Workshop: Spatial models in population genetics

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

Martina Baar

Institute for Applied Mathematics Bonn

Bath, September 2017
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 \( x_1(t), ..., x_{N_t}(t) \in \mathcal{X} \) their traits

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

\[
\nu^K_t = \frac{1}{K} \sum_{i=1}^{N_t} \delta_{x_i(t)} \in \mathcal{M}^K_F(\mathcal{X})
\]
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 $x_1(t), \ldots, x_{N_t}(t) \in \mathcal{X}$ their traits

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

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

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, a new individual with the same trait appears. \( \circ \rightarrow \circ \circ \)

4. If the mutation clock rings, a new individual with trait \( y = x + \sigma_K h \) appears. \( \circ \rightarrow \circ \circ \)

5. If the death clock rings, the individual disappears. \( \circ \rightarrow \dagger \)
The microscopic process

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

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

birth without mutation (linear in $\nu^K$)

$$+ \int_{\mathcal{X}} \int_{\mathbb{Z}} \left( \phi(\nu^K + \frac{\delta_x + \sigma_K h}{K}) - \phi(\nu^K) \right) u_K m(x) b(x) M(x, dh) K \nu(dx)$$

birth with mutation (linear in $\nu^K$)

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

death due to age and competition (non-linear in $\nu^K$)
Theorem 1. \((u, \sigma \text{ fixed and } K \to \infty)\) Fournier and Méléard, 2004

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

\[
(\nu^K_t)_{0 \leq t \leq T} \xrightarrow{D} \xi \quad \text{(as } K \to \infty),
\]

where \(\xi\) is given by the unique solution of an integro-differential equation.
Theorem 1. \((u, \sigma \text{ fixed and } K \to \infty)\) Fournier and Méléard, 2004

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

\[
\left( \nu^K_t \right)_{0 \leq t \leq T} \xrightarrow{\mathcal{D}} \xi \quad \text{(as } K \to \infty),
\]

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

If \(u_K \equiv 0\) and \(\text{Supp}(\nu^K_0) = \{x_1, x_2\}\), 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 \(\text{LV}(2, (x_1, x_2))\).

\[
\dot{z}_i = z_i \left( b(x_i) - d(x_i) - c(x_i, x_1) z_1(t) - c(x_i, x_2) z_2(t) \right) \quad \text{for } i \in \{1, 2\}
\]
Theorem 1. \((u, \sigma \text{ fixed and } K \to \infty)\)  

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

\[
(\nu^K_t)_{0 \leq t \leq T} \xrightarrow{\mathcal{D}} \xi \quad \text{(as } K \to \infty),
\]

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

If \(u_K \equiv 0\) and \(\text{Supp}(\nu^K_0) = \{x_1, x_2\}\), 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 \(\text{LV}(2, (x_1, x_2))\).
Theorem 2. \((\sigma \text{ fixed and } (K, u_K) \to (\infty, 0))\) 

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

\[
\forall V > 0, \quad \exp(-VK) \ll u_K \ll \frac{1}{K \ln(K)} \quad \text{(as } K \to \infty)\]

Then for every \(T > 0\)

\[
\left(\nu^K_{t/(u_K K)}\right)_{0 \leq t \leq T} \xrightarrow{\text{f.d.d.}} \bar{z}(X^\sigma) \delta_{X^\sigma} \quad \text{(as } K \to \infty),
\]

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 \(LV(1, x): \quad \dot{z} = z(b(x) - d(x) - c(x, x)z)\).
Large population with rare mutations

number of individuals / K

population density

microscopic process

limit process
Theorem 3. \((\sigma \to 0 \text{ for the TSS})\) 

Champagnat and Mélaard, 2009

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

\[
\left( X^\sigma_{t/\sigma^2} \right)_{0 \leq t \leq T} \xrightarrow{\mathcal{D}} x \quad \text{(as } \sigma \to 0\text{),}
\]

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

\[
\dot{x}_t = \int_Z h \, m(x_t) \overline{Z}(x_t) \left[ h \, \partial_1 f(x_t, x_t) \right] + M(x_t, dh)
\]

and \(f(y, x) \equiv b(y) - d(y) - c(y, x)\overline{Z}(x)\) the invasion fitness.
Our result:

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

Previous results:

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

- no statement possible about \(\lim_{\sigma \to 0} \lim_{K \to \infty} \nu^{\sigma,K}_{t/(u_K K \sigma^2)}\)

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.** \((K, u_K, \sigma_K) \to (\infty, 0, 0)\) \hspace{1cm} B., Bovier and Champagnat, 2017

Let \(\nu^K\) be the microscopic process and \(\nu^K_0\) monomorphic. Assume that there exists a small \(\alpha > 0\):

\[
K^{-\frac{1}{2} + \alpha} \ll \sigma_K \ll 1
\]

and

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

Then for every \(T \geq 0\)

\[
\left(\nu^K_{t/(u_K K \sigma_K^2)}\right)_{0 \leq t \leq T} \xrightarrow{p} \tilde{Z}(x) \delta_x \quad \text{(as} \ K \to \infty \text{),}
\]

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

Anzahl Individuen / K

Zeit

\( z(x) \)

\( z(y) \)

\( 2M\varepsilon\sigma_K \)

\( C_{\text{cross}}^\varepsilon \)

\( \varepsilon \sigma_K \)

\( \varepsilon \)

\( O(1/\sigma_K u_K K) \)

\( O(\ln(K)\sigma_K^{-1}) \)

\( \langle \nu^K_t, 1 \rangle \)

\( \langle \nu^K_t, 1_{\{x\}} \rangle \)

\( \langle \nu^K_t, 1_{\{y\}} \rangle \)
Idea of the proof

Large population with rare and small mutations

number of individuals / $K$

coupling and potential-theoretic methods
(moderate deviations)

$\bar{z}(x)$

$2M\varepsilon\sigma_K$

$\bar{z}(y)$

$\varepsilon\sigma_K$

$O(1/\sigma_K u_K K)$

$O(\ln(K)\sigma_K^{-1})$

time

$\varepsilon$

$C_{\text{cross}}$

$\langle \nu^K_t, 1 \rangle$

$\langle \nu^K_t, 1_{\{x\}} \rangle$

$\langle \nu^K_t, 1_{\{y\}} \rangle$

M. Baar (University of Bonn)
Large population with rare and small mutations

Idea of the proof

Anzahl Individuen / \( K \)

Zeit

\( z(x) \)

\( z(y) \)

\( \bar{z}, \sigma_K \)

number of individuals / \( K \)

couple mutant populations with branching processes

\( C^\epsilon_{\text{cross}} \)

\( \varepsilon \sigma_K \)

\( O(1/\sigma_K u_K K) \)

\( O(\ln(K)\sigma_K^{-1}) \)

\( 2M\varepsilon\sigma_K \)

1. Phase: \( O(1/\varepsilon \sigma_K u_K K) \)

2. Phase: \( O(\ln(K)\varepsilon \sigma_K^{-1}) \)
Large population with rare and small mutations

Idea of the proof

\[ \frac{\text{number of individuals}}{K} \]

\[ \bar{z}(x) \]

\[ \bar{z}(y) \]

\[ 2M \varepsilon \sigma_K \]

1. Phase: \[ O\left(\frac{1}{\varepsilon K} \right) \]
2. Phase: \[ O\left(\ln(K)\varepsilon K \right) \]

\[ \mathbb{P}\left[ \nu^K_t, 1_{\{x+\sigma_K h\}} \right] \text{ reaches } \varepsilon \sigma_K \]

\[ = \sigma_K \left[ \frac{h \partial f(x,x)}{b(x)} \right]_+ + o(\sigma_K) \]

\[ C_{\text{cross}} \]

\[ \varepsilon \sigma_K \]

\[ O\left(1/\sigma_K u_K K^\lambda\right) \]

\[ O\left(\ln(K)\sigma_K^{-1}\right) \]

M. Baar (University of Bonn)

Adaptive Dynamics and Phenotypic Plasticity
Idea of the proof

- Law of Large Numbers
- Fitness advantage only $O(\sigma_K)$
- $LV(2,(x,y))$ does not reach $z(y)$ in finite time

$O(1/\sigma_K u_K K)$ $\Rightarrow$ $O(\ln(K)\sigma_K^{-1})$
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

Large population with rare and small mutations

M. Baar (University of Bonn)
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 reinjected

- 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**

- ACT with cytotoxic T-cells

**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 $(\nu^K_t)_{t \geq 0}$ with infinitesimal generator

$$(\mathcal{L}^K \phi)(\nu^K) = \sum_{(g,p)\in \mathcal{X}} \left( \phi(\nu^K + \frac{\delta(g,p)}{K} - \phi(\nu^K)) (1 - u_K m(g)) b(p) K \nu^K(g,p) ight)$$

$$+ \sum_{(g,p)\in \mathcal{X}} \sum_{(\tilde{g},\tilde{p})\in \mathcal{X}} \left( \phi(\nu^K + \frac{\delta(\tilde{g},\tilde{p})}{K} - \phi(\nu^K)) u_K m(g) M((g,p),(\tilde{g},\tilde{p})) b(p) K \nu^K(g,p) ight)$$

$$+ \sum_{(g,p)\in \mathcal{X}} \left( \phi(\nu^K - \frac{\delta(g,p)}{K}) - \phi(\nu^K) \right) \left( d(p) + \sum_{\tilde{p}\in \mathcal{P}} c(p,\tilde{p}) \nu^K(\tilde{p}) \right) K \nu^K(g,p)$$

$$+ \sum_{(g,p)\in \mathcal{X}} \sum_{\tilde{p}\in \mathcal{P}} \left( \phi(\nu^K + \frac{\delta(g,\tilde{p})}{K} - \frac{\delta(g,p)}{K}) - \phi(\nu^K) \right) \left( s^g_{\text{nat.}}(p,\tilde{p}) + \sum_{\hat{p}\in \mathcal{P}} s^g_{\text{ind.}}(p,\tilde{p})(\hat{p}) \nu^K(\hat{p}) \right) K \nu^K(g,p).$$
Theorem 5. \((K, u_K) \to (\infty, 0)\)

B. and Bovier, 2017

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

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

Then for every \(T > 0\)

\[
\left(\nu^K_{t/(u_K K)}\right)_{0 \leq t \leq T} \xrightarrow{\text{f.d.d.}} \Lambda \quad \text{as } K \to \infty,
\]

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.
Idea of the proof

Figure: The three invasion steps.
Idea of the proof

The figure illustrates the three invasion steps.

**Figure:** The three invasion steps.
Idea of the proof

Figure: The three invasion steps.
Thank you for your attention!

Publications

