Stochastic dynamics of a population of microorganisms with competition and horizontal transfers

TRAN Viet Chi
Labo P. Painlevé, Université de Lille, France

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Motivation (1)

★ 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 (2): Case of study

★ Conjugation

$$(x, y) \to (x, x)$$

★ Frequency dependent rate

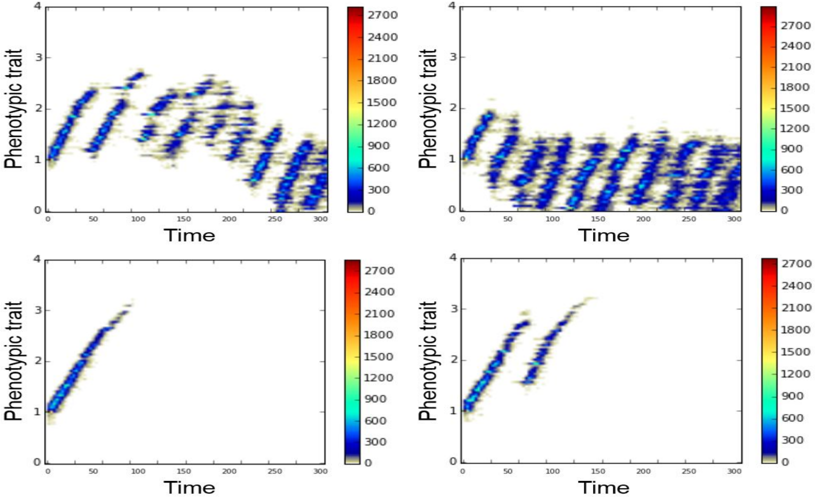
$$\frac{\tau}{N(t)} N_x(t) N_y(t).$$

Prop: Consider a population with 2 traits x and y. For a constant competition kernel and a frequency dependent conjugation rate, there is invasion implies fixation. □

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

1. Billiard et al., *JEMS*, 2018.

Motivation (3): Simulations



Importance of the small fluctuations?
Mutations are not rare.

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

Toy model

★ 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 $K^{-\alpha}$: mutant with trait $x + \delta$.
- With probability $1 - K^{-\alpha}$: clone.

★ **Deaths**:

$$d(x) = 1 + C\frac{N_t}{K}$$

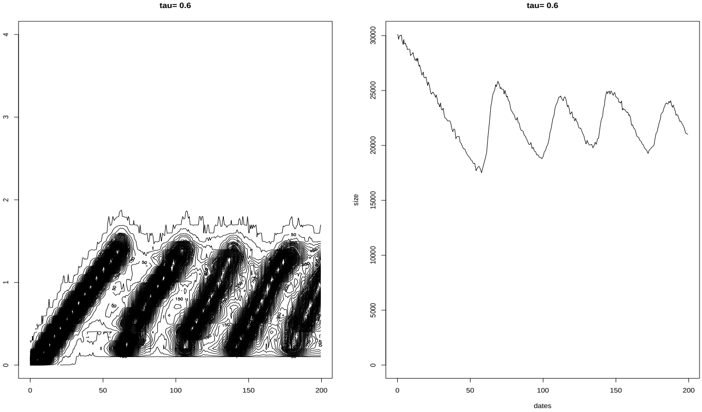
★ **Horizontal transfers**: unilateral conjugation, frequency-dependent transfer rate: $(x, y) \to (x, x)$ with rate

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

★ **Initial population sizes**:

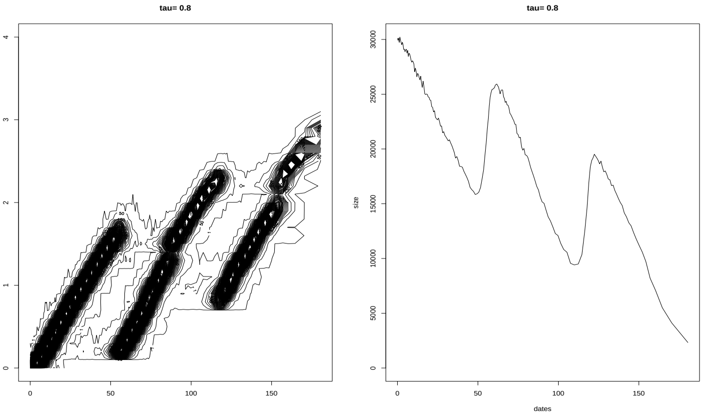
$$N_0 = \lfloor\frac{3K}{C}\rfloor, \quad \lfloor K^{1-\alpha}\rfloor, \dots, \lfloor K^{1-\ell\alpha}\rfloor, \dots, 0, \dots 0.$$

Simulations of the toy model - IBM (1)



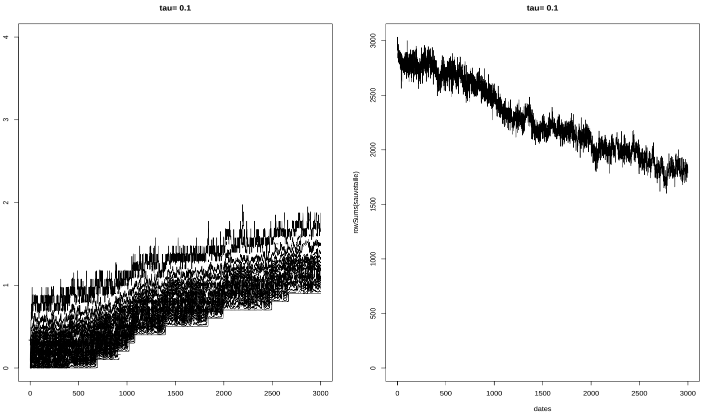
$$K = 10000,\ \delta = 0.1,\ \alpha = 0.5,\ \tau = 0.6$$

Simulations of the toy model - IBM (2)



$$K = 10000,\ \delta = 0.1,\ \alpha = 0.5,\ \tau = 0.8$$

Simulations of the toy model - IBM (3)



$$K = 1000,\ \delta = 0.1,\ \alpha = 0.5,\ \tau = 0.1$$

First properties of the toy model

★ Letting $K \to +\infty$, we obtain in the limit a population with only trait 0, whose size is governed by:

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

★ 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:

$$\begin{aligned} S(y; x) =& (4 - y) - \left(1 + \frac{(3 - x)K}{C}\frac{C}{K}\right) + \tau \mathbf{1}_{x<y} - \tau \mathbf{1}_{y<x} \\ =& x - y + \tau \text{sign}(y - x). \end{aligned}$$

Exponents in birth-death processes

★ Need to follow small populations, of size K^β. On timescales $\log K$. This explains possible resurgences.

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

★ 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 birth-death 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,

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

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

1. Durrett and Mayberry, *AAP*, 2011.
2. Bovier, Coquille, Smadi, 2018.

Exponents in birth-death processes with immigration

★ A small population with trait y in a resident population of trait x, with $y > x$, behaves as a branching process with rates:

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

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

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

★ **Lemma**: we consider the assumptions of the previous lemma + add immigration at rate $K^c e^{as}$, for $a, c \in \mathbb{R}$.

Then,

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

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 $0 < \alpha < 1$.

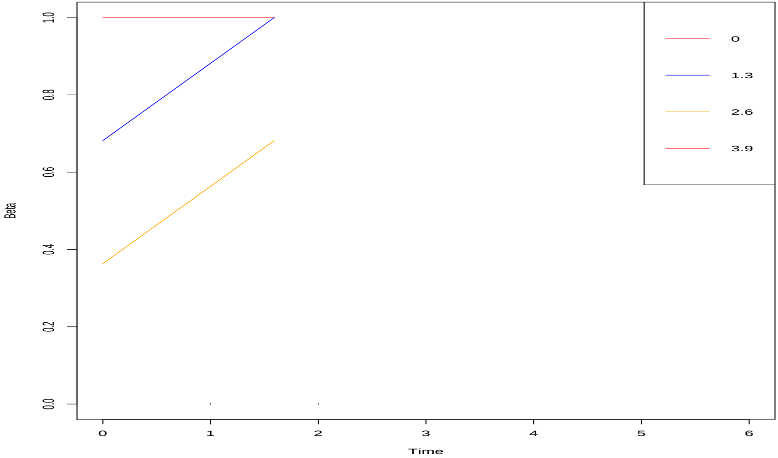
★ At time $t_0 = 0$:

- **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:

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



$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$

Case of three traits (2)

★ At time $t_1 = \frac{\alpha}{\tau-\delta}$:

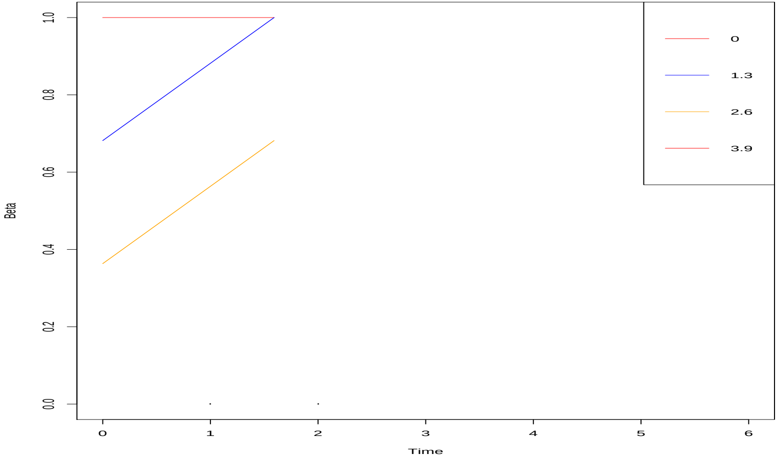
- **Trait 0**:
  - $\beta_0(t_1) = 1$
  - $S_0(t_1) = \delta - \tau < 0$,

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

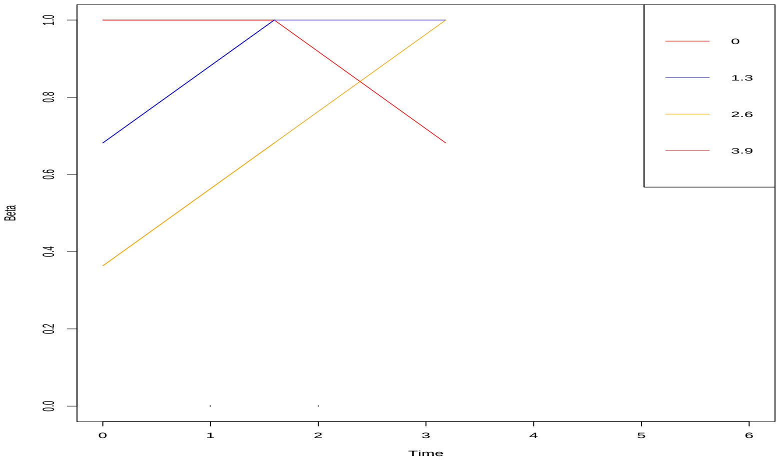
- **Trait** δ:
  - $\beta_1(t_1) = 1$
  - $S_1(t_1) = 0,\ N_1(t_1) = \frac{(3-\delta)K}{C}$

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

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



$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$



$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$

Case of three traits (3)

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

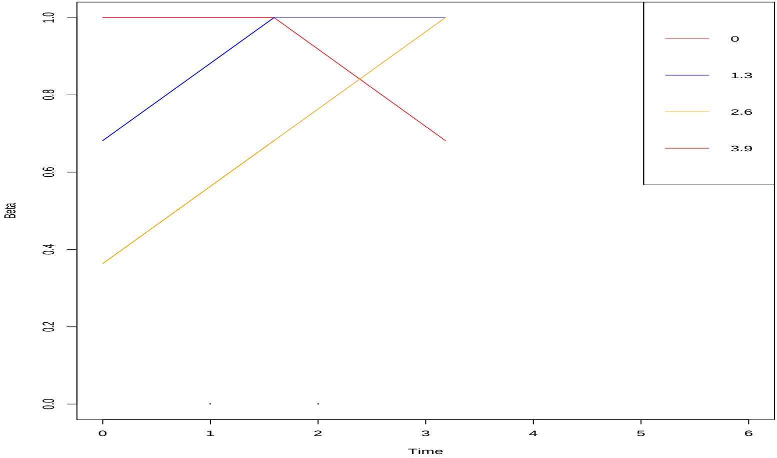
- **Trait 0**:
  - $\beta_0(t_2) = 1 - \alpha$
  - $S_0(t_2) = 2\delta - \tau > 0$,

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

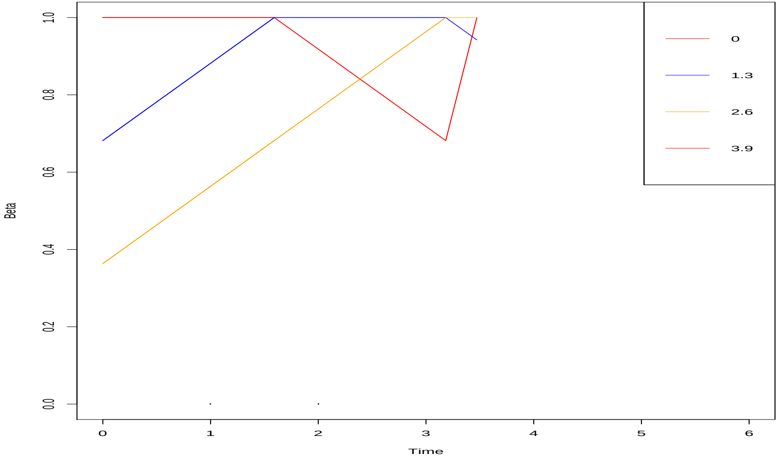
- **Trait** δ:
  - $\beta_1(t_1) = 1$
  - $S_1(t_2) = \delta - \tau < 0$,

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

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



$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$



$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$

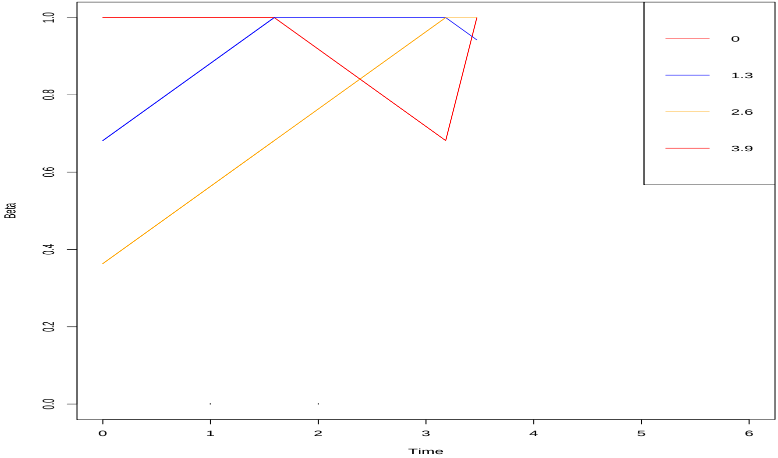
Case of three traits (4)

- ★ 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:
    - $\beta_1(t_3) = 1 + (\delta - \tau)\frac{\alpha}{2\delta-\tau} \qquad > 1 - \frac{\alpha}{2}$
    - $S_1(t_3) = \tau - \delta > 0$,

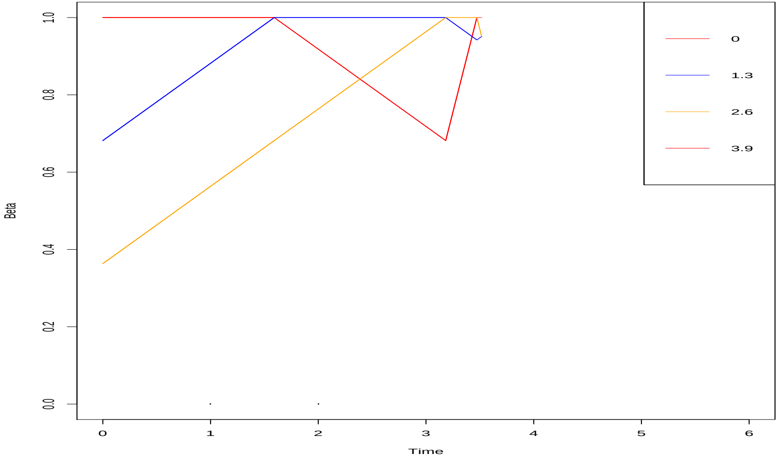
$$\beta_1(t) = 1 + \frac{\delta - \tau}{2\delta - \tau}\alpha + (\tau - \delta)(t - t_3)$$

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

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



$$\delta = 1.3, \ \alpha = \frac{1}{\pi}, \ \tau = 1.5.$$



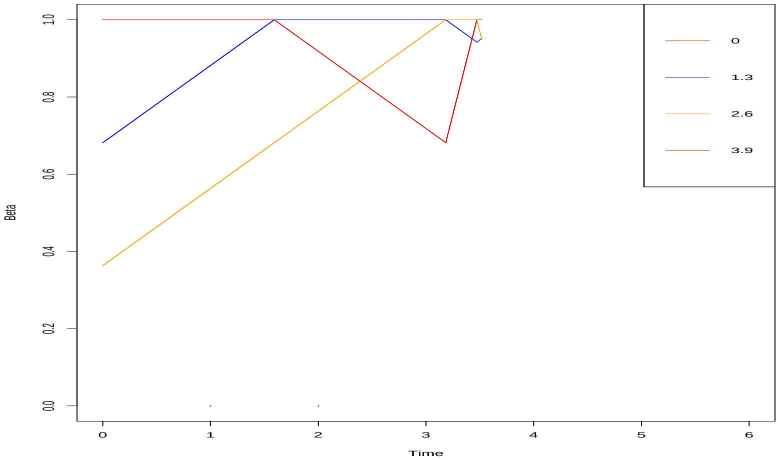
$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$

Case of three traits (5)

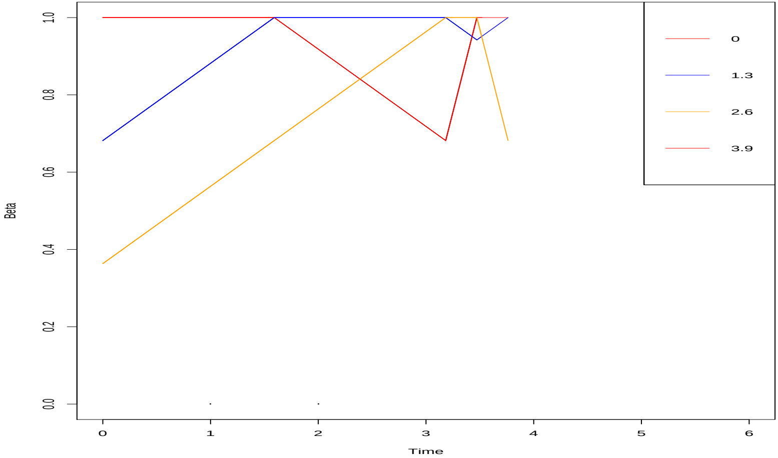
★ At time $t_4 = \frac{\alpha}{\tau-\delta} + \frac{\alpha}{\tau-\delta} + \frac{\alpha}{2\delta-\tau} + \frac{\alpha}{2\delta-\tau}$:

- **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:
  - $\beta_2(t_4) = 1 - \alpha$
  - $S_2(t_4) = \tau - \delta > 0$

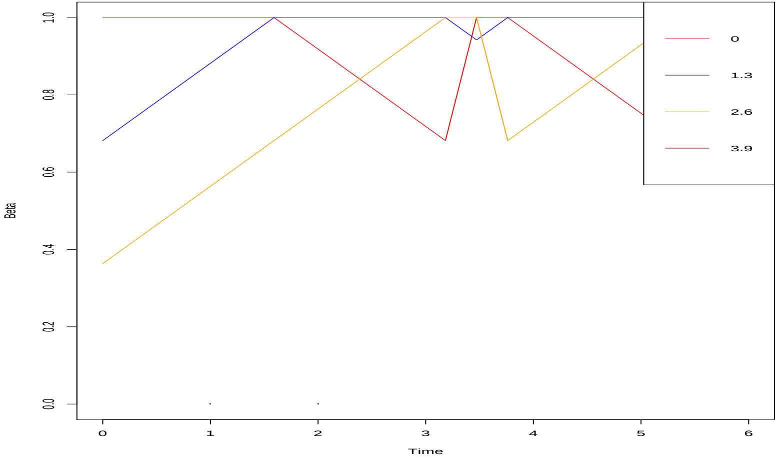
Same situation as in t_1.



$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$

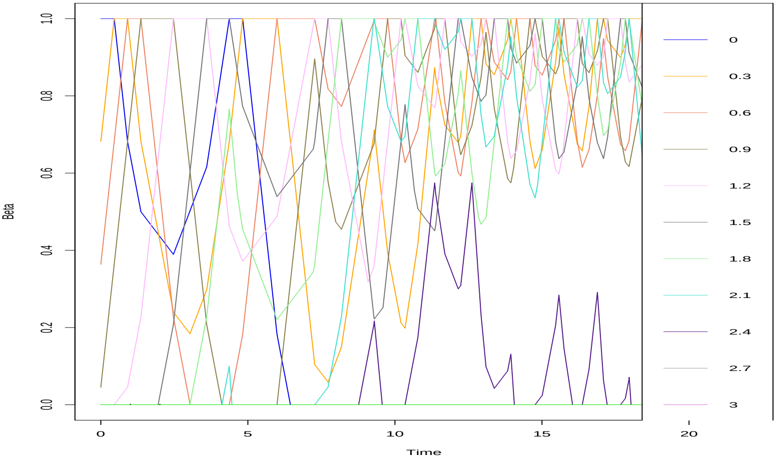


$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$



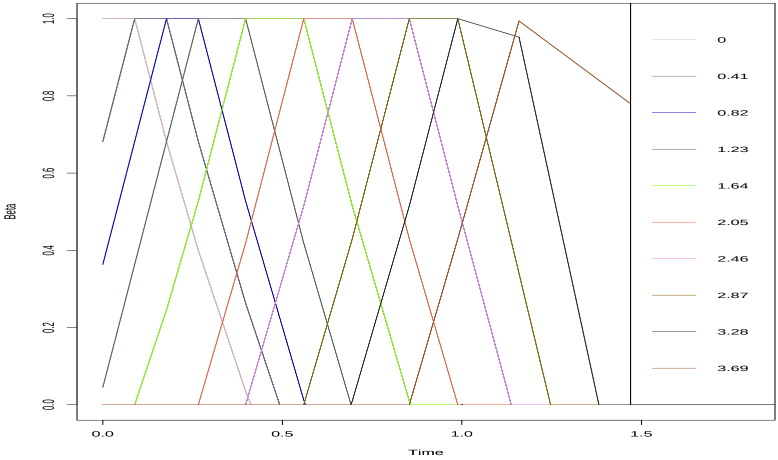
$$\delta = 1.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.5.$$

Representation of the Toy model (1)



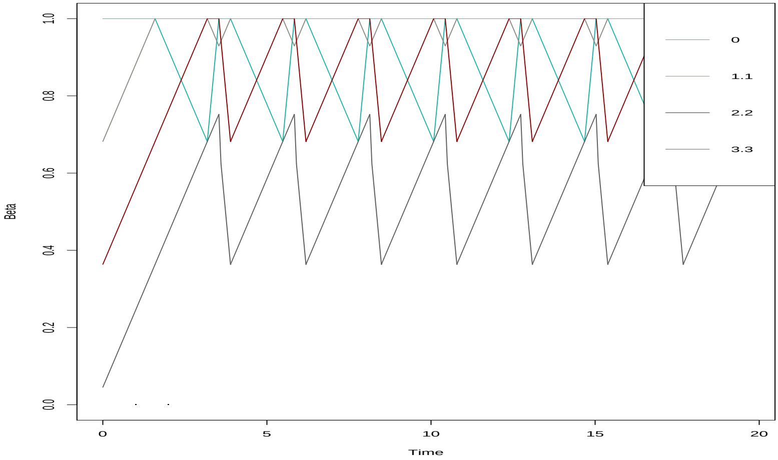
$$\delta = 0.3,\ \alpha = \frac{1}{\pi},\ \tau = 1.$$

Representation of the Toy model (2)



$$\delta = 0.41,\ \alpha = \frac{1}{\pi},\ \tau = 4.$$

Representation of the Toy model (3)



$$\delta = 1.1,\ \alpha = \frac{1}{\pi},\ \tau = 1.3.$$

Main result

★ 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 $\beta_{\ell-1}(t) \le \alpha$, and else:

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

★ deduce the time breakpoints:

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