Stochastic modeling and asymptotic analysis of a population of microorganisms with competition and horizontal transfer II

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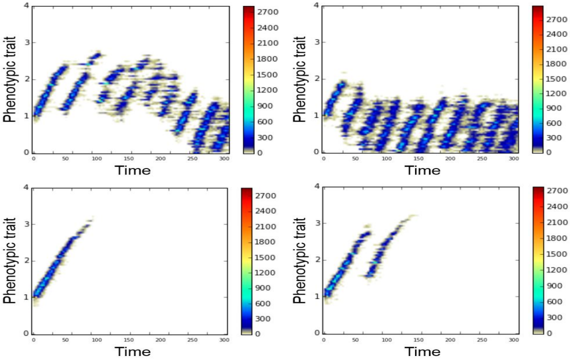
Biological context

- Horizontal transfer (HT) is recognized as a major process in the evolution and adaptation of populations, especially for micro-organisms (e.g. E. coli)
  - A main role in the evolution, maintenance, and transmission of virulence.
  - The primary reason for bacterial antibiotic resistance.
  - Transfer of CRISPR-Cas9 for fighting against virulent or antibiotic resistant bacteria (Duportet, El Karoui)
- Plasmid transfer: having a plasmid is costly
- Purpose here: describe the joint evolution of trait distribution and population size

1. Tenaillon et al., *Nature Reviews*, 2010.
2. Novozhilov et al., *Molecular Biol. and Evol.*, 2005.
3. Tazzyman, Bonhoeffer, *TPB*, 2013.
4. Baumdicker, Pfaffelhuber, *EJP*, 2014.
5. Billiard et al., *J. Theor. Biol.*, 2016.

Motivation: understand these simulations



Evolutionary suicide or cyclic evolutionary dynamics?
Mutations are not rare otherwise evolutionary suicide (Sylvie's talk)

1. Simulations by L. Fontaine and S. Krystal, 2016.
2. Billiard et al., *JEMS*, 2018.

Transfer modeling

- Quantitative trait $x \geq 0$ linked to the number of plasmids, e.g. modeling the effect of CRISPR-Cas9 on the survival of bacteria
- Transfer of all plasmids: for $y < x$,

$$(x, y) \rightarrow (x, x)$$

- Frequency dependent rate ($\beta = 0$ in Sylvie's talk)

$$\frac{\tau}{N(t)} N_x(t) N_y(t).$$

- Sylvie's talk: in a population with 2 traits x and y, the system of ODE for the densities (n_x, n_y) writes (with $n = n_x + n_y$ and $q = n_x/n$)

$$\begin{aligned}
\frac{dn}{dt} =& n \left(q\, r(y) + (1-q)\, r(x) - Cn\right) \\
\frac{dq}{dt} =& q\,(1-q) \Big(r(y) - r(x) + \tau\Big).
\end{aligned}$$

- Invasion implies fixation

Toy model [Durrett, Mayberry, 2011 and Bovier, Coquille, Smadi, 2018]

- Initial population size proportional to K.
  We denote by N_t the size of the population at time t
- Population structured by a trait

$$x = k\delta \in [0,4], \qquad k \in \{0, \dots \lfloor \frac{4}{\delta} \rfloor\}.$$

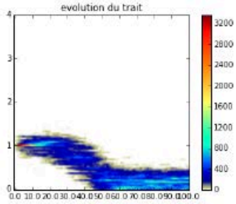
  We denote by $N_x(t)$ the size of the population with trait x
- **Births**: rate $b(x) = 4 - x$
  - With probability $K^{-\alpha}$ with $0 < \alpha < 1$: mutant with trait $x + \delta$.
  - With probability $1 - K^{-\alpha}$: clone.
- **Deaths**: rate $d(x) = 1 + C\dfrac{N_t}{K}$
- **Horizontal transfers**: unilateral conjugation, frequency-dependent transfer rate: $(x,y) \to (x,x)$ with rate

$$\tau(x,y,N) = \frac{\tau}{N}\mathbb{1}_{x>y}$$

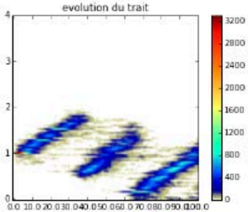
- **Initial population sizes**:

$$N_0 = \lfloor \frac{3K}{C} \rfloor, \quad \lfloor K^{1-\alpha} \rfloor, \dots, \lfloor K^{1-\ell\alpha} \rfloor, \dots, 0, \dots 0.$$

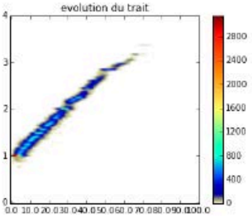
Simulations



$\tau = 0.2$

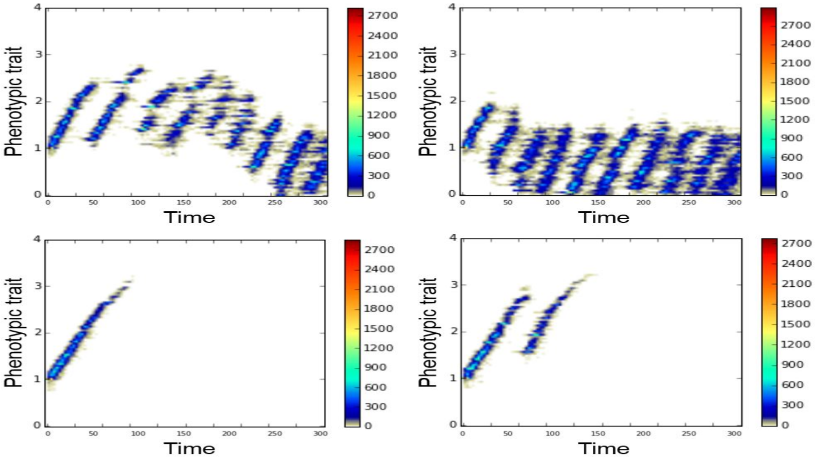


$\tau = 0.6$



$\tau = 1$

Simulations: $\tau = 0.7$



First properties of the toy model

- In absence of mutation, a population of only trait x with initial condition K has a size that converges, when $K \to +\infty$, to the solution of:

$$\dot{n}(t) = n(t)(3 - x - Cn(t)),$$

whose unique positive stable equilibrium is

$$\bar{n}(x) = \frac{3 - x}{C}.$$

- The invasion fitness of a mutant y in the population with trait x at equilibrium is:

$$\begin{aligned} S(y; x) =& (4 - y) - \left(1 + \frac{(3 - x)K}{C}\frac{C}{K}\right) + \tau \mathbb{1}_{x<y} - \tau \not\mathbb{1}_{y<x} \\ =& x - y + \tau \operatorname{sign}(y - x). \end{aligned}$$

Exponents in birth-death processes

- Possible resurgences: need to follow small populations, of size K^β, on timescales $\log K$

$$\text{Rk: if } N \sim CK^\beta, \qquad \text{then} \qquad \beta \approx \frac{\log(1+N)}{\log K}.$$

- A small population with trait y in a resident population of trait x (say $y < x$) behaves as a branching process with rates:

$$(4-y), \qquad \left(1 - \frac{CN_x(t)}{K}\right) - \tau.$$

Lemma

Consider a linear birth-death (branching) process $(Z_t)_{t\geq 0}$ with rates b and d, starting from an initial condition of size K^β (with $\beta \leq 1$). Then,

$$\left(\frac{\log(1+Z^K_{s\log K})}{\log K}, s \geq 0\right) \xrightarrow[K\to+\infty]{} \big((\beta + s(b-d)) \vee 0, s \geq 0\big),$$

uniformly on any $[0,T]$, in probability.

Exponents in birth-death processes with immigration

A small population with trait y in a resident population of trait x, with $y = x + \delta$, behaves as a branching process with rates:

$$(4-y)+\tau, \qquad \left(1-\frac{CN_x(t)}{K}\right).$$

But y may also receive a contribution from x due to mutations:

$$N_x(t)K^{-\alpha}.$$

Last lemma: $N_x(t\log K)$ is expected to behave like K^{c+as} for some constants $a, c \in \mathbb{R}$.

Lemma

We consider the assumptions of the previous lemma + add immigration at rate $K^c e^{as}$, for $a, c \in \mathbb{R}$.
Then,

$$\left(\frac{\log(1+Z^K_{s\log K})}{\log K}, s\geq 0\right) \xrightarrow[K\to+\infty]{} ((\beta+s(b-d))\vee(c+as), s\geq 0),$$

uniformly on any $[0,T]$ and in probability.

Case of three traits (1)

Three traits: 0, δ, 2δ. Assume that

$$\delta < \tau < 2\delta < 3 < 4 < 3\delta.$$

Also, assume that $0 < \alpha < 1$

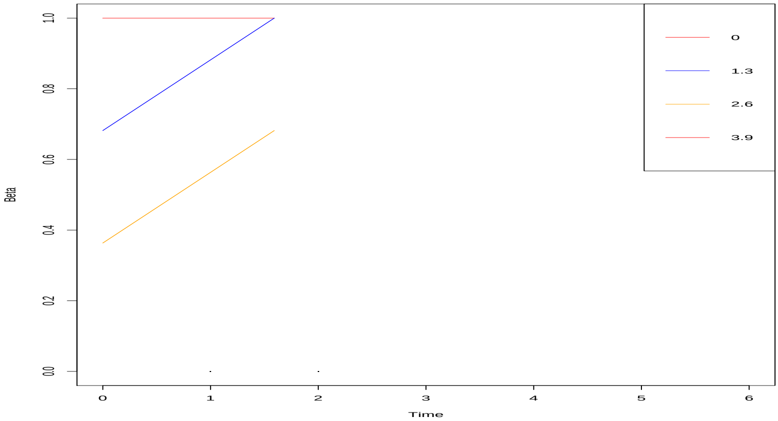
At time $t_0 = 0$:

- **Trait 0**:
  - $\beta_0(0) = 1$
  - $S_0(0) = 0,\ N_0(0) = \frac{3K}{C}$
- **Trait** δ:
  - $\beta_1(0) = 1 - \alpha$
  - $S_1(0) = \tau - \delta > 0$

$$\beta_1(t) = (1-\alpha) + (\tau - \delta)t \qquad (\geq 1 - \alpha)$$

- **Trait** 2δ:
  - $\beta_2(0) = 1 - 2\alpha$
  - $S_2(0) = \tau - 2\delta < 0 \quad \rightarrow \quad \beta_2(t) = (1 - 2\alpha) + (\tau - 2\delta)t$
  - But there are mutations from trait δ:

$$\beta_2(t) = (1-2\alpha) + (\tau - \delta)t \qquad (\geq 1 - \alpha)$$



$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$

Case of three traits (2)

At time $t_1 = \frac{\alpha}{\tau-\delta}$, the traits 0 and δ both have exponent 1
$\rightsquigarrow$ invasion implies fixation

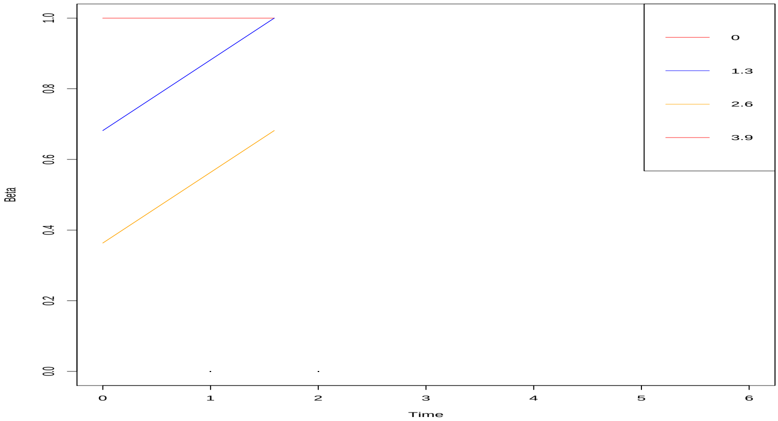
- **Trait 0**:
  - $\beta_0(t_1) = 1$
  - $S_0(t_1) = \delta - \tau < 0$,

$$\beta_0(t) = 1 + (\delta - \tau)(t - t_1)$$

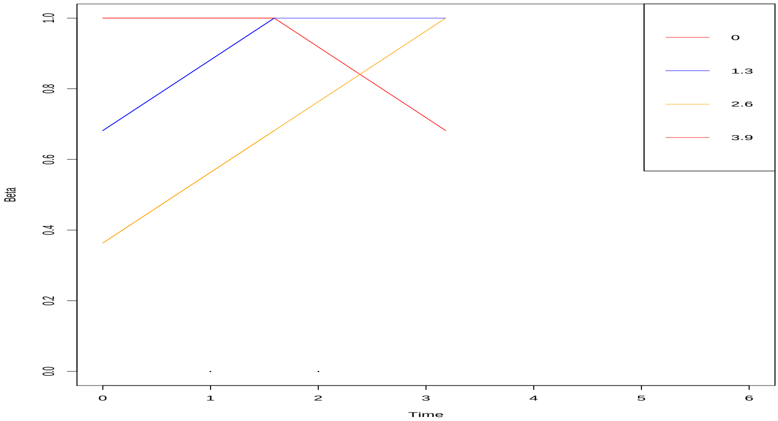
- **Trait** δ:
  - $\beta_1(t_1) = 1$
  - $S_1(t_1) = 0,\ N_1(t_1) = \frac{(3-\delta)K}{C}$

- **Trait** 2δ:
  - $\beta_2(t_1) = 1 - \alpha$
  - $S_2(t_1) = \tau - \delta > 0 \quad \rightarrow \quad \beta_2(t) \geq 1 - \alpha$

$$\beta_2(t) = (1 - \alpha) + (\tau - \delta)(t - t_1)$$



$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$



$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$

Case of three traits (3)

At time $t_2 = \frac{\alpha}{\tau-\delta} + \frac{\alpha}{\tau-\delta}$:

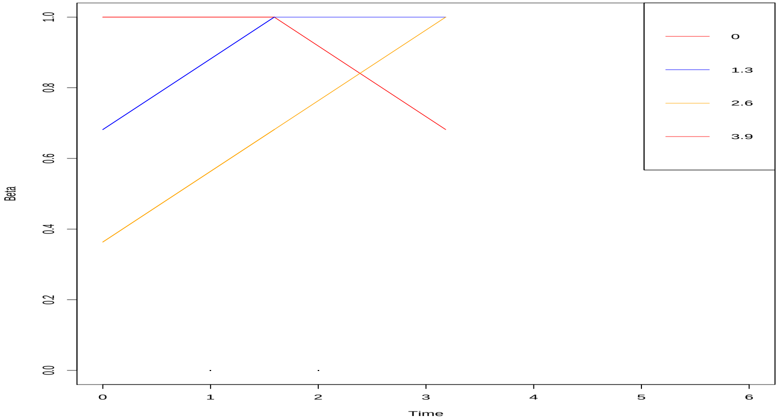
- **Trait 0:**
  - $\beta_0(t_2) = 1 - \alpha$
  - $S_0(t_2) = 2\delta - \tau > 0$,

$$\beta_0(t) = (1-\alpha) + (2\delta - \tau)(t - t_2)$$

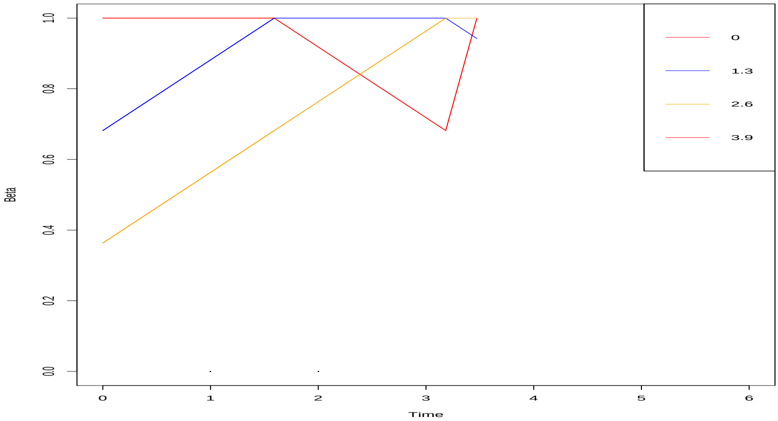
- **Trait** δ:
  - $\beta_1(t_1) = 1$
  - $S_1(t_2) = \delta - \tau < 0$,

$$\beta_1(t) = \max\left[1 + (\delta - \tau)(t - t_2)\ ,\ (1-2\alpha) + (2\delta - \tau)(t - t_2)\right]$$

- **Trait** 2δ:
  - $\beta_2(t_2) = 1$
  - $S_2(t_2) = 0$



$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$



$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$

Case of three traits (4)

Assume that $0 < \tau - \delta < 2\delta - \tau$.

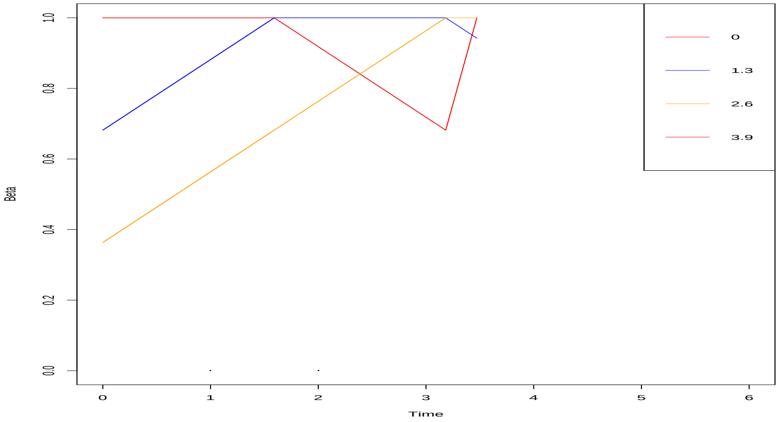
At time $t_3 = \frac{\alpha}{\tau-\delta} + \frac{\alpha}{\tau-\delta} + \frac{\alpha}{2\delta-\tau}$:

- **Trait 0**:
  - $\beta_0(t_3) = 1$
  - $S_0(t_3) = 0$,
- **Trait** δ:
  - $\beta_1(t_3) = 1 + (\delta - \tau)\frac{\alpha}{2\delta-\tau} > 1 - \frac{\alpha}{2}$
  - $S_1(t_3) = \tau - \delta > 0$,

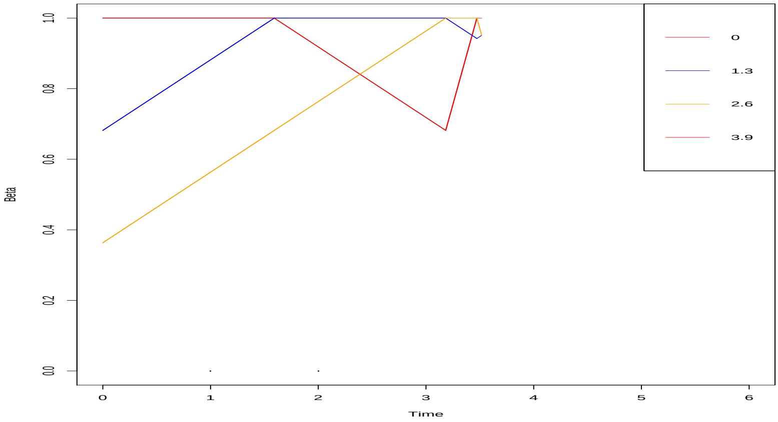
$$\beta_1(t) = 1 + \frac{\delta - \tau}{2\delta - \tau}\alpha + (\tau - \delta)(t - t_3)$$

- **Trait** 2δ:
  - $\beta_2(t_3) = 1$
  - $S_2(t_3) = \tau - 2\delta < 0$

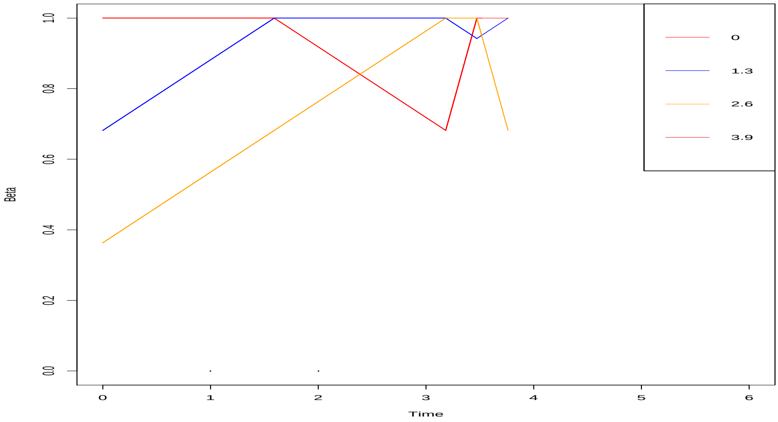
$$\beta_2(t) = \max\left[1 + (\tau - 2\delta)(t - t_3)\ ,\ 1 - \frac{\delta\alpha}{2\delta - tau} + (\tau - \delta)(t - t_3)\right]$$



$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$



$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$



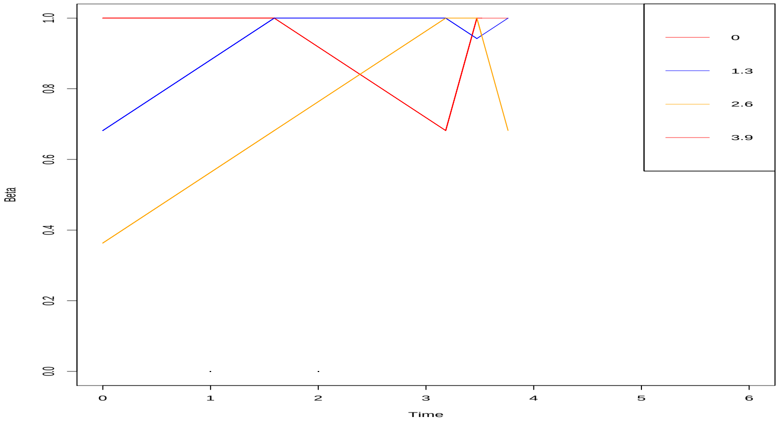
$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$

Case of three traits (5)

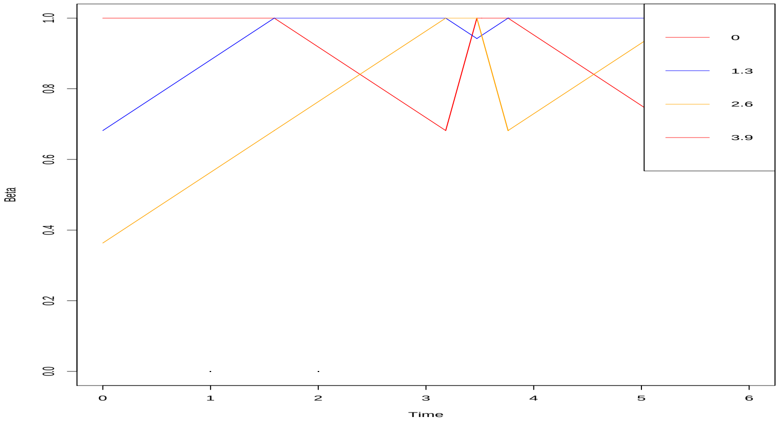
At time $t_4 = \frac{\alpha}{\tau-\delta} + \frac{\alpha}{\tau-\delta} + \frac{\alpha}{2\delta-\tau} + \frac{\alpha}{2\delta-\tau}$:

- **Trait 0**:
  - $\beta_0(t_4) = 1$
  - $S_0(0) = \delta - \tau < 0$,
- **Trait** δ:
  - $\beta_1(t_4) = 1$
  - $S_1(t_4) = 0$
- **Trait** 2δ:
  - $\beta_2(t_4) = 1 - \alpha$
  - $S_2(t_4) = \tau - \delta > 0$

Same situation as at time t_1.

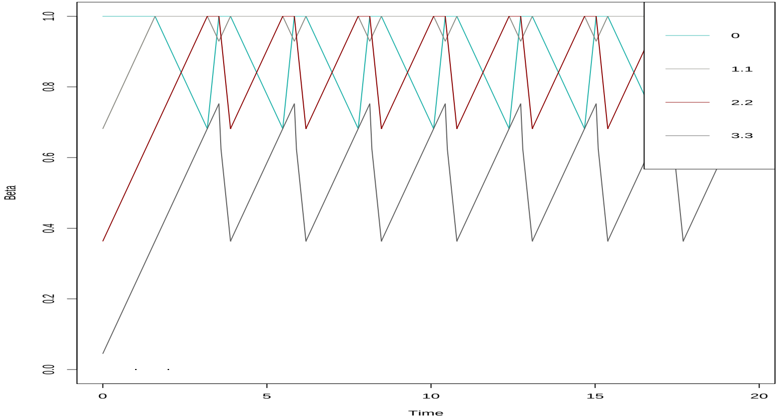


$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$



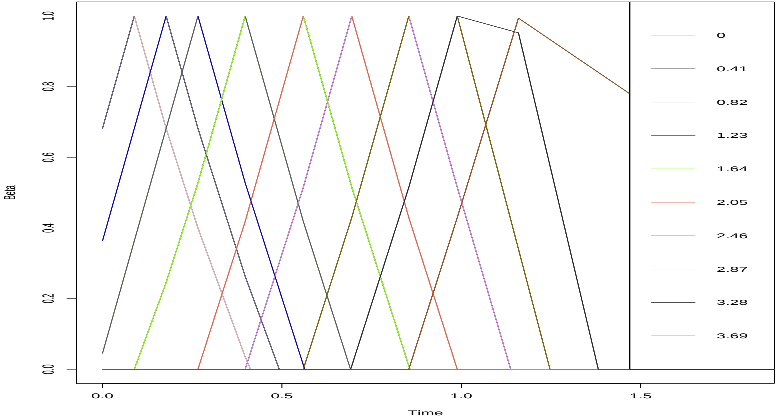
$$\delta = 1.3,\ \alpha = 0.32,\ \tau = 1.5.$$

Asymptotic behavior of the Toy model (1)



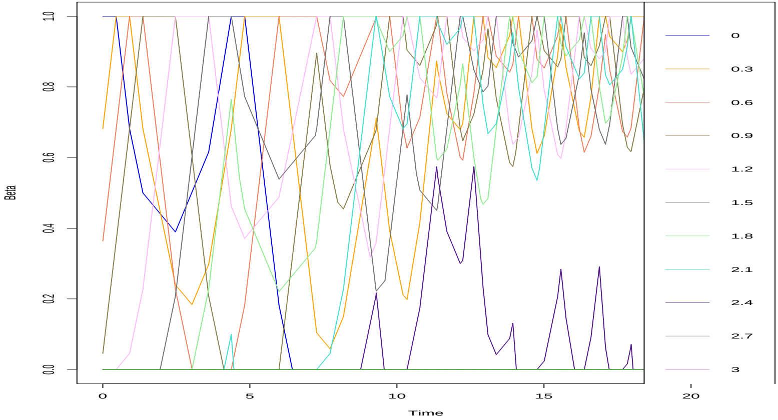
$$\delta = 1.1,\ \alpha = 0.32,\ \tau = 1.3.$$

Asymptotic behavior of the Toy model (2)



$$\delta = 0.41,\ \alpha = 0.32,\ \tau = 4.$$

Asymptotic behavior of the Toy model (3)



$$\delta = 0.3,\ \alpha = 0.32,\ \tau = 1.$$

Main result

For all $k \in \{0, 1, \dots, \lfloor 4/\delta \rfloor\}$,

$$\left(\frac{\log(1 + N_{k\delta}(s \log K))}{\log K}, \, s \geq 0 \right) \xrightarrow[K \to +\infty]{} (\beta_k(s), s \geq 0)$$

uniformly on any $[0, T]$, in probability,
where β_k is continuous, piecewise affine and solution to a system of ODE with $\beta_k(0) = (1 - k\alpha) \vee 0$
and where the changes of slopes of the exponents $(\beta_0(s), \dots, \beta_{\lfloor 4/\delta \rfloor}(s))$ may occur at times where

- a new exponent reaches 1 $\rightsquigarrow$ change of resident trait)
- a new exponent hits 0 $\rightsquigarrow$ extinction of a trait
- the slope of an exponent which was driven by its fitness becomes driven by mutations

Main result: system of ODE for the exponents

- Assume that the trait $x = \ell^\star \delta$ is the resident with $\beta_x(0) = 1$ (for sake of simplicity of the presentation)
- Compute the fitnesses $S(y;x)$ for all the traits $y = \ell\delta$.

$$\dot{\beta}_\ell(t) = \Sigma^0_\ell(t),$$

where $\Sigma^0_\ell(t) = 0$ if $\beta_\ell(t) = 0$ and $\beta_{\ell-1}(t) \leq \alpha$, and else:

$$\Sigma^0_\ell(t) = \max\Big\{S((\ell-i)\delta; \ell^*(t)\delta); 0 \leq i \leq \ell \text{ s.t. } \forall 1 \leq j \leq i,\ \beta_{\ell-j}(t) = \beta_\ell(t) + j\alpha\Big\}$$

- deduce the next time of change of slopes:

$$t_{k+1} = t_k + \left(\inf\left\{\frac{1-\beta_\ell(t_k)}{\Sigma^0_\ell(t_k)}; \ell \neq \ell^*_k \text{ s.t. } \Sigma^0_\ell(t_k) > 0\right\}\right.$$
$$\wedge \inf\left\{\frac{\beta_\ell(t_k)}{-\Sigma^0_\ell(t_k)}; \ell \text{ s.t. } \beta_\ell(t_k) > 0 \text{ and } \Sigma^0_\ell(t_k) < 0\right\}$$
$$\wedge \inf\left\{\frac{\beta_\ell(t_k) - \beta_{\ell-1}(t_k) + \alpha}{\Sigma^0_{\ell-1}(t_k) - S(\ell\delta, \ell^*_k\delta)\mathbb{1}_{\beta_\ell(t_k)>0}}; \ell \neq \ell^*_k \text{ s.t. } \beta_\ell(t_k) > \beta_{\ell-1}(t_k) - \alpha\right.$$
$$\left.\left.\text{and } \Sigma^0_{\ell-1}(t_k) - S(\ell\delta, \ell^*_k\delta)\mathbb{1}_{\beta_\ell(t_k)>0} > 0\right\}\right).$$

Evolutionary suicide or resurgence of trait 0? [in progress]

- The full classification of the behaviors of the system can be done in the case of three traits
  $\rightsquigarrow$ either convergence to a periodic solution or evolutionary suicide
- For a large number of traits, criteria for the existence of periodic dynamics or evolutionary suicide are unclear
- However, it is possible to give explicit criteria for the first resurgence of trait 0

"Diagonal" behavior of exponents

Assume $\tau > \delta$. For $s \le t_1 = \frac{\alpha}{\tau-\delta}$,

- $\beta_0(s) = 1$,
- $\beta_k(s) = (1 - k\alpha + (\tau-\delta)s) \vee 0$ for all $k \ge 1$

For $t_1 \le s \le t_2 = \frac{2\alpha}{\tau-\delta}$,

- $\beta_0(s) = 1 - (\tau-\delta)(s - t_1)$,
- $\beta_1(s) = 1$,
- $\beta_k(s) = (1 - (k-1)\alpha + (\tau-\delta)(s-t_1)) \vee 0$ for all $k \ge 2$

For $t_2 \le s \le t_3 = \frac{3\alpha}{\tau-\delta}$,

- $\beta_0(s) = 1 - (\tau-\delta)(t_2 - t_1) - (\tau - 2\delta)(s - t_2)$,
- $\beta_1(s) = 1 - (\tau-\delta)(s - t_2)$,
- $\beta_2(s) = 1$,
- $\beta_k(s) = (1 - (k-2)\alpha + (\tau-\delta)(s-t_1)) \vee 0$ for all $k \ge 3$

Dynamics of $\beta_0(s)$

We obtain

$$\begin{aligned}\beta_0(t_\ell) &= 1 - \frac{\alpha}{\tau-\delta}\left(\tau-\delta+\tau-2\delta+\ldots+\tau-(\ell-1)\delta\right) \\ &= 1 - \frac{\alpha(\ell-1)}{\tau-\delta}\left(\tau - \frac{\ell-2}{2}\delta\right) \qquad (1)\end{aligned}$$

until

- either $\beta_0(s)$ hits 0 (extinction of trait 0) or 1 (resurgence of trait 0), i.e. the above formula takes a value out of $(0,1)$
- or the resident population becomes unable to survive, i.e. until $\ell = \lceil \frac{3}{\delta} \rceil$

The minimal value in (1) is reached for $\ell = \ell^* := \lfloor \frac{\tau}{\delta} \rfloor + 1$

Criteria for resurgence or evolutionary suicide

Theorem

- *If* $1 - \frac{\alpha(\ell^* - 1)}{\tau - \delta}\left(\tau - \frac{\ell^* - 2}{2}\delta\right) > 0$ *and* $\ell^* < \lfloor \frac{\tau}{\delta} \rfloor + 1$, *there is resurgence of trait* 0.

  [open question: is there a periodic solution?]
- *If* $1 - \frac{\alpha(\ell^* - 1)}{\tau - \delta}\left(\tau - \frac{\ell^* - 2}{2}\delta\right) < 0$ *and* $\ell^* < \lfloor \frac{\tau}{\delta} \rfloor + 1$, *the trait* 0 *gets lost and there is evolutionary suicide*
- *If* $\ell^* \geq \lfloor \frac{\tau}{\delta} \rfloor + 1$, *there will be apparent extinction of the population after time* $\lceil \frac{3}{\delta} \rceil \alpha / (\tau - \delta)$,

  but the exponent of trait 0 will start increase again after this time, leading to a resurgence of the population.

  However, there will be resurgence of trait 0 only if β_0 *is the first exponent to reach level 1 after this time or if the first resurging trait is far enough from 0*

  $\rightsquigarrow$ *case not fully understood (yet?)*