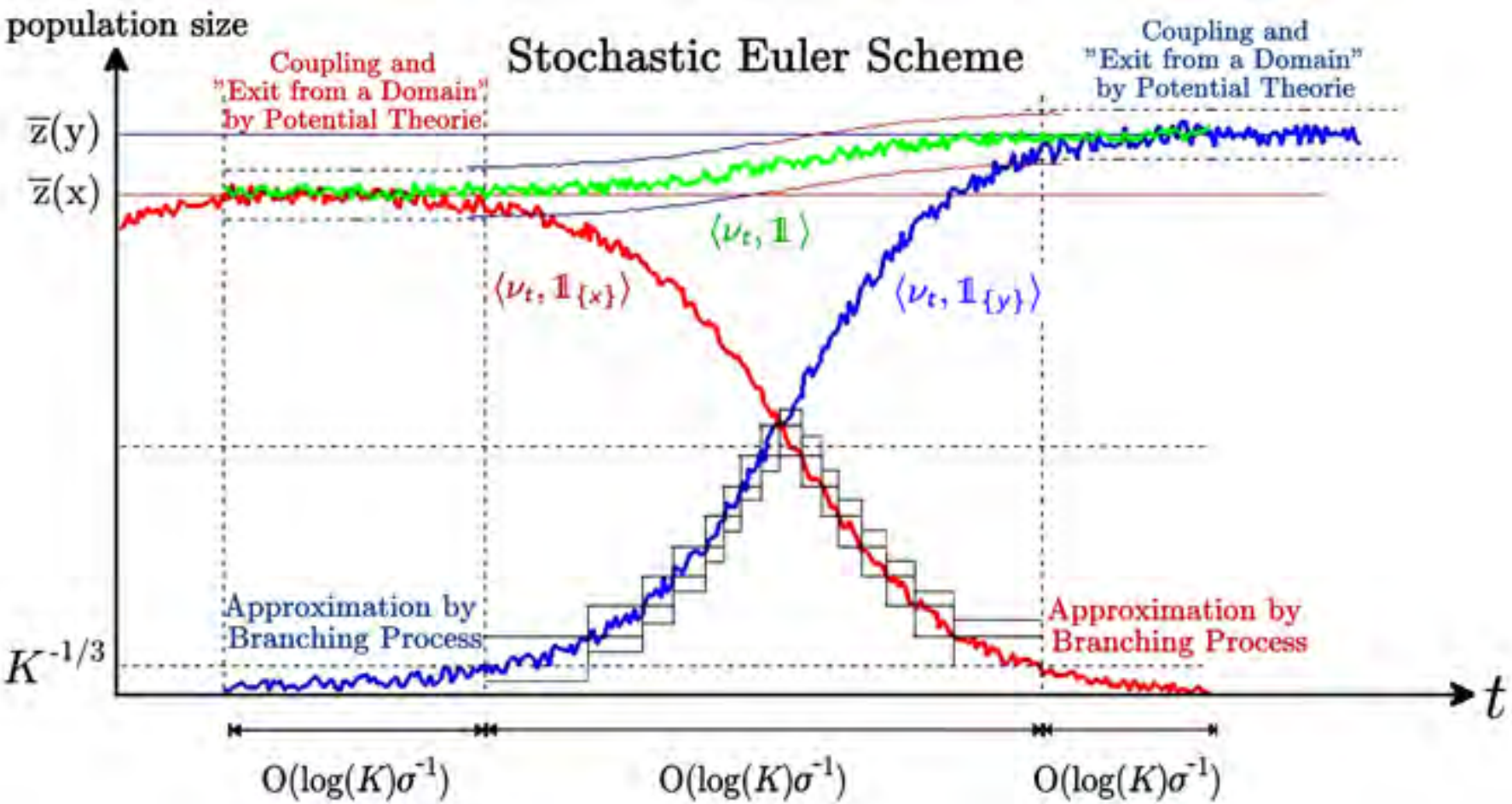
Approximate $\langle \nu^{K,\mu,\sigma}, \mathbb{1} \rangle$
by $\langle \nu^{K,\mu,\sigma}, \mathbb{1}_{\{x\}} \rangle$.

$\Rightarrow$ $\langle \nu_t, \mathbb{1}_{\{x\}} \rangle$ drift of order $-\sigma$

$\Rightarrow$ In little steps prove that
$\langle \nu_t, \mathbb{1}_{\{x\}} \rangle$ decreases to $K^{-1/3}$.

$\Rightarrow$ Simultaneously $\langle \nu_t, \mathbb{1}_{\{y\}} \rangle$
increases to $\overline{z}(y)$.

Sketch of the proof: The three steps of invasion.



Step 3:
- $\langle \nu_t^{K,\mu,\sigma}, \mathbb{1}_{\{y\}} \rangle$ stays in $B_{MK^{-1/3}}\overline{z}(y)$
- $\langle \nu_t^{K,\mu,\sigma}, \mathbb{1}_{\{x\}} \rangle$ becomes extinct a.s..

Sketch of the proof: The three steps of invasion.

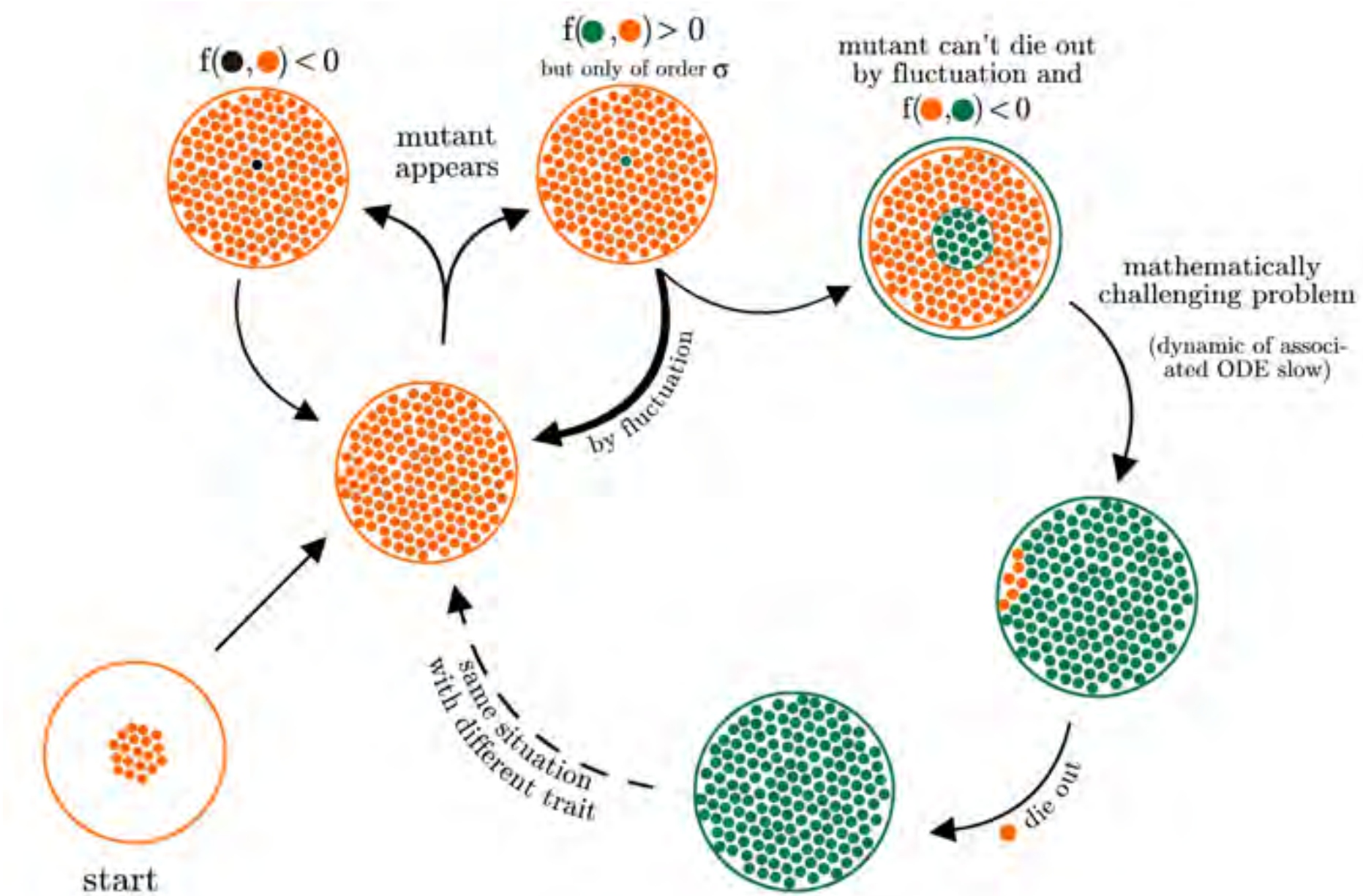
Since the time between two mutations is of order $1/(\mu K) \gg \log(K)\sigma^{-1}$, we obtain with high probablity that

- The three invasion steps are completed before a new mutation occurs.

  $\Rightarrow$ The population is again monomorphic, when a new mutation occurs.

- The time intervals where the population is dimorphic convergences to zero for the rescaled process.

Invasion of a mutant trait



Sketch of the proof: Approximation by a jump process

Therefore, $\nu^{K,\mu,\sigma}_{t/K\mu\sigma^2}$ is close to $\overline{z}(Y^\sigma_t)\delta_{Y^\sigma_t}$, where Y^σ_t is a Markov jump process with state space $\mathcal{X}$ and it is constructed as follows:

- it jumps only if a mutant trait invades
- # of mutation until a mutant succeeds is geometrical distributed with an parameter of order σ.
- the jump times of Y^σ_t are again exponentially distributed.

Therefore, Y^σ_t has following generator

$$L^\sigma f(Y) = \int_{\mathbb{R}} (f(Y+\sigma k) - f(Y))\sigma^{-1}\Big(m(Y)\overline{z}(Y)[k\partial_1 f(Y,Y)]_+\Big)M(Y,k)dk$$

But, we can apply the LLN to $(Y^\sigma_t)_{0\le t\le T}$ s.t. for all $0 \le t \le T$:

Y^σ_t is close to $x(t)$, the solution of the CEAD for σ small enough.

Finally, we obtain for $t < T$: $\nu^{K,\mu,\sigma}_{t/K\mu\sigma^2}$ converges to $\overline{z}(x(t))\delta_{x(t)}$.

Summary and Outlook

- have studied the limits $(K, \mu, \sigma) \to (\infty, 0, 0)$ in a single step
- interesting to consider other time scales, where coexistence is possible
  $\Rightarrow$ phenomenon of evolutionary branchings appears

  N. Champagnat, S. Méléard, Polymorphic evolution sequence and evolutionary branching. *Prob. Th. Rel. Fields.* 151(1-2): 45-94, 2011.

- interesting to expand the model to one with a fast and a slow timescale for trait changes, i.e. migration and mutation

  A. Bovier, S.-D. Wang, Trait substitution trees on two time scales. *Markov Proc. Rel. Fields.* 19, 607-642, 2013.

An application or extension of the model

This will be joint work with A. Bovier, L. Coquille, H. Mayer and B. Prochnau.

Landsberg J. et al. Melanomas resist T-cell therapy through inflammation-induced reversible dedifferentiation. *Nature* 490(7420):412-6, 2012

M. Hölzel, A. Bovier and T. Tüting, Plasticity of tumor and immune cells: a source of heterogeneity and a cause for therapy resistance? *Nat. Rev. Cancer* 13: 365-376, 2013.

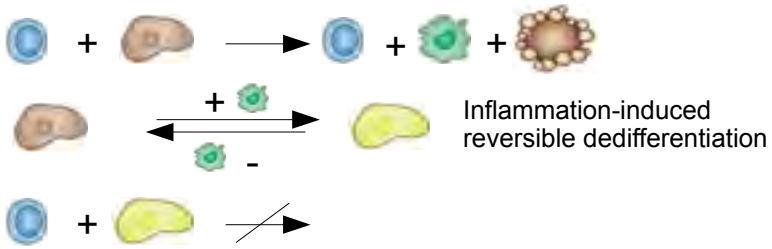
- Melanomas are tumors associated with skin cancer.
- There are several therapeutic approaches in treat cancer cells.

  $\Rightarrow$ One way is to use cytotoxic T-cells which are specific for the melanoma cells and kill these cells.

The following problem is reported in the first article:

- During the treatment occurs an inflammation and the cancer cells react to the inflammation by switching their phenotype.
- More precisely, the switch occurs if so called TNF-alpha (Tumor necrosis factor) proteins are present.
- The T-cells are not able to attack this cancer cells with the new phenotype of and thus very often a relapse occurs.
- Furthermore, Landsberg et al. observed that this switch is reversible, i.e. the melanoma cell population switches back again in the absence of TNF-alpha molecules.

Relevant mechanism



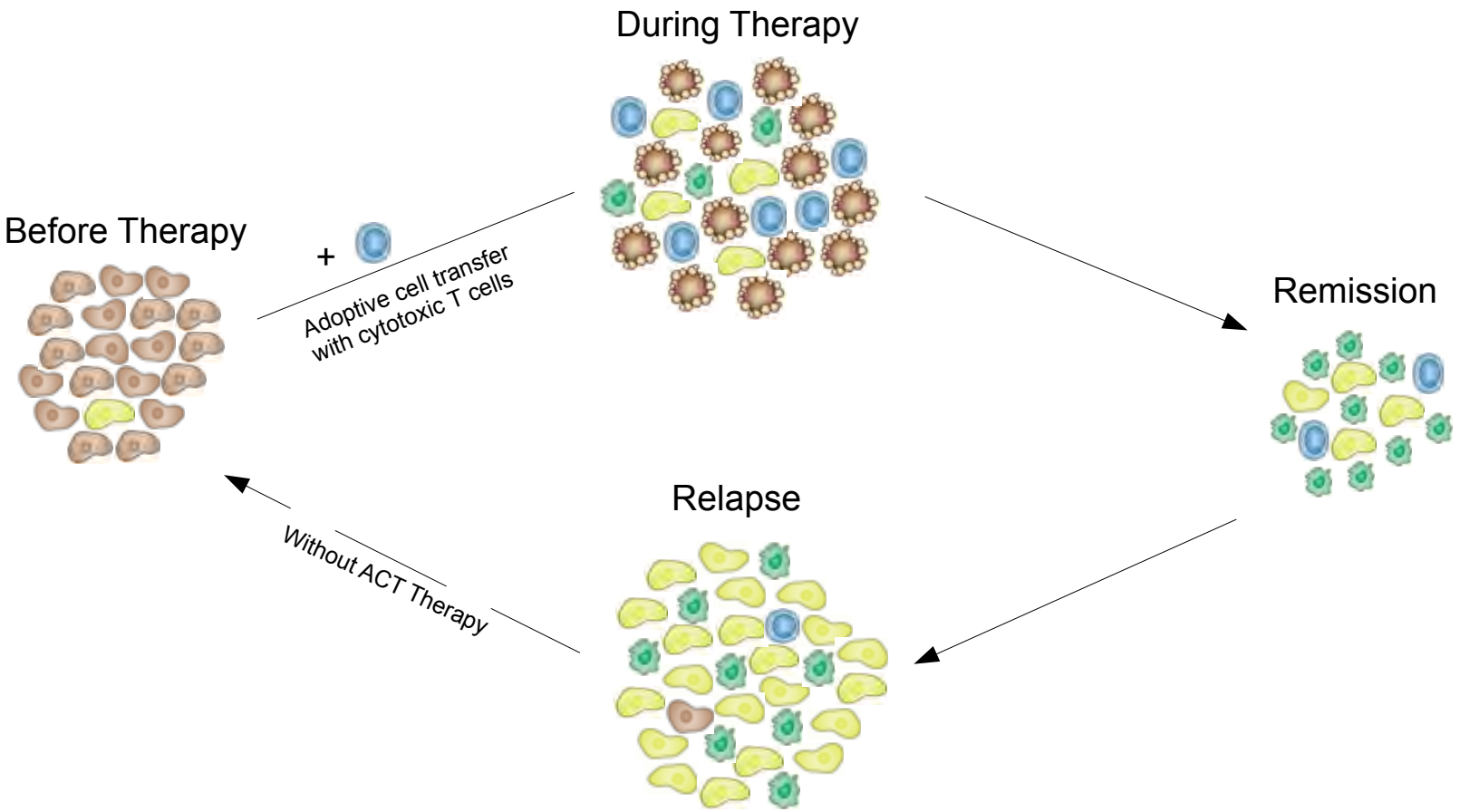
Tumour cell

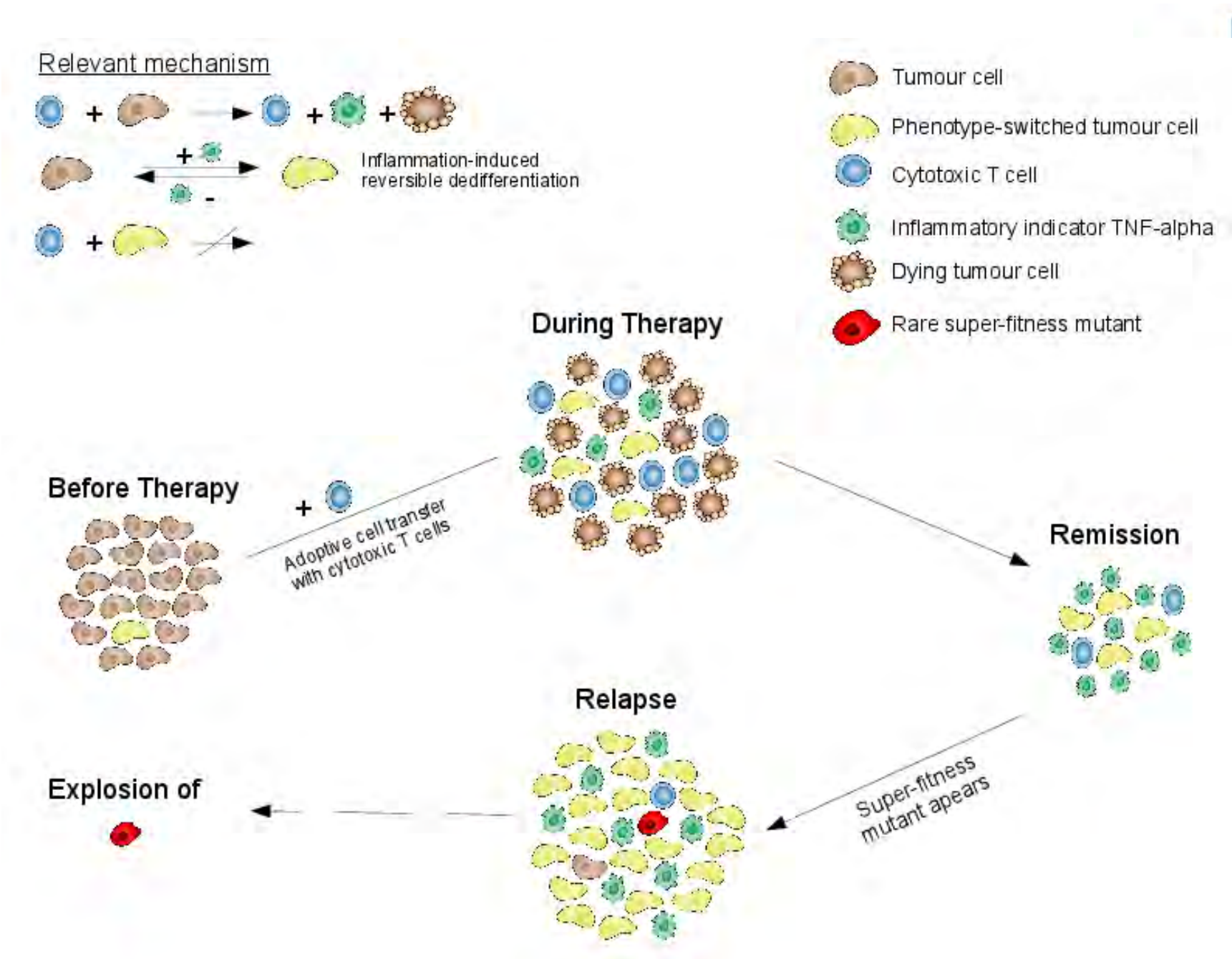
Phenotype-switched tumour cell

Cytotoxic T cell

Inflammatory indicator TNF-alpha

Dying tumour cell




Relevant mechanism
Inflammation-induced
reversible dedifferentiation
Tumour cell
Phenotype-switched tumour cell
Cytotoxic T cell
Inflammatory indicator TNF-alpha
Dying tumour cell
Rare super-fitness mutant
During Therapy
Before Therapy
Adoptive cell transfer
with cytotoxic T cells
Remission
Relapse
Super-fitness
mutant apears
Explosion of

Goals: Investigate a model for the whole system and numerical simulations.

More precisely, a system which describes the dynamics of

1. TNF-alpha proteins
2. cytotoxic T-cells, perhaps more than one type and
3. melanoma cells with different phenotype and also with different genotype to be able to include superfit mutants

What will change in the model?

1. have to include an extra death rate due to cytotoxic T-cells treatment for some melanoma cells .
2. have to include natural switching rates between the different phenotypes for the melanoma cells with the same genotype and some due to inflammation.
3. like to include a competition which lowers the birth rate
   $\Rightarrow$ increases probability of a mutations in a small tumor.
4. have to take care of the dynamics of the TNF-alpha protein and the cytotoxic T-cells

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Thank you for your attention!