

Modèles *replicator-mutator* en biologie évolutive

Matthieu Alfaro

Université Montpellier

50 ans du LJLL
Roscoff, Mars 2019

Spatialized mutation/selection models under our eyes

- ▶ From “**Spatiotemporal microbial evolution on antibiotic landscapes**” by Michael Baym, Tami D. Lieberman, Eric D. Kelsic, Remy Chait, Rotem Gross, Idan Yelin, Roy Kishony (2016):


Mutation/selection movie.

The replicator-mutator equation

Model proposed by Kimura 1965 ¹

$$\partial_t u = \underbrace{\sigma^2 \partial_{xx} u}_{\text{mutator}} + \underbrace{u \left(W(x) - \int_{\mathbb{R}} W(y) u(t, y) dy \right)}_{\text{replicator}}.$$

- ▶ $x \in \mathbb{R}$: a one dimensional phenotypical trait space.
- ▶ $u(t, x)$: **frequency** at time t of individuals with trait x .
- ▶ $W(x)$: **fitness function**.
- ▶ $\bar{W}(t) = \int_{\mathbb{R}} W(y) u(t, y) dy$: mean fitness at time t .

¹see also Lande 1975, Fleming 1979, Bürger 1986, 1988. 

Formal conservation of mass...

We assume

$$u_0 \geq 0, \quad \int_{\mathbb{R}} u_0(x) dx = 1.$$

Define $m(t) := \int_{\mathbb{R}} u(t, x) dx$. Integrating the equation yields

$$\frac{d}{dt} m(t) = (1 - m(t)) \overline{W}(t), \quad m(0) = 1,$$

so that $m(t) = 1$ as long as $\overline{W}(t)$ is meaningful.

Actually, conservation of mass may completely fail: solution may become extinct in finite time...

Contents

- 1 When infinitely well-adapted phenotypes exist
- 2 When phenotypes are confined
- 3 Branching or not
- 4 Introducing a birth-death model...

Contents

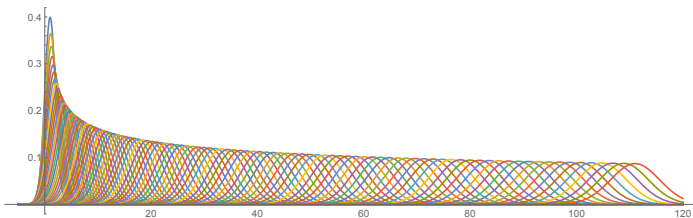
- 1 When infinitely well-adapted phenotypes exist
- 2 When phenotypes are confined
- 3 Branching or not
- 4 Introducing a birth-death model...

The linear case $W(x) = x$

- ▶ Introduced by Tsimring, Levine and Kessler 1996 (a mean-field theory for the evolution of RNA virus population).

$$\partial_t u = \partial_{xx} u + u(x - \bar{x}(t)), \quad \text{Equation for arms run.}$$

- ▶ Self similar gaussian solutions (Biktashev 2014) of mean $m_0 + V_0 t + t^2$ (**ACCELERATION!**) and variance $V_0 + 2t$ (**FLATTENING!**).



The linear case $W(x) = x$

Theorem (A. and Carles, 2014)

The *solution is explicit* and defined until

$$T^{\text{extinction}} = \sup \left\{ t \geq 0, \int_0^\infty e^{ty} u_0(y) dy < \infty \right\}.$$

In other words, the right initial tail decides between extinction at infinite time (e.g. gaussian tail), at a finite time (e.g. exponential tail) or even immediately (e.g. algebraic tail).

- ▶ Adapting the so-called **Avron–Herbst formula** for the Schrödinger equation reduces the problem to the heat equation.

The linear case $W(x) = x$

Corollary (A. and Carles, 2014)

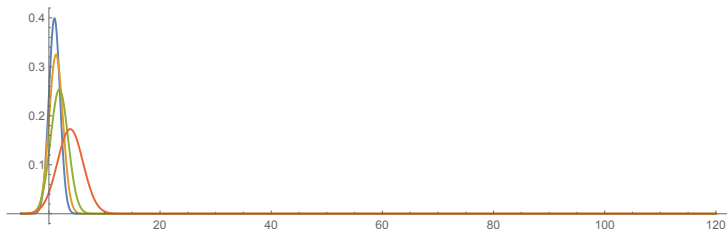
If u_0 is compactly supported, then

$$\sup_{x \in \mathbb{R}} \left| u(t, x) - \underbrace{\frac{1}{\sqrt{4\pi t}} e^{-(x-t)^2/4t}}_{\text{elementary solution, } u_0(y)=\delta_0(y)} \right| \leq \frac{C}{t}.$$

The quadratic case $W(x) = x^2$

Theorem (A. and Carles, 2017)

Again we collect the solution explicitly but, in some sense, the situation is worse: *all solutions become extinct in finite time.*



- ▶ This corresponds to a **compactification of time** w.r.t. the linear case.

Remediations

“The above fitness functions are not bounded from above” + “the mass has to be preserved” \Rightarrow an accelerating run towards infinity and extinction...

- ▶ consider a **cut-off version of the equation**, see Rouzine, Wakekey, and Coffin 2003, Sniegowski and Gerrish 2010.
- ▶ provide a **proper stochastic treatment** for large fitness region, see Rouzine, Brunet, and Wilke 2008.
- ▶ consider **confining fitness functions...**

Contents

- 1 When infinitely well-adapted phenotypes exist
- 2 When phenotypes are confined**
- 3 Branching or not
- 4 Introducing a birth-death model...

The equation under consideration

$$\partial_t u = \sigma^2 \partial_{xx} u + u (W(x) - \bar{W}(t)) .$$

- ▶ Key assumption: $\lim_{|x| \rightarrow +\infty} W(x) = -\infty$.

Reduction to a linear equation

We have

$$u(t, x) = \frac{v(t, x)}{m_v(t)}, \quad m_v(t) := \int_{\mathbb{R}} v(t, y) dy.$$

where

$$\partial_t v = \sigma^2 \partial_{xx} v + W(x)v.$$

Solving the linear equation

The Schrödinger operator with confining potential

$$-\sigma^2 \frac{d^2}{dx^2} - W(x)$$

admits eigenfunctions $(\phi_k)_{k \in \mathbb{N}}$ which forms a orthonormal basis of $L^2(\mathbb{R})$, and thus

$$v(t) = \sum_{k=0}^{+\infty} (u_0, \phi_k)_{L^2(\mathbb{R})} \phi_k e^{-\lambda_k t} \quad \text{in } L^2(\mathbb{R})$$

which is not the adequate space for our problem...

Moving to the adequate spaces

For a **polynomial** confining fitness function

$$W(x) = -x^{2s} + \dots,$$

an asymptotics of the eigenvalues (λ_k) is known (Titchmarsh 1946)

$$\lambda_k \sim C_{s,\sigma} k^{\frac{2s}{s+1}}.$$

Based on it, we derive **non standard estimates of the eigenfunctions in $L^\infty(\mathbb{R})$, $L^1(\mathbb{R})$ and $L^1_{-W}(\mathbb{R})$.**

Putting all together

Theorem (A. and Veruete, 2018)

For a polynomial confining fitness function, there is a *unique solution to the replicator-mutator Cauchy problem*. Moreover it is smooth on $(0, +\infty) \times \mathbb{R}$ and is given by

$$u(t, x) = \frac{\sum_{k=0}^{+\infty} (u_0, \phi_k)_{L^2(\mathbb{R})} \phi_k(x) e^{-\lambda_k t}}{\sum_{k=0}^{+\infty} (u_0, \phi_k)_{L^2(\mathbb{R})} m_k e^{-\lambda_k t}}, \quad t > 0, x \in \mathbb{R},$$

where $m_k := \int_{\mathbb{R}} \phi_k(y) dy$ is the mass of the eigenfunction ϕ_k .

Long time behaviour

Corollary (A. and Veruete, 2018)

For any $1 \leq p \leq +\infty$,

$$u(t, \cdot) - \frac{\phi_0(\cdot)}{m_0} \longrightarrow 0 \quad \text{in } L^p(\mathbb{R}), \quad \text{as } t \rightarrow +\infty.$$

Contents

- 1 When infinitely well-adapted phenotypes exist
- 2 When phenotypes are confined
- 3 Branching or not**
- 4 Introducing a birth-death model...

Branching phenomena: some very recent references

- ▶ Lorz, Mirrahimi and Perthame 2011: Hamilton-Jacobi technics.
- ▶ Wakano and Iwasa 2013: finite populations.
- ▶ Meleard and Mirrahimi 2015: a Lotka-Volterra system in a bounded domain.
- ▶ Ito and Sasaki 2016: adaptive dynamics, multi dimensional analysis.
- ▶ Gil, Hamel, Martin and Roques 2017: integro differential replicator mutator equation with "a deleterious kernel vs. fitness $W(x) = x$ ".

Our tool is the simple replicator-mutator equation (diffusive case).

Branching?

- ▶ Does a uni-modal population switch to multi-modal?
- ▶ If yes, how many phenotypical traits are selected?

These issues reduce to the shape of the ground state ϕ_0 solution of

$$-\sigma^2 \phi_0'' - W(x)\phi_0 = \lambda_0 \phi_0, \quad \phi_0 > 0.$$

Obstacles to branching

- ▶ $\sigma \gg 1 \implies$ Homogenization, the ground state is **uni-modal**.
- ▶ **Fitness W concave** \implies the ground state is **uni-modal**.
Ex: if $W(x) = -x^2$ then $\phi_0(x) = \frac{1}{\sqrt{\pi\sigma}} \exp\left(-\frac{x^2}{2\sigma}\right)$.
- ▶ **If the fitness has a unique global maximum**, the ground state is expected to remain **uni-modal**, whatever the values of σ .

When infinitely adapted phenotypes exist
 When phenotypes are confined
Branching or not
 Introducing a birth-death model...

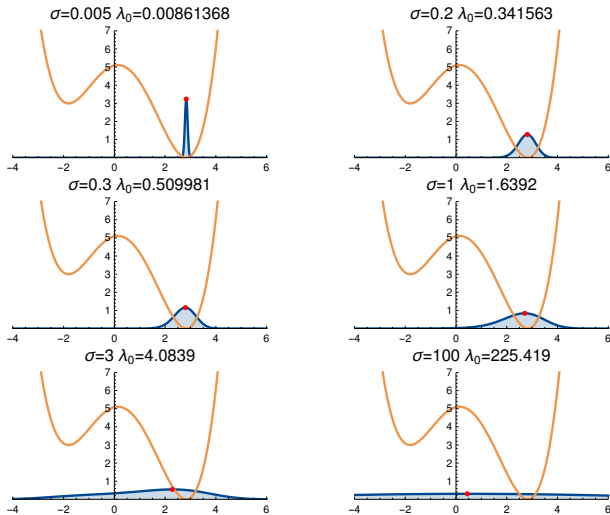


Figure: Ground state $\phi_0(\sigma)$, increasing parameter σ , in the case

$$-\mathcal{W}(x) = \frac{299}{2520}x^4 - \frac{233}{1260}x^3 - \frac{2971}{2520}x^2 + \frac{139}{420}x + \text{constant.}$$

The typical situation leading to branching

- ▶ A small σ .
- ▶ A symmetric fitness W reaching many times its global maxima.

When infinitely well-adapted phenotypes exist
 When phenotypes are confined
Branching or not
 Introducing a birth-death model...

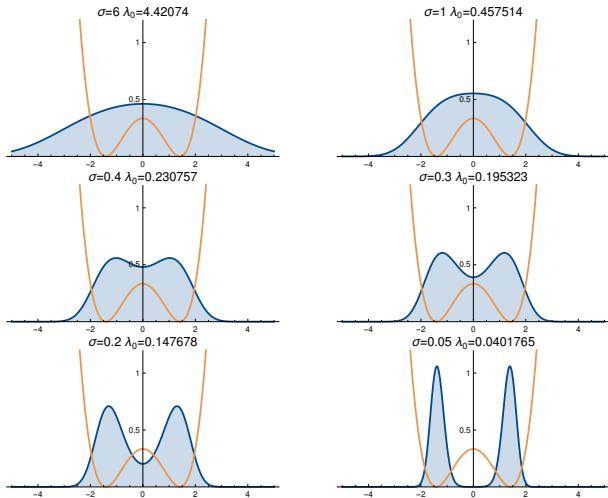


Figure: Ground state $\phi_0(\sigma)$, decreasing parameter σ , in the case $-\mathcal{W}(x) = \frac{1}{12}(x^2 - 2)^2$.

Branching from a centered initial data

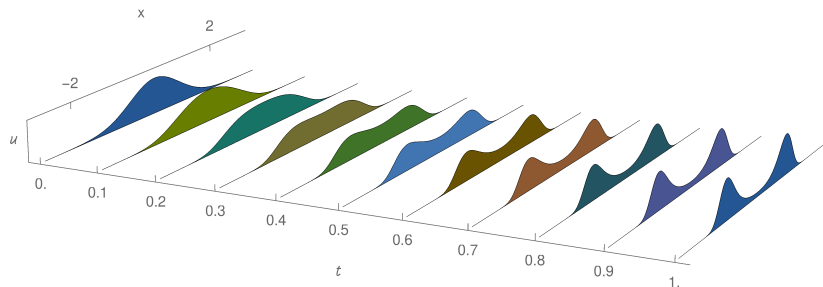


Figure: Numerical solution of the Cauchy problem, $-W(x) = (x^2 - 4)x^2$, $\sigma = 10^{-3}$.

Branching from a off-centered initial data

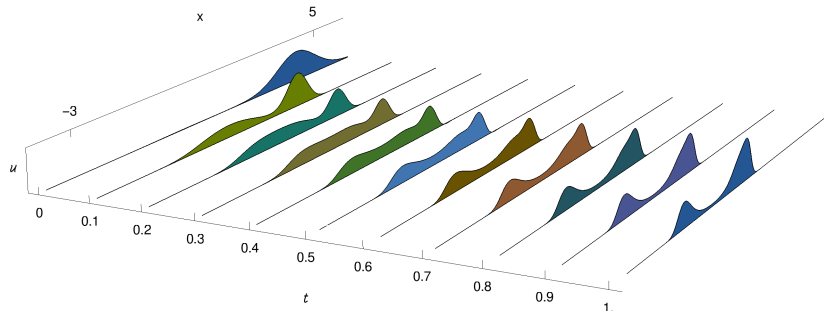


Figure: Numerical solution of the Cauchy problem, $-W(x) = (x^2 - 4)x^2$, $\sigma = 10^{-3}$.

On the number of selected phenotypes

When the fitness function (assumed to be symmetric) reaches its global maximum at $N \geq 2$ points, say $x_1 < \dots < x_N$, it is expected² that, as $\sigma \rightarrow 0$, the ground state concentrates in the x_i points where the biological niche is the widest since, at these points, individuals suffer less when their traits are slightly changed by mutations. Mathematically this means that ϕ_0 is p -modal where

$$p := \# \left\{ 1 \leq i \leq N : |\mathcal{W}''(x_i)| = \min_{1 \leq j \leq N} |\mathcal{W}''(x_j)| \right\}.$$

²See Djidjou-Demasse, Ducrot and Fabre 2017 for related observations in the context of evolutionary epidemiology.

Number of modes in the “narrow-wide-narrow” situation

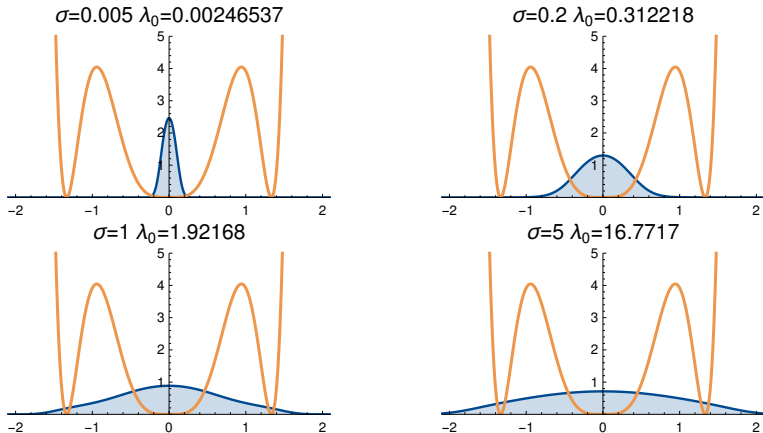


Figure: Ground state $\phi_0(\sigma)$, increasing parameter σ .

But...

As the bifurcation parameter σ increases, it may happen that, because of the position of the wells, the number of global maxima of the population distribution varies.

Hence, the combination of the position of the wells of the potential and of the value of the parameter σ is of great importance on the number of emerging phenotypes.

Number of modes in the “wide-narrow-wide” situation

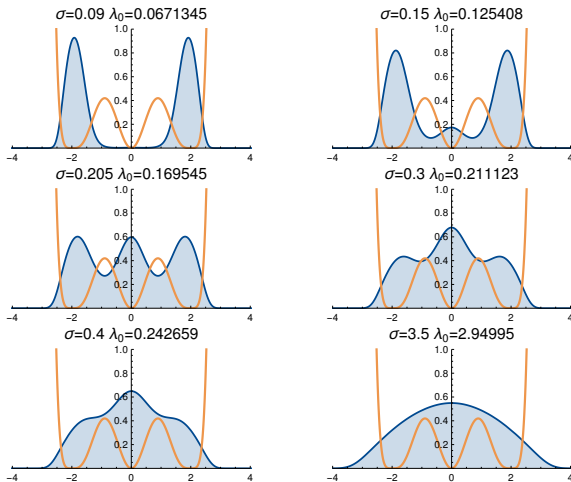


Figure: Ground state $\phi_0(\sigma)$, increasing parameter σ .

Contents

- 1 When infinitely well-adapted phenotypes exist
- 2 When phenotypes are confined
- 3 Branching or not
- 4 Introducing a birth-death model...

Mutations and births are coupled

Indeed, mutations occur during replication of DNA.

The mutation rate should evolve as the birth rate changes, via

▶ a “mean field approach” ...

or

▶ a “refined approach” ...

Mean field approach: a toy model ³

The diffusion coefficient is “socially determined”:

$$\partial_t u = \bar{x}(t) \partial_{xx} u + u(x - \bar{x}(t)).$$

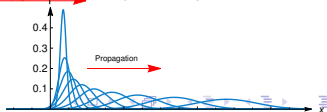
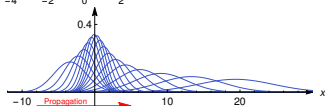
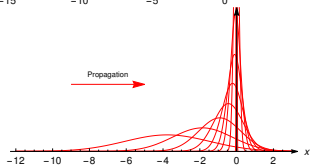
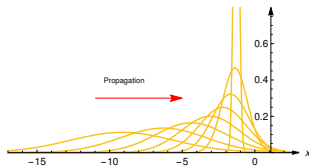
Theorem (A. and Veruete, 2019)

Combining a “CGF approach” and a “change of unknown approach” we reach the solution implicitly/explicitly. In particular, acceleration and flattening occur exponentially (for initial datum lighter than any exponential).

³coming from $\partial_t u = \sigma^2 \partial_{xx} u + u \frac{x - \bar{x}(t)}{\bar{x}(t)}$, see Zadorin et Rondelez (2017).

When infinitely well-adapted phenotypes exist
When phenotypes are confined
Branching or not
Introducing a birth-death model...

Various mathematical outcomes



Ongoing works and projects with

- ▶ Guillaume Martin (ISEM, Montpellier)
- ▶ Alvaro Mateos-González (IMAG, Montpellier)
- ▶ Lionel Roques (INRA, Avignon)

Mean field approach: introducing a birth model

$$\partial_t u = \sigma^2 (b_{max} - \overline{x^2}(t)) \partial_{xx} u + u(-x^2 + \overline{x^2}(t)),$$

where the fitness

$$W(x) = b(x) = -x^2 \text{ is maximal at } x_{opt} = 0.$$

On the other hand, if the population concentrates at x_{opt} the mutations (which, from x_{opt} , are all deleterious) are maximal.

► The mutation-selection equilibrium should be altered (in position and shape) by the influence of birth on mutations...

A birth-death ("local") model

$$\partial_t u = \sigma^2 \partial_{xx} (\varphi(b(x)) u) + u ((b - d)(x) - \overline{b - d}(t))$$

where the birth rate is maximal at some $x = x_{birth}^{opt}$, while the death rate is minimized at some $x = x_{death}^{opt}$, and where $\varphi(b(x))$ is maximal around $x = x_{birth}^{opt}$.

- ▶ Equilibrium? Position? Shape?...
- ▶ Birth strategy? Death strategy? Evolutionary compromise?⁴...
- ▶ Adaptive answers to stresses that reduce birth? that increase death?...

⁴cf analogous issue in evolutionary epidemiology.

When infinitely well-adapted phenotypes exist
When phenotypes are confined
Branching or not
Introducing a birth-death model...

Thanks for your attention.