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# Equilibria in quantitative genetics models

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*Joint work with Adrian Lam (OSU); Jimmy Garnier (Chambéry),
Florian Patout (Lyon), and Ophélie Ronce (ISEM)*

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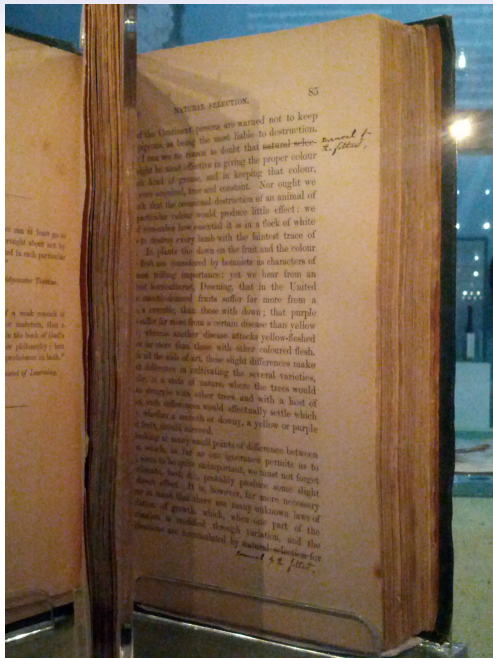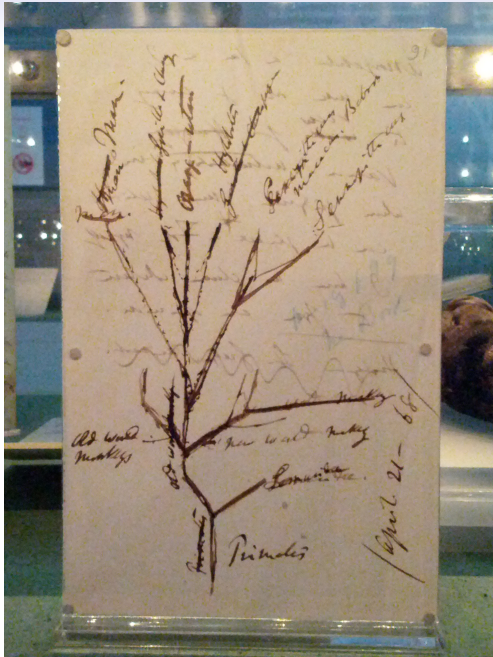
Phenotypic distribution

=

selection
vs.
diversity

Darwin's *On the origin of species*, personal
copy of A.R. Wallace (Cambridge Library).

Darwin's *original drawing* (Cambridge Library).

## Quantitative genetics models

An individual is indexed by its phenotypical trait $x \in \mathbb{R}$

The phenotypical distribution is denoted by $f(t, x)$

$$\partial_t f(t, x) = \text{birth} - \text{death}$$
$$(+ \text{ migration } / \text{ aging} \dots)$$

- birth: various modes of reproduction;
  mutation/ recombination $\rightarrow$ phenotypic diversity
- death: both trait-dependent and density dependent

## Selection only: concentration effect

Example: pure clonal reproduction (no diversity at birth)

$$\begin{cases} \partial_t f(t,x) = b(x,\rho(t))f(t,x) - m(x,\rho(t))f(t,x)\,, \\ \rho(t) = \int f(t,x)\,dx \end{cases}$$

Under certain assumptions on $b, m$:

- $\rho$ converges to a constant $\overline{\rho}$ (self-regulation)
- $f$ converges to a Dirac mass at $\overline{x}$ such that

$$b(\overline{x},\overline{\rho}) = m(\overline{x},\overline{\rho})$$

(all the population is concentrated around a common trait)

An important assumption is the *monotonicity* of $b - m$ with respect to $\rho$: competition decreases fertility and increases mortality.

Perthame: Transport equations in biology (2007); Barles-Mirrahimi-Perthame (2009); Lorz-Mirrahimi-Perthame (2011)

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## Various modes of reproduction (2 options so far)

Two modes of reproduction are considered here: ($'$ parental trait)

- Asexual: clonal + mutations

$$x' \longrightarrow x = x' + \sigma Y, \quad Y \text{ random number (any distribution)}$$

- Sexual: mating + recombination (Fisher's infinitesimal model):

$$(x_1', x_2') \longrightarrow x = \frac{x_1' + x_2'}{2} + \sigma Y, \quad Y \text{ normally distributed}$$

Asymptotic analysis in the case of small deviation $\sigma$:

$$\varepsilon = \frac{\sigma}{selection\ unit} \ll 1$$

Fisher (1918); Bulmer (1980); Mirrahimi and Raoul (2013); Barton, Etheridge and Véber (2017)

## Integro-differential equations

**Asexual reproduction**

$$\varepsilon\partial_t f_\varepsilon(t,x) + m(x,\rho_\varepsilon(t))f_\varepsilon(t,x) = \frac{1}{\varepsilon^d}\int_{\mathbb{R}} K\left(\frac{x-x'}{\varepsilon}\right)b(x',\rho_\varepsilon(t))f_\varepsilon(t,x')\,dx'\,.$$

**Sexual reproduction** (Fisher's infinitesimal model)

$$\varepsilon^2\partial_t f_\varepsilon(t,x) + (m(x)+\rho_\varepsilon(t))\,f_\varepsilon(t,x) =$$
$$\frac{1}{(\varepsilon\sqrt{\pi})^d}\iint_{\mathbb{R}^2}\exp\left(-\frac{1}{\varepsilon^2}\left(x-\frac{x_1+x_2}{2}\right)^2\right)f_\varepsilon(t,x_1)\frac{f_\varepsilon(t,x_2)}{\int_{\mathbb{R}} f_\varepsilon(t,y)\,dy}\,dx_1 dx_2\,.$$

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**Objectives:**

- Comparison between various modes of reproduction.

- Quantification of (*mal*-)adaptation of a population to a changing environment

**Tools:**

Asymptotic analysis as $\varepsilon \to 0$

**Asexual Reproduction**

$\mathbf{F}(\mathbf{z})$

Standard deviation:
$\sim \sqrt{\varepsilon}$

$U(z) = -\varepsilon \log \mathbf{F}(\mathbf{z})$

Phenotypical trait

**Sexual Reproduction**

$\mathbf{F}(\mathbf{z})$

Standard deviation:
$\sim \varepsilon$

$U(z) = -\varepsilon^{2} \log \mathbf{F}(\mathbf{z})$

Phenotypical trait

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## Asexual mode of reproduction: singular limit

Main observation: the density $f^\varepsilon$ is expected to converge to a singular measure as $\varepsilon \to 0$, but

$$u_\varepsilon(t, x) = -\varepsilon \log f_\varepsilon(t, x)$$

converges to a non-singular object
(as for a Gaussian with variance $\mathcal{O}(\varepsilon)$).

Rk. This fits in the framework of Large Deviations theory.

Diekmann-Jabin-Mischler-Perthame (2005); Barles-Perthame (2008); Barles-Mirrahimi-Perthame (2009)

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## Hamilton-Jacobi equation

$$\varepsilon\partial_t f_\varepsilon(t,x) + m(x,\rho_\varepsilon(t)) f_\varepsilon(t,x) = \frac{1}{\varepsilon^d} \int_{\mathbb{R}} K\left(\frac{x-x'}{\varepsilon}\right) b(x',\rho_\varepsilon(t)) f_\varepsilon(t,x')\, dx' \,.$$

On the left hand side:
$$\frac{\varepsilon\partial_t f_\varepsilon(t,x) + m(x,\rho_\varepsilon(t)) f_\varepsilon(t,x)}{f_\varepsilon(t,x)} = -\partial_t u_\varepsilon(t,x) + m(x,\rho_\varepsilon(t))$$

On the right hand side:
$$\frac{1}{\varepsilon^d} \int_{\mathbb{R}} K\left(\frac{x-x'}{\varepsilon}\right) b(x',\rho_\varepsilon(t)) \frac{f_\varepsilon(t,x')}{f_\varepsilon(t,x)}\, dx' \to \, ?$$

Diekmann-Jabin-Mischler-Perthame (2005); Barles-Perthame (2008); Barles-Mirrahimi-Perthame (2009)

## Convergence result

### Theorem (Barles-Mirrahimi-Perthame)

*Under suitable assumptions on $(b, m)$, $\rho_\varepsilon(t)$ is locally uniformly BV, and, after extraction of a subsequence, $u_\varepsilon$ converges locally uniformly towards $u$ solution of the following constrained Hamilton-Jacobi problem in the viscosity sense:*

$$\begin{cases} \partial_t u(t,x) + H(\rho(t), x, \nabla_x u(t,x)) = 0, & t > 0, \ x \in \mathbb{R}^d \\ (\forall t > 0) \quad \min_{x \in \mathbb{R}^d} u(t,x) = 0, \\ u(0,x) = g(x). \end{cases}$$

- The Hamiltonian is given by:

$$H(\rho, x, p) = b(x, \rho) \int e^{pz} K(z) \, dz - m(x, \rho).$$

- There is no equation for $\rho$!, but see the constraint $\min u = 0$.

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## Uniqueness of the limit problem?

Lack of uniqueness prevents from passing to the full limit $\varepsilon \to 0$.

Uniqueness results were available under stringent assumptions:

- Competition on reproduction or mortality (but not both) & multiplicative form (Barles-Perthame 2008)
- Particular regime of mutations: $H(\rho, x, p) = |p|^2 + R(\rho, x)$ & convexity of the initial data & concavity with respect to $x$ (Mirrahimi-Roquejoffre 2016)

### Theorem (C-Lam (2018))

*Assume that H is $\mathcal{C}^2$, convex with respect to p and monotonic with respect to $\rho$. Under some technical assumptions on the Lagrangian, there is a unique $\rho$ in the class of BV functions such that the constrained Hamilton-Jacobi admits a viscosity solution.*

**Method:** By convexity, reformulation as a variational solution:

$$
\begin{cases}
u(t,x) = \inf_{\substack{\gamma \in AC(0,t) \\ \gamma(t)=x}} \left\{ \int_0^t L(\rho(s), \gamma(s), \dot{\gamma}(s)) \, ds + g(\gamma(0)) \right\}, \\
(\forall t > 0) \quad \min_{x \in \mathbb{R}^d} u(t,x) = 0,
\end{cases}
$$

$$
(\forall t > 0) \quad \inf_{\gamma \in AC(0,t)} \left\{ \int_0^t L(\rho(s), \gamma(s), \dot{\gamma}(s)) \, ds + g(\gamma(0)) \right\} = 0.
$$

Then, compare $\rho_1$ and $\rho_2$.

## Sexual mode of reproduction: similar singular limit

So far, we restrict to equilibrium solutions in dimension $d = 1$:

$$(m(x) + \rho_\varepsilon) \, F_\varepsilon(x) =$$
$$\frac{1}{(\varepsilon\sqrt{\pi})^d} \iint\limits_{\mathbb{R}^2} \exp\left(-\frac{1}{\varepsilon^2}\left(x - \frac{x_1 + x_2}{2}\right)^2\right) F_\varepsilon(x_1) \frac{F_\varepsilon(x_2)}{\int_\mathbb{R} F_\varepsilon(y) \, dy} \, dx_1 \, dx_2 \,.$$

Main observation: the density $F^\varepsilon$ is expected to converge to a singular measure as $\varepsilon \to 0$, but

$$U_\varepsilon(x) = -\varepsilon^2 \log F_\varepsilon(x)$$

converges to a non-singular object.

## Main differences with the asexual problem

- Non-linear operator, but one-homogeneous (amenable to exponential change of unknown)
- No maximum principle (no theory of viscosity solutions)
- Reproduction is the dominant part of the problem: The operator

$$\mathcal{B}_{\varepsilon^2}(F) = \iint G_{\frac{\varepsilon^2}{2}} \left( x - \frac{x_1 + x_2}{2} \right) F(x_1) \frac{F(x_2)}{\int F(y)\,dy}\,dx_1\,dx_2$$

admits a family of fixed points: $\lambda G_{\varepsilon^2}(x - x_0)$. These are equilibria without selection.

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## Formal computations

Expand $U_\varepsilon(x) = \dfrac{(x - x_0)^2}{2} + \varepsilon^2 V_\varepsilon(x)$.

Suppose that $\rho_\varepsilon \to \rho_0$, and $V_\varepsilon \to V_0$ then formally we get:

$$\log(m(x) + \rho_0) = V_0(x) - 2V_0\left(\frac{x + x_0}{2}\right) + V_0(x_0)\,.$$

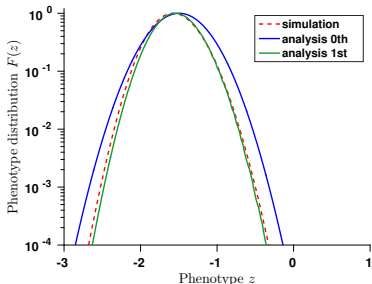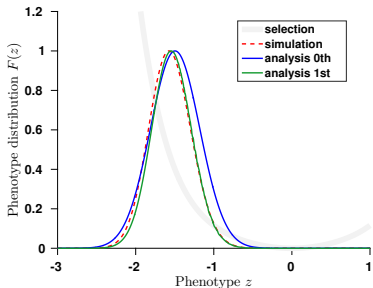The values of $x_0$ and $\rho_0$ follow directly from solvability conditions:

$$m'(x_0) = 0\,,$$
$$\rho_0 + m(x_0) = 1\,.$$

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# What are the most likely parental traits?



$$z = \frac{1}{2}\left(z_1 + z_2\right) + \varepsilon Y$$

$$Y \sim \mathcal{N}\left(0, \tfrac{1}{2}\right)$$

$F(z)$

$z_1 \; z_2$    $z_1$ $z_2$      $z_1$       $z_2$

**A**      **B**      **C**

$z$      $\bar{z}$      $z_0^*$      $z$

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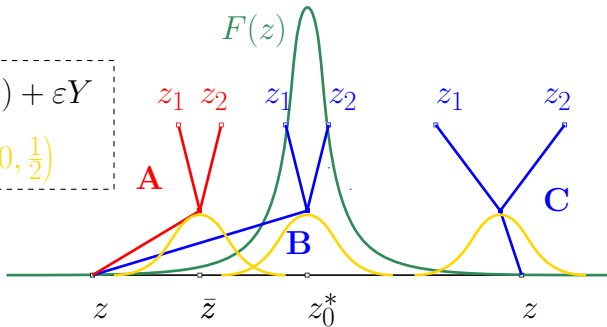
# Gaussian at the leading order + correction

## Rigorous construction: perturbative result

Assume that $m$ is smooth, uniformly convex with minimum at the origin, with polynomial growth at most.

### Theorem (C-Garnier-Patout (2018))

*There exists a compact subset $K$ of $\mathcal{C}^3$ with uniformly decaying third derivatives, and $\varepsilon_0 > 0$ such that for all $\varepsilon < \varepsilon_0$ there exists a unique $(\rho_\varepsilon, V_\varepsilon) \in \mathbb{R} \times K$. Moreover, $\rho_\varepsilon \to 1 - m(0)$, and $V_\varepsilon \to V_0$:*

$$V_0(x) = \left( \frac{\partial_x^3 m(0)}{2\partial_x^2 m(0)} \right) x + \sum_{k=0}^{\infty} 2^k \log \left( 1 - m(0) + m \left( 2^{-k} x \right) \right)$$

**Method:** Decompose $V_\varepsilon(x) = \gamma_\varepsilon x + W_\varepsilon(x)$: the linear part should be dealt with separately.

Derive contraction estimates on the third derivative $W_\varepsilon^{(3)}$.

The number $\gamma_\varepsilon$ is derived using a solvability condition within the fixed point operator.

## Alternative scaling

Raoul (2018) analyzed a different scaling:

$$\partial_t f_\varepsilon(t,x) + (m(x) + \rho_\varepsilon(t)) f_\varepsilon(t,x) = \frac{1}{\varepsilon} \left( \mathcal{B}_1(f_\varepsilon(t,\cdot)) - f_\varepsilon(t,\cdot) \right) .$$

with an additional space variable. He uses strongly contraction in the quadratic Wasserstein distance.

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## Application: mal-adaptation to a changing environment

Assume that selection acts on mortality only (for simplicity), but it gradually changes in time:
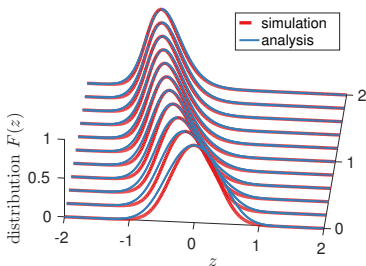
$$m(x - ct) + \rho(t)$$

where $m$ is a uniform convex function.
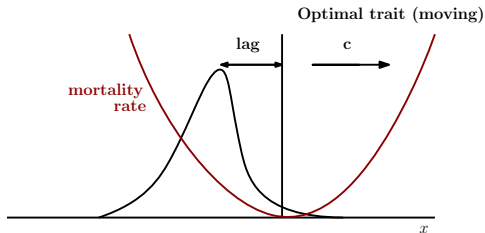
Aim: Compute the equilibrium distribution $F$ as $\sigma \ll$ *selection unit* which is stationary in the moving frame:

$$z = x - ct, \quad \partial_t \to \partial_t - c\partial_z$$

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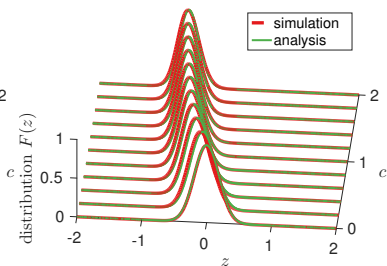
## Integro-differential equations

**Asexual reproduction**

$$- \varepsilon c \partial_z F(z) + (\rho + m(z)) \, F(z) = \frac{1}{\varepsilon} \int_{\mathbb{R}} K \left( \frac{z - z'}{\varepsilon} \right) F(z') \, dz' \, .$$

**Sexual reproduction** (Fisher's infinitesimal model)

$$- \varepsilon^2 c \partial_z F(z) + (\rho + m(z)) \, F(z) =$$
$$\frac{1}{\varepsilon \sqrt{\pi}} \iint_{\mathbb{R}^2} \exp \left( - \frac{1}{\varepsilon^2} \left( z - \frac{z_1 + z_2}{2} \right)^2 \right) F(z_1) \frac{F(z_2)}{\int_{\mathbb{R}} F(y) \, dy} \, dz_1 dz_2 \, .$$

## Asexual case (formal results)

The stationary Hamilton-Jacobi equation is:

$$c\partial_z U_0(z) + \rho_0 + m(z) = 1 + H\left(\partial_z U_0(z)\right).$$

The Hamiltonian function $H$ depends only on the effects of mutations:

$$H(p) = \int K(y)e^{py}\, dy - 1,$$

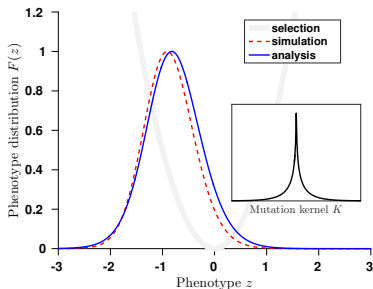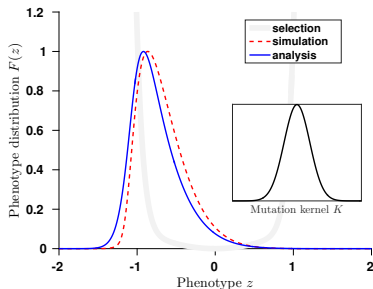$H$ comes with the Lagrangian function (convex conjugate):

$$L(v) = \max_p \left(p \cdot v - H(p)\right)$$

Fathi, Lecture notes on weak KAM theory (2010); Barles and Roquejoffre (2006)

# Explicit formula

The number $\rho_0$ is obtained explicitly:

$$\rho_0 = 1 - m(0) - L(c) \, .$$

$L(c)$ comes as an additional cost due to mutations (lag load).



As a by-product, we obtain the value of the lag $z_0$:

$$\rho_0 + m(z_0) = 1 \quad \Longleftrightarrow \quad m(z_0) - m(0) = L(c)$$

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## Sexual case (formal results)

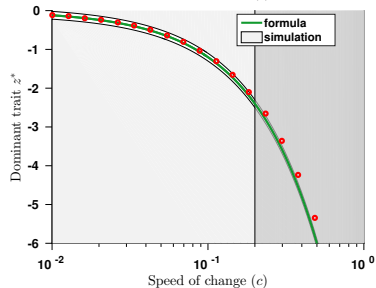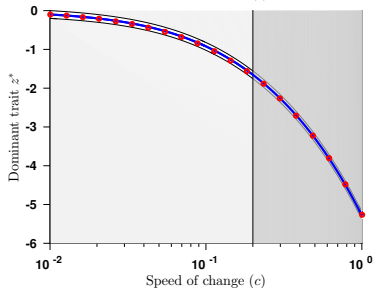$$U(z) = \frac{(z - z_0)^2}{2} + \varepsilon^2 V(z) + \dots$$

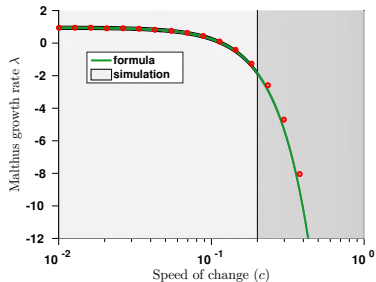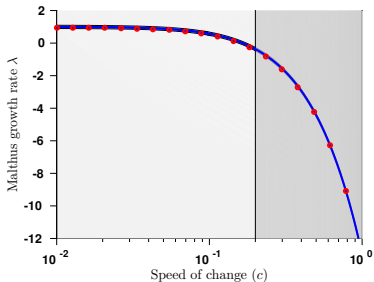where $V$ is solution of a difference equation:

$$\log\left(c(z - z_0) + \rho_0 + m(z)\right) = U_1(z) - 2U_1\left(\frac{z + z_0}{2}\right) + U_1(z_0).$$

Again, the values of $z_0$ and $\rho_0$ follow directly from solvability conditions:

$$m'(z_0) = -c\,,$$
$$\rho_0 + m(z_0) = 1\,.$$

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Joint work with Bouin, Bourgeron, Cotto, Garnier, Lepoutre, Ronce.

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# The loads and the lags

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# Evolution of aging

# Age-dependent selection

Suppose selection acts at a given age (or after some age threshold)

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Hamilton (1966); Charlesworth (1994, 2001).

Trait $x$

Age $a$

Selection acts at $a = a^*$

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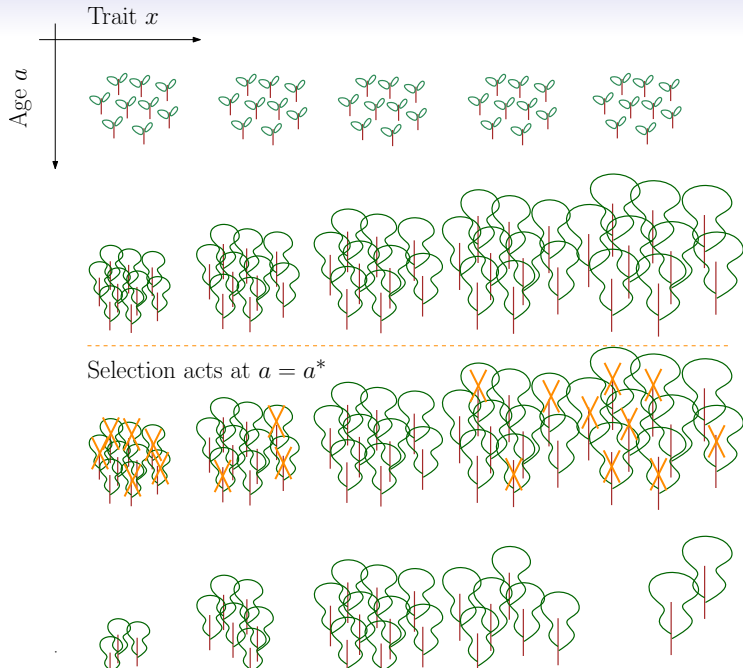
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# MALADAPTATION AS A SOURCE OF SENESCENCE IN HABITATS VARIABLE IN SPACE AND TIME

**Olivier Cotto[1] and Ophélie Ronce[1,2]**

In this study, we use a quantitative genetics model of structured populations to investigate the evolution of senescence in a variable environment. Adaptation to local environments depends on phenotypic traits whose optimal values vary with age and

— a changing environment can have a different impact on different age classes. —

results highlight the need to study age-specific adaptation, as a changing environment can have a different impact on different age classes.

## A quantitative genetics model of aging populations

(adapted from Cotto and Ronce 2014 to a continous setting)

$$\begin{cases} \partial_t f(t,a,z) + \partial_a f(t,a,z) + (\mu(a,m(z)) + \rho(t))\, f(t,a,z) = 0 \\ f(t,0,z) = \int_{\mathbb{R}} K(z-z') \left( \int_0^\infty \beta(a) f(t,a,z')\, da \right)\, dz' \,. \end{cases}$$

Ex. $\mu(a,m) = \mu(a) + m\delta_{a=a*}$, $m(z) = \alpha|z|^2$.

**Rk.** Here, asexual reproduction, but similar framework in the case of sexual reproduction.

**Goal:** Investigate the mutation/selection balance as a function of the age class $a*$ .

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# A quantitative genetics model of aging populations

(adapted from Cotto and Ronce 2014 to a continous setting)

$$
\begin{cases}
\partial_t f(t, a, z) + \partial_a f(t, a, z) + (\mu(a, m(z - ct)) + \rho(t)) \, f(t, a, z) = 0 \\
f(t, 0, z) = \displaystyle\int_{\mathbb{R}} K(z - z') \left( \int_0^\infty \beta(a) f(t, a, z') \, da \right) \, dz' \, .
\end{cases}
$$

Ex. $\mu(a, m) = \mu(a) + m\delta_{a=a*}$, $m(z) = \alpha|z|^2$.

**Rk.** Here, asexual reproduction, but similar framework in the case of sexual reproduction.

**Goal:** Investigate the mutation/selection balance as a function of the age class $a*$ in a changing environment.
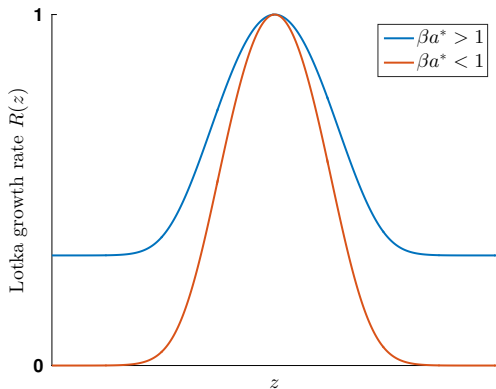
## Maladaptation under age structure (I)

$$\begin{cases} -\varepsilon c\partial_z F(a,z) + \partial_a F(a,z) + \left(\mu(a, m(z)) + \rho\right) F(a,z) = 0 \\ F(0,z) = \int_{\mathbb{R}} K_\varepsilon(z - z') \left(\int_0^\infty \beta(a)F(a,z')\,da\right)\,dz'. \end{cases}$$

Dynamics of an isolated trait (without mutations) are encoded in the spectral problem:

$$\begin{cases} r(m)\,G(a,m) + \partial_a G(a,m) + \mu(a,m)G(a,m) = 0 \\ G(0,m) = \int_0^\infty \beta(a)\,G(a,m)\,da, \end{cases}$$

where the eigenvalue $r(m)$ is given by:

$$\int_0^\infty \beta(a) \exp\left(-r(m)a - \int_0^a \mu(a', m)\,da'\right)\,da = 1\,.$$

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Shape of the eigenvalue $r(m(z))$ (effective fitness)

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## Maladaptation under age structure (II)

The logarithmic density

$$U^\varepsilon(a, z) = -\varepsilon \log\left(\frac{F^\varepsilon(a, z)}{G(a, m(z))}\right).$$

converges towards a viscosity solution of the Hamilton-Jacobi
equation

$$\rho_0 + c\partial_z U(z) = R(m(z), \partial_z U(z)).$$

where the hamiltonian $R(m, p)$ is defined by

$$\int_0^\infty \beta(a) \exp\left(-aR(m, p) - \int_0^a \mu(a', m)\, da'\right)\, da = \frac{1}{\widehat{K}(p)}.$$

For a rigorous derivation, see recent work with Gabriel and Mateos González in the context of anomalous diffusion,
and also Nordmann, Perthame and Taing.

# (Severe) maladaptation

In the age-free model, the lag $z_0$ increases gradually with $c$.

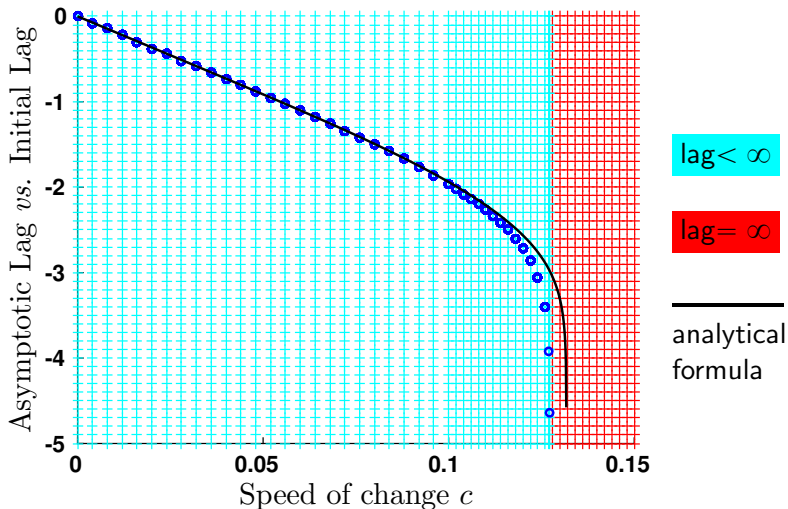It can be more singular in the age-structured model. It can even diverge for some critical speed $c**$:

$$\lim_{c \to c**} z_0(c) = \infty$$

It means that the population in the age classes $a > a^*$ goes extinct if $c** < c < c*$ (the critical speed for population extinction)

More precisely, we find,

$$z_0 = \left( -\frac{1}{\alpha} \log \left( 1 - \frac{L(c)e^{-L(c)a^*}}{\beta e^{-\beta a^*}} \right) \right)^{1/2}$$

# Numerical vs. analytical results (asexual mode)

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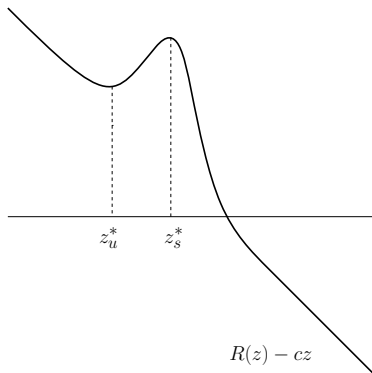00000000

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# Severe maladaptation

Similar analysis in the case of sexual reproduction.
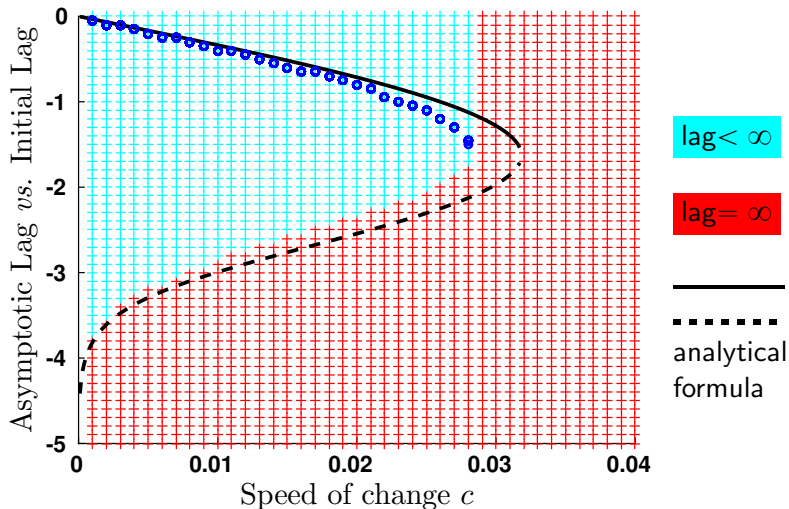
In this case, the lag is given by the simple formula:

$$\frac{d}{dz}r(m(z)) = c$$



$\Longleftrightarrow$ critical point for the modified fitness $r(m(z)) - cz$

$\Longrightarrow$ **Bistability**!

$z_u^*$    $z_s^*$

$R(z) - cz$

# Numerical vs. analytical results (sexual mode)

Introduction
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Asexual mode
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Sexual mode
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Maladaptation
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Thank your attention!