

Workshop: Spatial models in population genetics

# Individual-based models of adaptive dynamics and applications to cancer immunotherapy

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# Adaptive dynamics

- Adaptive dynamics is a theoretical approach for **modeling long-term evolution of quantitative trait in asexual reproducing species**
  - ▶ integrates **ecological dynamics** in the evolutionary process
  - ▶ developed in the 1990's (Hofbauer&Sigmund, Marrow et al., Metz et al., Dieckmann&Law, Geritz et al.)
- evolution of a quantitative trait is the consequence of the three basic mechanism: **heredity**, **variation by mutation**, and **selection**
- **canonical equation** of adaptive dynamics (CEAD)  
ODE describing the evolution of the quantitative trait on a macroscopic level (Dieckmann&Law '96)

The heuristics leading to CEAD are based on the assumptions of

- large population size
- rare mutations
- small mutational effects

Mathematical challenges:

- to define an exact well-defined microscopic process (Fournier&Méléard '04)
- to identify how the three limits have to be applied to the microscopic process model to recover the CEAD

# The individual-based model

Let  $\mathcal{X} \subset \mathbb{R}$  be the **trait space**. For any  $x, y \in \mathcal{X}$ ,

$b(x)$	rate of birth
$d(x)$	rate of natural death
$K$	carrying capacity (scaling parameter for the population size)
$c(x, y)K^{-1}$	competition kernel
$u_K m(x)$	probability of mutation in a birth
$M(x, dh)$	mutation law, i.e. the mutant's trait is $x + \sigma_K h \in \mathcal{X}$ , where $h \sim M(x, dh)$

Let  $N_t = \{\# \text{ individuals at time } t\}$  and  $x_1(t), \dots, x_{N_t}(t) \in \mathcal{X}$  their traits

The **state of the population at time  $t$**  is described by a rescaled finite point measure on  $\mathcal{X}$  :

$$\nu_t^K = \frac{1}{K} \sum_{i=1}^{N_t} \delta_{x_i(t)} \in \mathcal{M}_F^K(\mathcal{X})$$

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**simultaneous limits**, i.e.  $u_K$  and  $\sigma_K$  are zero sequences in  $K$

# Dynamics of the population

- ① Population state at time  $t = 0$  is given by a measure  $\nu_0^K$
- ② Each individual has three independent exponential clocks:
  - ▶ a birth clock with parameter  $b(x)(1 - u_K m(x))$
  - ▶ a mutation clock with parameter  $b(x)u_K m(x)$
  - ▶ a death clock with parameter  $d(x) + \sum_{i=1}^{N_t} \frac{c(x, x_i(t))}{K}$
- ③ If the birth clock rings,  $\odot \rightarrow \odot \odot$   
a new individual with the same trait appears.
- ④ If the mutation clock rings,  $\odot \rightarrow \odot \odot$   
a new individual with trait  $y = x + \sigma_K h$  appears.
- ⑤ If the death clock rings,  $\odot \rightarrow \dagger$   
the individual disappears.

# The microscopic process

The evolution of the population is described by a  $\mathcal{M}_F^K(\mathcal{X})$ -valued Markov process  $(\nu_t^K)_{t \geq 0}$  with infinitesimal generator

$$\begin{aligned}
 \mathcal{L}^K \phi(\nu^K) &= \int_{\mathcal{X}} \left( \phi\left(\nu^K + \frac{\delta_x}{K}\right) - \phi(\nu^K) \right) (1 - u_K m(x)) b(x) K \nu^K(dx) \\
 &\quad \text{birth without mutation (linear in } \nu^K) \\
 &+ \int_{\mathcal{X}} \int_{\mathbb{Z}} \left( \phi\left(\nu^K + \frac{\delta_{x+\sigma_K h}}{K}\right) - \phi(\nu^K) \right) u_K m(x) b(x) M(x, dh) K \nu(dx) \\
 &\quad \text{birth with mutation (linear in } \nu^K) \\
 &+ \int_{\mathcal{X}} \left( \phi\left(\nu^K - \frac{\delta_x}{K}\right) - \phi(\nu^K) \right) \left( d(x) + \int_{\mathcal{X}} c(x, y) \nu^K(dy) \right) K \nu^K(dx). \\
 &\quad \text{death due to age and competition (non-linear in } \nu^K)
 \end{aligned}$$

Theorem 1. ( $u, \sigma$  fixed and  $K \rightarrow \infty$ )

Fournier and Méléard, 2004

Let  $u_K \equiv u$  and  $\sigma_K \equiv \sigma$  be fixed. Then for every  $T \geq 0$

$$(\nu_t^K)_{0 \leq t \leq T} \xrightarrow{\mathcal{D}} \xi \quad (\text{as } K \rightarrow \infty),$$

where  $\xi$  is given by the unique solution of an integro-differential equation.



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If  $u_K \equiv 0$  and  $\text{Supp}(\nu_0^K) = \{x_1, x_2\}$ , then  $\xi_t = z_1(t)\delta_{x_1} + z_2(t)\delta_{x_2}$ ,  
 where  $z$  is the solution of the **competitive Lotka-Volterra** equations  $\text{LV}(2, (x_1, x_2))$ .

$$\dot{z}_i = z_i (b(x_i) - d(x_i) - c(x_i, x_1)z_1(t) - c(x_i, x_2)z_2(t)) \quad \text{for } i \in \{1, 2\}$$

Theorem 1. ( $u, \sigma$  fixed and  $K \rightarrow \infty$ )

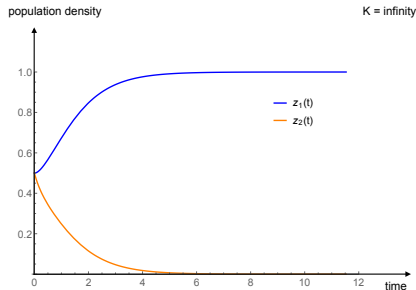
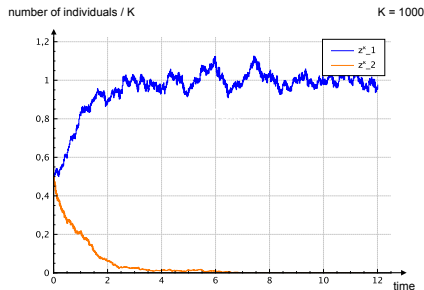
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Theorem 2. ( $\sigma$  fixed and  $(K, u_K) \rightarrow (\infty, 0)$ )

Champagnat, 2006

Fix  $\sigma_K \equiv \sigma$ . Assume that an **invasion-implies-fixation principle** holds and that

$$\forall V > 0, \quad \exp(-VK) \ll u_K \ll \frac{1}{K \ln(K)} \quad (\text{as } K \rightarrow \infty).$$

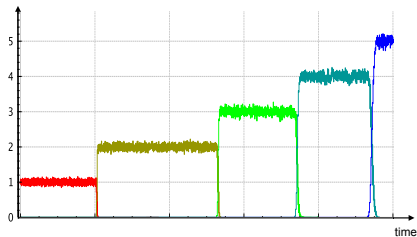
Then for every  $T > 0$

$$\left( \nu_{t/(u_K K)}^K \right)_{0 \leq t \leq T} \xrightarrow{\text{f.d.d.}} \bar{z}(X^\sigma) \delta_{X^\sigma} \quad (\text{as } K \rightarrow \infty),$$

where  $X^\sigma$  is a  $\mathcal{X}$ -valued Markov jump process and  $\bar{z}(x) = \frac{b(x) - d(x)}{c(x, x)}$ .

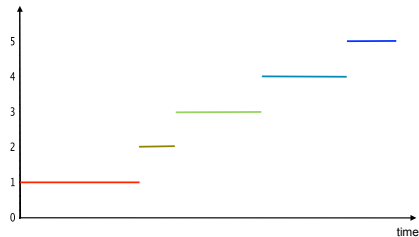
$X^\sigma$  is called **Trait Substitution Sequence (TSS)**.

$\bar{z}(x)$  is the stable **fixed point** of  $\text{LV}(1, x)$ :  $\dot{z} = z(b(x) - d(x) - c(x, x)z)$ .

number of individuals /  $K$ 

microscopic process

population density



limit process

**Theorem 3.** ( $\sigma \rightarrow 0$  for the TSS)

Champagnat and Méléard, 2009

 Let  $X^\sigma$  be the Trait Substitution Sequence. Then for every  $T > 0$ 

$$(X_{t/\sigma^2}^\sigma)_{0 \leq t \leq T} \xrightarrow{\mathcal{D}} \mathbf{x} \quad (\text{as } \sigma \rightarrow 0),$$

 where  $\mathbf{x} = (x_t)_{0 \leq t \leq T}$  is the solution of the canonical equation (CEAD)

$$\dot{x}_t = \int_{\mathbb{Z}} h m(x_t) \bar{z}(x_t) [h \partial_1 f(x_t, x_t)]_+ M(x_t, dh)$$

 and  $f(y, x) \equiv b(y) - d(y) - c(y, x) \bar{z}(x)$  the invasion fitness.

## Our result:

Apply simultaneous limits  $(K, u_K, \sigma_K) \rightarrow (\infty, 0, 0)$  to the microscopic process

## Previous results:

Theorem 2 and 3 do **not imply** the convergence to the CEAD:

- no statement possible about  $\lim_{\sigma \rightarrow 0} \lim_{K \rightarrow \infty} \nu_{t/(u_K K \sigma^2)}^{\sigma, K}$

Problems:

- Theorem 2 holds only for **finite** time intervals  
Theorem 3 considers the TSS on a **divergent** time scale
- gives no clue about how  $K$ ,  $u$  and  $\sigma$  should be compared to ensure that the CEAD approximation of the microscopic model is correct

**Theorem 4.**  $(K, u_K, \sigma_K) \rightarrow (\infty, 0, 0)$  B., Bovier and Champagnat, 2017

Let  $\nu^K$  be the microscopic process and  $\nu_0^K$  monomorphic. Assume that there exists a small  $\alpha > 0$ :

$$K^{-\frac{1}{2}+\alpha} \ll \sigma_K \ll 1 \quad \text{and}$$

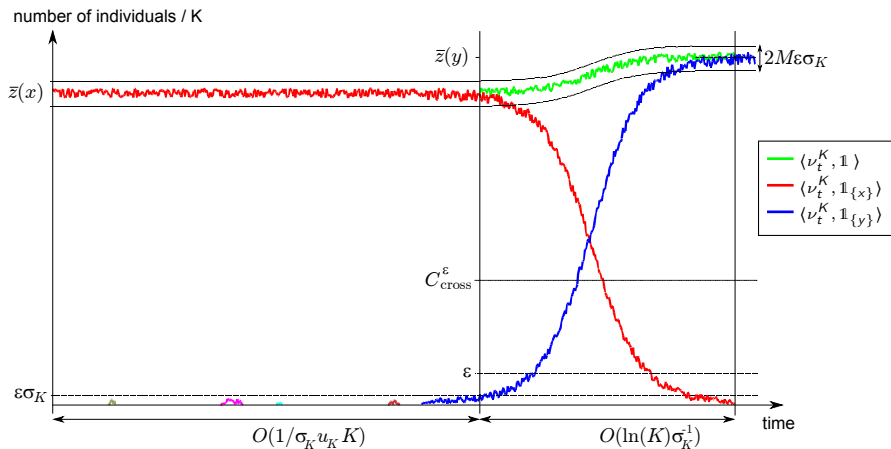
$$\exp(-K^\alpha) \ll u_K \ll \frac{\sigma_K^{1+\alpha}}{K \ln K} \quad (\text{as } K \rightarrow \infty).$$

Then for every  $T \geq 0$

$$\left( \nu_{t/(u_K K \sigma_K^2)}^K \right)_{0 \leq t \leq T} \xrightarrow{P} \bar{z}(\mathbf{x}) \delta_{\mathbf{x}} \quad (\text{as } K \rightarrow \infty),$$

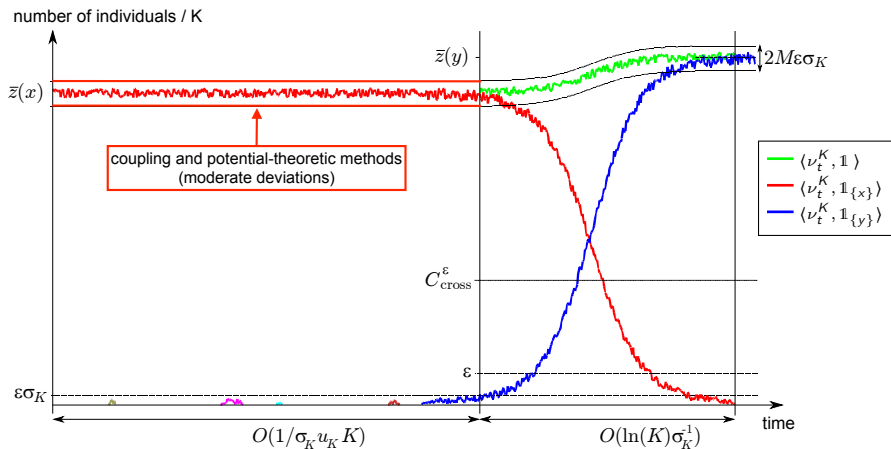
where  $\mathbf{x} = (x_t)_{0 \leq t \leq T}$  is the solution of the canonical equation (CEAD).

## Idea of the proof

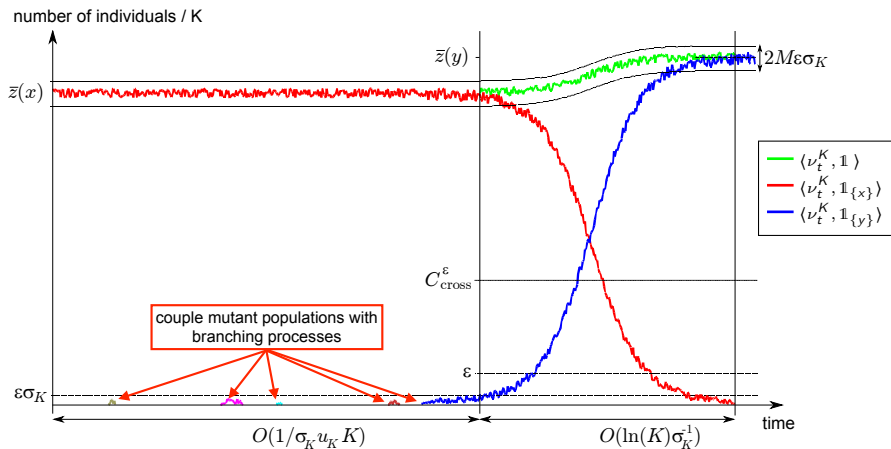




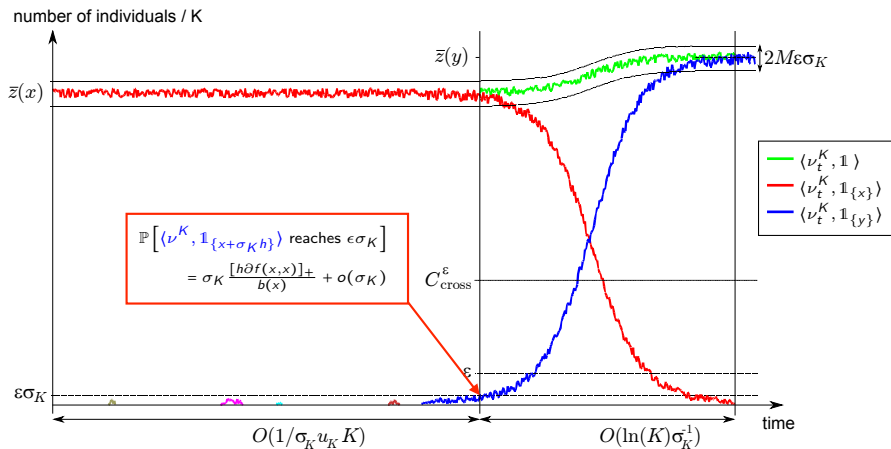
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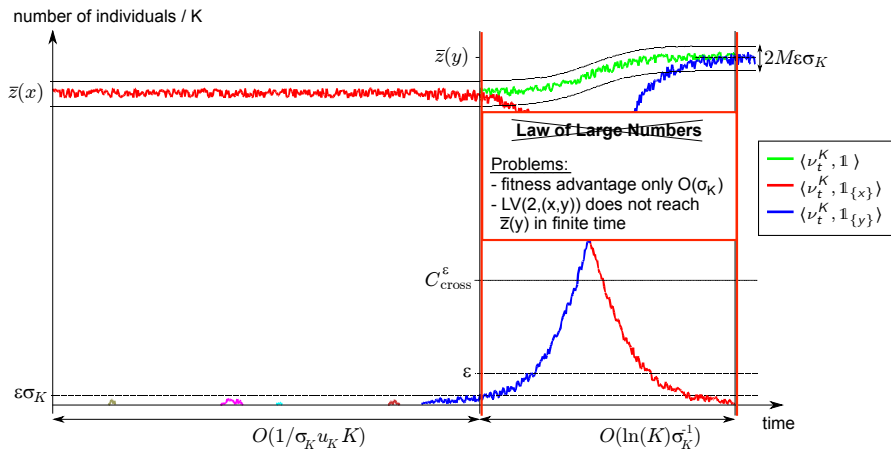
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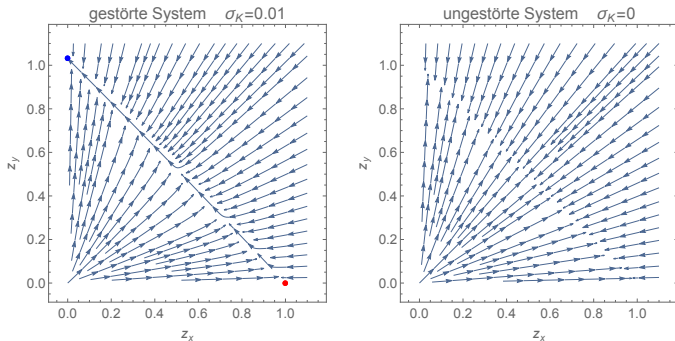
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## Idea of the proof



# Properties of the deterministic system

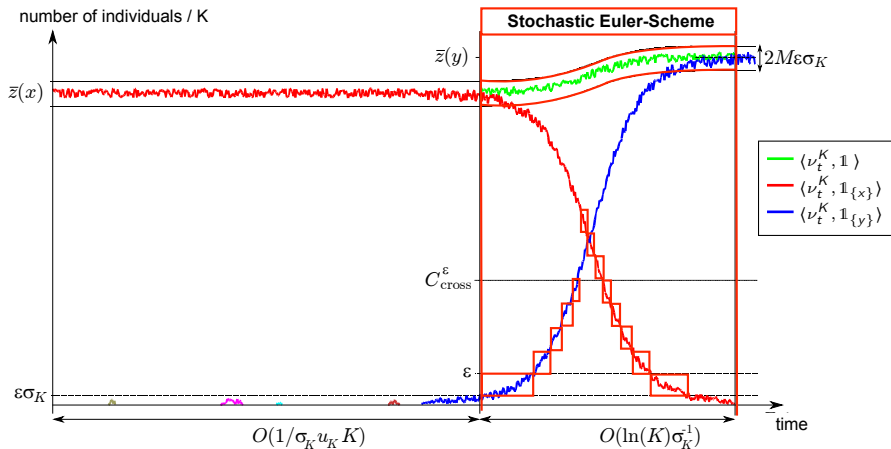


The perturbed deterministic system will move **quickly towards** the **invariant manifold** and then move **slowly** with speed  $O(\sigma_K)$  along it.

We **expect** that the stochastic systems also evolves along this curve.

In fact, we **show in little steps** that the density mutant population increases while the total mass stays close to the curve.

## Idea of the proof

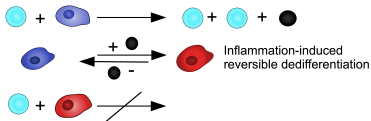






# Applications to cancer immunotherapy

- Starting point: research of the medical faculty in **cancer immunotherapy** for treatment of **melanoma** (skin cancer)
- Type of treatment: **Adoptive Cell Transfer (ACT)** with cytotoxic T-cells
  - ▶ are extracted, sensitised **ex vivo**, such that they can target the tumour, and re injected
- Problems: **relapse** and **resistance**
  - ▶ the melanoma cells resist therapy through **phenotypic plasticity** [**Landsberg et al. (Nature '12)**]
- Goal of the cooperation project:
  - ▶ **extend** the **individual-based model** to be able to reproduce the experiments of Landsberg et al.
  - ▶ study the interplay between **mutations** (genotypical alteration) and **phenotypical plasticity** on different time scales

# Course of therapy

## Relevant mechanisms



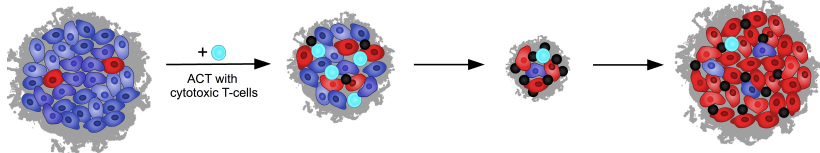
-  Differentiated melanoma cell
-  Dedifferentiated melanoma cell
-  Cytotoxic T-cell
-  TNF-alpha

Before Therapy

During Therapy

Remission

Relapse





# Phenotypical plasticity and mutations

Standard model expanded by rates for **natural** and **induced switching**

Trait space: Finite set of the form  $\mathcal{X} \equiv \mathcal{G} \times \mathcal{P}$

The evolution of the population is described by a  $\mathcal{M}_F^K(\mathcal{X})$ -valued Markov process  $(\nu_t^K)_{t \geq 0}$  with infinitesimal generator

$$\begin{aligned}
 & (\mathcal{L}^K \phi)(\nu^K) \\
 &= \sum_{(g,p) \in \mathcal{X}} \left( \phi\left(\nu^K + \frac{\delta_{(g,p)}}{K}\right) - \phi(\nu^K) \right) (1 - u_K m(g)) b(p) K \nu^K(g, p) \\
 &+ \sum_{(g,p) \in \mathcal{X}} \sum_{(\tilde{g}, \tilde{p}) \in \mathcal{X}} \left( \phi\left(\nu^K + \frac{\delta_{(\tilde{g}, \tilde{p})}}{K}\right) - \phi(\nu^K) \right) u_K m(g) M((g, p), (\tilde{g}, \tilde{p})) b(p) K \nu^K(g, p) \\
 &+ \sum_{(g,p) \in \mathcal{X}} \left( \phi\left(\nu^K - \frac{\delta_{(g,p)}}{K}\right) - \phi(\nu^K) \right) \left( d(p) + \sum_{\tilde{p} \in \mathcal{P}} c(p, \tilde{p}) \nu^K(\tilde{p}) \right) K \nu^K(g, p) \\
 &+ \sum_{(g,p) \in \mathcal{X}} \sum_{\tilde{p} \in \mathcal{P}} \left( \phi\left(\nu^K + \frac{\delta_{(g, \tilde{p})}}{K} - \frac{\delta_{(g,p)}}{K}\right) - \phi(\nu^K) \right) \left( s_{\text{nat.}}^g(p, \tilde{p}) + \sum_{\hat{p} \in \mathcal{P}} s_{\text{ind.}}^g(p, \tilde{p})(\hat{p}) \nu^K(\hat{p}) \right) K \nu^K(g, p).
 \end{aligned}$$

Theorem 5.  $(K, u_K) \rightarrow (\infty, 0)$

B. and Bovier, 2017

Let  $\nu^K$  be the standard process extended by phenotypic plasticity and assume that

$$\forall V > 0, \quad \exp(-VK) \ll u_K \ll \frac{1}{K \ln(K)}, \quad \text{as } K \rightarrow \infty.$$

Then for every  $T > 0$

$$\left( \nu_{t/(u_K K)}^K \right)_{0 \leq t \leq T} \xrightarrow{\text{f.d.d.}} \Lambda \quad (\text{as } K \rightarrow \infty),$$

where  $\Lambda$  is a  $\mathcal{M}_F(\mathcal{X})$ -valued Markov process, which jumps from one ecological equilibrium to the next and is an expansion of the [Polymorphic Evolution Sequence](#).

## Idea of the proof

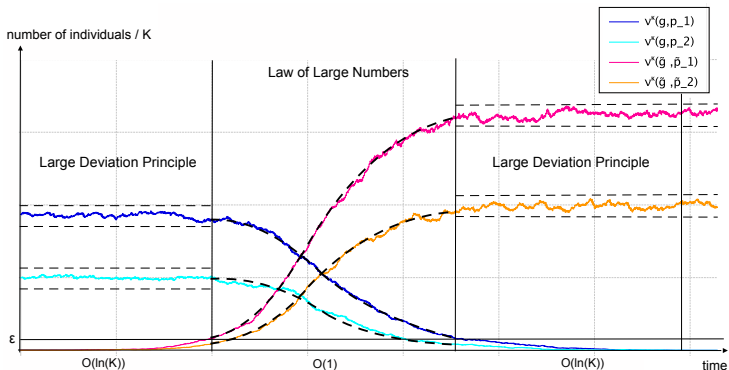


Figure: The three invasion steps.

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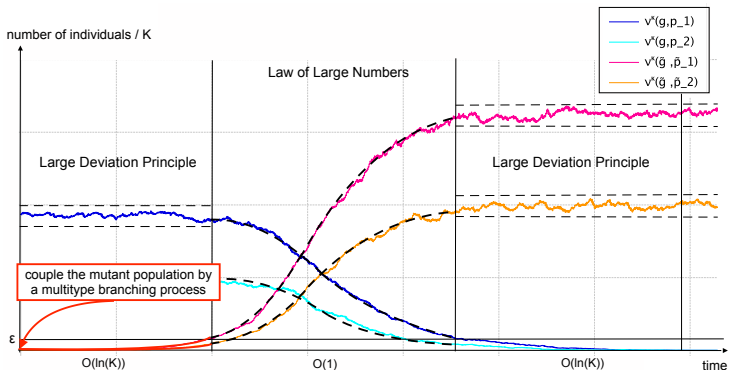


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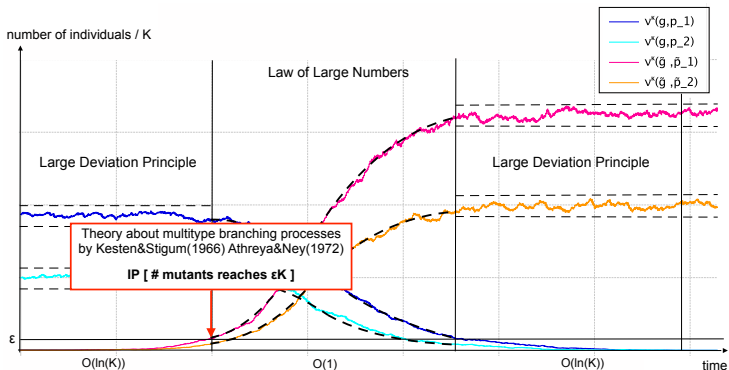


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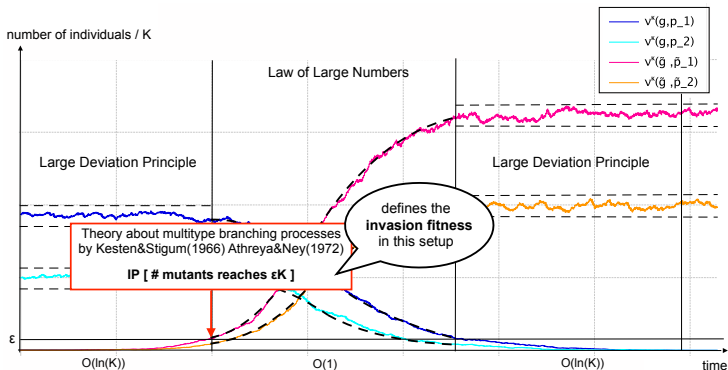
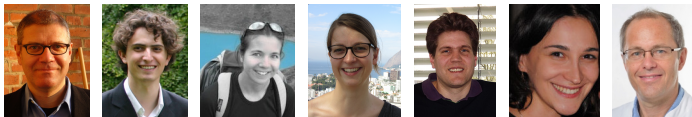


Figure: The three invasion steps.

# Thank you for your attention!



## Publications

- (P1) M. Baar and A. Bovier. The polymorphic evolution sequence for populations with phenotypic plasticity. [Preprint \(arXiv:1708.01528\)](#), 2017.
- (P2) M. Baar, A. Bovier, and N. Champagnat. From stochastic, individual-based models to the canonical equation of adaptive dynamics - In one step. [Ann. Appl. Probab.](#), 27:1093–1170, 2017.
- (P3) M. Baar, L. Coquille, H. Mayer, M. Hölzel, M. Rogava, T. Tüting, and A. Bovier. A stochastic model for immunotherapy of cancer. [Scientific Reports](#), 6:24169, 2016.