Dynamique adaptative d'un modèle individu-centré de chemostat avec plusieurs ressources

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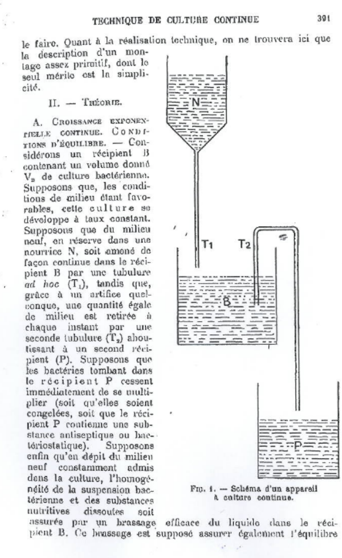
Chemostat

J. Monod (1950) and A. Novik and L. Szilar (1950) have developed a procedure allowing to

- maintain a population of bacteria at a stationary size
- while keeping the bacteria growth rate at a positive level.

⇝ chemostat



TECHNIQUE DE CULTURE CONTINUE 391

le faire. Quant à la réalisation technique, on ne trouvera ici que la description d'un montage assez primitif, dont le seul mérite est la simplicité.

II. — THÉORIE.

A. CROISSANCE EXPONENTIELLE CONTINUE. CONDITIONS D'ÉQUILIBRE. — Considérons un récipient B contenant un volume donné V_B de culture bactérienne. Supposons que, les conditions de milieu étant favorables, cette culture se développe à taux constant. Supposons que du milieu neuf, en réserve dans une nourrice N, soit amené de façon continue dans le récipient B par une tubulure *ad hoc* (T_1), tandis que, grâce à un artifice quelconque, une quantité égale de milieu est retirée à chaque instant par une seconde tubulure (T_2) aboutissant à un second récipient (P). Supposons que les bactéries tombant dans le récipient P cessent immédiatement de se multiplier (soit qu'elles soient congelées, soit que le récipient P contienne une substance antiseptique ou bactériostatique). Supposons enfin qu'en dépit du milieu neuf constamment admis dans la culture, l'homogénéité de la suspension bactérienne et des substances nutritives dissoutes soit assurée par un brassage efficace du liquide dans le récipient B. Ce brassage est supposé assurer également l'équilibre

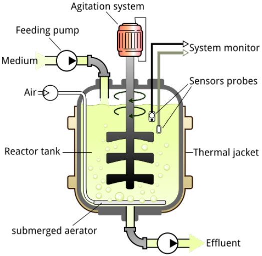
FIG. 1. — Schéma d'un appareil à culture continue.

Chemostat

A chemostat is a bioreactor in which liquid is continuously injected while volume is kept constant by an equal outflow:

- allows to control the growth rate of a microorganism in a constant environment (temperature, pH, nutrient concentration...)
- used to grow cells or to perform a biochemical process (e.g. wastewater treatment)

The chemostat is an efficient device to make bacteria adapt to given environmental conditions, for example in order to improve nutrients consumption (e.g. nitrogen or phosphorus in wastewater).



About chemostat models

Our Goal: Study adaptation in a multi-resources chemostat model.

- Basic chemostat model (system of ODEs)

$$\dot{u} = u(-1 - d + \eta R), \qquad \dot{R} = 1 - R - R\eta u.$$

  Multi-resources extensions have been studied in many contexts, but very little is known in general about their long time behavior (Smith and Waltman, 1995)
- Nearly no individual-based stochastic models (Crump and Young, 1979)
- In the context of adaptive dynamics, individual-based models are widely used (Metz, Geritz et al. 1996, Doebeli and Dieckmann 2003, Fournier and Méléard, 2004, C. 2006, Méléard, Tran, 2009, C. and Méléard, 2011, Klebaner et al. 2011, Collet, Méléard, Metz 2011), but nearly all deal with direct competition.
- Recently, the PDE approach for adaptive dynamics (Diekmann, Jabin, Mischler, Perthame, 2005) was also extended to multi-resources chemostat models (Mirrahimi, Perthame, Wakano, 2011)

Adaptive dynamics

Basic idea (Metz et al. 1996): look at the invasion and fixation of a mutant type in a population, to construct a fitness landscape and describe the long-time evolution of the population.

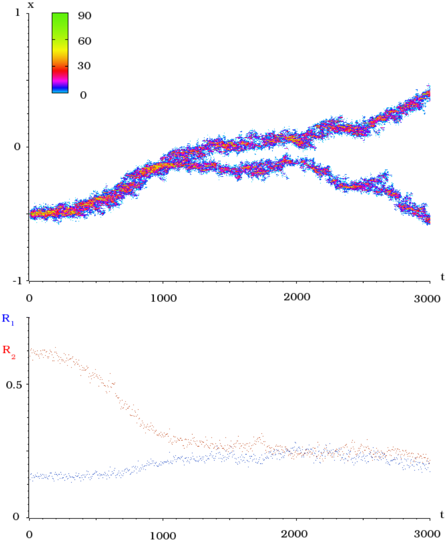
Assumptions:

- large populations
- rare mutations
- small mutation steps

Our contribution:

- Obtain general large-time behavior results for multi-resources chemostat ODE systems
- Construct an individual-based multi-resources chemostat model
- Characterize the adaptive dynamics of this model in the limit of rare mutations.

Evolutionary banching



Individual-based model

- K scales the size of the population (large K means large population)
- μ_K scales the probability of mutation (small μ_K means rare mutations)

Birth-death-mutation discrete process coupled with a piecewise deterministic dynamics for r continuous resources with concentrations $R_1^K(t), \ldots, R_r^K(t)$:

- each individual is characterized by a phenotypic trait x (rate of nutrient intake, body size at maturity, age at maturity...) in a compact subset $\mathcal{X}$ of $\mathbb{R}^d$
- a population of $N^K(t)$ individuals holding traits

  $x_1, \ldots, x_{N(t)} \in \mathcal{X}$ is represented by $\nu_t^K = \frac{1}{K} \sum_{i=1}^{N^K(t)} \delta_{x_i}$

Transitions

- Each individual with trait x gives birth at (inhomogeneous) rate $\sum_{k=1}^{r} \eta_k(x) R_k^K(t)$ to a single individual.
  $\eta_k(x)$ represents the consumption efficiency of resource k by bacteria with trait x. At each birth time:
  - with probability $(1-\mu_K)p(x)$, clonal reproduction (trait x)
  - with probability $\mu_K p(x)$, mutation; the mutant trait is $x+h$ where h has given law $m(x,h)dh$.
- Each individual with trait x dies or is removed from the chemostat at rate $d(x)$.
- Resources concentrations are solution to

$$\frac{dR_k^K(t)}{dt} = g_k - R_k^K - R_k^K \left(\frac{1}{K} \sum_{i=1}^{N(t)} \eta_k(x_i) \right) = g_k - R_k^K - R_k^K \langle \nu^K, \eta_k \rangle.$$

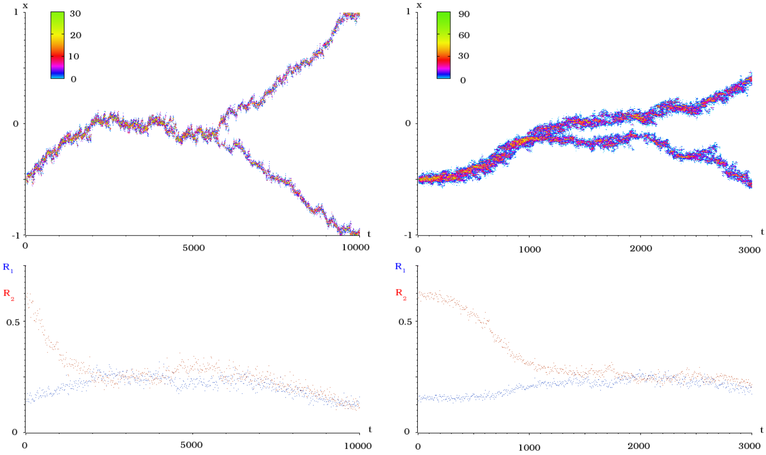
$g_k > 0$ is incoming concentration of resource k.

Example

Two resources, one-dimensional trait having opposite effects on the two resources consumption.

- $\mathcal{X} = [-1,1], \quad \mu_K p(x) \equiv p$
- $m(x,h)dh = \mathcal{N}(0,\sigma^2)$ (conditioned on $x+h \in \mathcal{X}$)
- $r = 2$ (2 resources), $g_1 = g_2 = 1$
- $d(x) = 1 + x^2$ minimum at 0.
- $\eta_1(x) = 2(x-1)^2, \quad \eta_2(x) = 2(x+1)^2.$

Simulations



$K = 100,\ p = 0.1,\ \sigma = 0.01$ $K = 300,\ p = 0.1,\ \sigma = 0.01$

$K \to +\infty$ without time scaling

Theorem

If $R^K(0) = R(0) \in \mathbb{R}_+^r$, $\mu_K \to 0$ *when* $K \to +\infty$ *and* ν_0^K *converges in distribution to a deterministic measure* $\nu_0 = \sum_{i=1}^n u_i(0)\delta_{x_i}$, *then* $((\nu_t^K, R^K(t)), t \geq 0)$ *converges in distribution to the function* $((\sum_{i=1}^n u_i(t)\delta_{x_i}, R(t)), t \geq 0)$, *where*

$$\dot{u}_i = u_i(-d(x_i) + \sum_{k=1}^r \eta_k(x_i)\, R_k), \quad \forall 1 \leq i \leq n,$$

$$\dot{R}_k = g_k - R_k - R_k \sum_{i=1}^n \eta_k(x_i)\, u_i, \quad \forall 1 \leq k \leq r.$$

Multi-resources and multi-species chemostat ODE system.

Assumptions

(A1) For all $x \in \mathcal{X}$, $\sum_{k=1}^{r} \eta_k(x) g_k > d(x)$.

(A2) For all $n \geq 1$ and distinct $x_1, \cdots, x_n \in \mathcal{X}$, the equation

$$d(x_i) - \sum_{k=1}^{r} \frac{\eta_k(x_i) g_k}{1 + \sum_{j=1}^{n} \eta_k(x_j) u_j} = 0 \ , \quad 1 \leq i \leq n$$

has at most one solution $(u_1, \cdots, u_n) \in \mathbb{R}_+^n$.

(A1) means that the trivial equilibrium $(0, \ldots, 0, g_1, \ldots, g_k)$ of the chemostat system is unstable.
(A2) means that there is at most one equilibrium with prescibed surviving species.

How to check (A2)?

Proposition

Assumption (A2) holds if for all distinct $x_1, \dots, x_{r+1}$, *the vectors*

$$\begin{pmatrix} \eta_1(x_1) \\ \vdots \\ \eta_1(x_{r+1}) \end{pmatrix} \dots \begin{pmatrix} \eta_r(x_1) \\ \vdots \\ \eta_r(x_{r+1}) \end{pmatrix}, \begin{pmatrix} d(x_1) \\ \vdots \\ d(x_{r+1}) \end{pmatrix}$$

are linearly independent, and for all distinct $x_1, \dots, x_r$, *the vectors*

$$\begin{pmatrix} \eta_1(x_1) \\ \vdots \\ \eta_r(x_1) \end{pmatrix} \dots \begin{pmatrix} \eta_1(x_r) \\ \vdots \\ \eta_r(x_r) \end{pmatrix}$$

are also linearly independent.

Long-time behavior of chemostat systems

Theorem (C., Jabin, Raoul, 2010)

Under Assumption (A2), for all $n \geq 1$ and all distinct $x_1, \cdots, x_n \in \mathcal{X}$, there exists a unique $(\bar{u}, \bar{R})$ in $(\mathbb{R}_+)^{n+r}$ such that any solution $(u(t), R(t))$ of the chemostat system with $u_i(0) > 0$ for any $1 \leq i \leq n$, converges to $(\bar{u}, \bar{R})$.

We shall denote by $(\bar{u}(\mathbf{x}), \bar{R}(\mathbf{x}))$ this equilibrium, where $\mathbf{x} := (x_1, \dots, x_n)$.

Some consequences of the theorem

In particular, the chemostat system can only have a single locally stable equilibrium, and it is actually globally stable.

The case of a single trait: If $n = 1$, since the trivial equilibrium $(0, g_1, \dots, g_r)$ is unstable, $(\bar{u}(x), \bar{R}(x))$ is the unique solution to

$$\sum_{k=1}^{r} \frac{\eta_k(x)\, g_k}{1 + \eta_k(x)\, \bar{u}(x)} = d(x), \qquad \bar{R}_k(x) = \frac{g_k}{1 + \eta_k(x)\, \bar{u}(x)}.$$

Some consequences of the theorem

The case of two trait: If $n = 2$, the equilibrium $(\bar{u}(x_1), 0, \bar{R}(x_1))$ is stable iff $f(x_2; x_1) \leq 0$, where

$$f(y; x) = -d(y) + \sum_{k=1}^{r} \frac{\eta_k(y)\, g_k}{1 + \eta_k(x)\, \bar{u}(x)}.$$

If both $(\bar{u}(x_1), 0, \bar{R}(x_1))$ and $(0, \bar{u}(x_2), \bar{R}(x_2))$ are unstable, i.e. if $f(x_1; x_2) > 0$ and $f(x_2; x_1) > 0$, then there exists a stable equilibrium where both traits coexist.

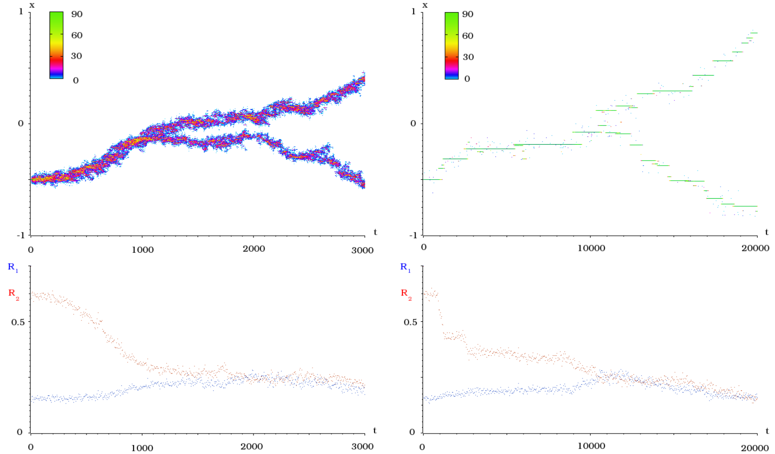
More generally, if $x_1, \dots, x_n$ coexist, we define the invasion fitness of a new (mutant) trait y as

$$f(y; x_1, \cdots, x_n) = -d(y) + \sum_{k=1}^{r} \eta_k(y)\, \bar{R}_k(\mathbf{x}).$$

Limit of rare mutations (Metz et al. 1996)

- The selection process has sufficient time between two mutations to eliminate disadvantaged traits (time scale separation)
- The assumption of large populations allows one to assume a deterministic population dynamics
  ⇝ one can predict the outcome of competition between several traits.
- Succession of phases of mutant invasion, and phases of competition between traits

Simulations: rare mutations



$K = 300, \; p = 0.1, \; \sigma = 0.01$ $\qquad$ $K = 300, \; p = 0.0003, \; \sigma = 0.06$

Convergence to the PES

Theorem

Assume (A). If $\nu_0^K = u_0^K \delta_x$ *with* $u_0^K \to \bar{u}(x)$ *in probability when* $K \to +\infty$. *Assume also that* $R_k^K(0) \to \bar{R}_k(x)$ *in probability for all* $1 \leq k \leq r$ *and*

$$\forall C > 0, \quad \log K \ll \frac{1}{K\mu_K} \ll \exp(CK),$$

then, the process $((\nu^K_{t/K\mu_K}, R^K(t/K\mu_K)), t \geq 0)$ *converges for f.d.d. to a pure jump Markov process* $((\Lambda_t, \mathcal{R}(t)), t \geq 0)$ *with explicit jump rates and taking values in*

$$\mathcal{M}_0 := \left\{ \left(\sum_{i=1}^{d} \bar{u}_i(\mathbf{x}) \delta_{x_i},\ \bar{\mathbf{R}}(\mathbf{x}) \right) ;\ d \geq 1,\ x_1, \ldots, x_n \in \mathcal{X} \text{ coexist} \right\}.$$

When Λ_t is monomorphic, it is called Trait Substitution Seq. (TSS); when it is polymorphic, we call it Polymorphic Evolution Seq. (PES).

Monomorphic case: the TSS

- Until the first coexistence time, the trait dynamics is given by a Markov jump process $(X_t, t \geq 0)$ such that $X_0 = x$ and with infinitesimal generator

$$A\varphi(x) = \int (\varphi(x+h) - \varphi(x)) p(x) \left(\sum_k \eta_k(x) \bar{R}_k(x) \right) \bar{u}(x) \frac{[f(x+h;x)]_+}{\sum_k \eta_k(x+h) \bar{R}_k(x)} m(x,h)\, dh$$

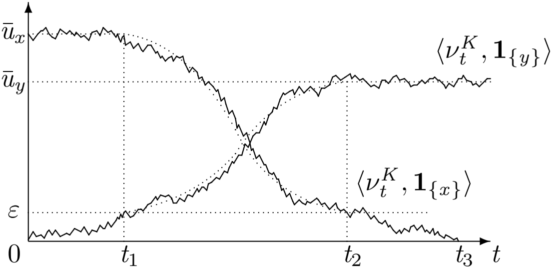
- Each jump corresponds to a successful invasion of a new mutant trait
- The first coexistence time is the first time t such that $f(X_t, X_{t-}) > 0$ and $f(X_{t-}, X_t) > 0$.

Before the first mutation in a monomorphic population

- $(\langle \nu_t^K, \mathbf{1}\rangle, R^K(t))$ is close to the solution of the monomorphic chemostat system.
  $\rightsquigarrow$ reaches an ε-neigborhood of $(\bar{u}(x), \bar{R}(x))$ in finite time.
- Large deviations (Feng and Kurtz, 2006): the exit time from this ε-neighborhood behaves as $\exp(KC_{\varepsilon,x})$, with $C_{\varepsilon,x} > 0$.
- Before this exit time, the rate of mutation is close to $\mu_K p(x) \left(\sum_k \eta_k(x) \bar{R}_k(x)\right) K \bar{u}(x)$.
- On the time scale $\frac{t}{K\mu_K}$: mutation rate $p(x) \left(\sum_k \eta_k(x) \bar{R}_k(x)\right) \bar{u}(x)$.

After the first mutation: competition phase

- **between 0 and $\mathbf{t_1}$**: the number of mutant individuals is close to a branching process with birth rate $\sum_k \eta_k(y)\bar{R}(x)$ and death rate $d(y)$
  $\rightsquigarrow$ survival probability $[f(y;x)]_+/(\sum_k \eta_k(y)\bar{R}(x))$
- **between $\mathbf{t_1}$ and $\mathbf{t_2}$**: close to the chemostat system
- **after $\mathbf{t_2}$**: the number of resident individuals is close to a sub-critical branching process
- If $\log K \ll \frac{1}{K\mu_K}$ the next mutation occurs after this phase with high probability.



PES after the first coexistence

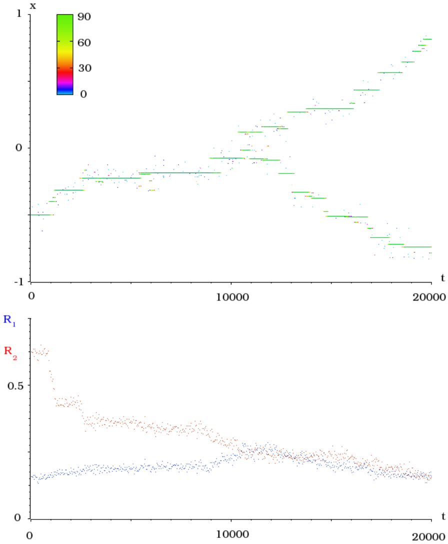
After the first coexistence time, two traits X_t, Y_t are coexisting, and

$$\Lambda_t = \bar{u}_1(X_t, Y_t)\delta_{X_t} + \bar{u}_2(X_t, Y_t)\delta_{Y_t}$$

where the jump process (X_t, Y_t) is obtained as follows.

- A mutant born from X_t appears with rate $p(X_t)\left(\sum_k \eta_k(X_t)\bar{R}_k(X_t, Y_t)\right)\bar{u}_1(X_t, Y_t)$ and a mutant born from Y_t appears independently with rate $p(Y_t)\left(\sum_k \eta_k(Y_t)\bar{R}_k(X_t, Y_t)\right)\bar{u}_2(X_t, Y_t)$.
- Once a mutant trait z has appeared, it invades the population with probability $[f(z; X_t, Y_t)]_+ / \left(\sum_k \eta_k(z)\bar{R}_k(X_t, Y_t)\right)$.
- If the mutant invades, the new state of Λ is given by $(\bar{u}(X_t, Y_t, z), \bar{R}(X_t, Y_t, z))$...

Evolutionary banching



Evolutionary singularities

Assume that $\mathcal{X} \subset \mathbb{R}$ (dimension 1).

- Since $f(x,x) = 0$, we have $\partial_1 f(x,x) + \partial_2 f(x,x) = 0$.
- For any $x \in \mathcal{X}$,

$$f(x+\varepsilon, x-\varepsilon) = 2\partial_1 f(x,x)\,\varepsilon + O(\varepsilon^2)$$
$$f(x-\varepsilon, x+\varepsilon) = -2\partial_1 f(x,x)\,\varepsilon + O(\varepsilon^2)$$

$\rightsquigarrow$ when mutations are small, coexistence can only occur in the neighborhood of points x^* such that $\partial_1 f(x^*, x^*) = 0$.

Such a point is called an evolutionary singularity.

The Canonical Equation of Adaptive Dynamics

- Small mutations: size of mutations scaled by ε, i.e. $m(x,h)dh$ replaced by $\frac{1}{\varepsilon}m(x,\frac{h}{\varepsilon})dh$.
- Renormalized PES: Λ^ε.
- Rescaled time: t/ε^2.

Theorem

The processes $(\Lambda^\varepsilon_{t/\varepsilon^2}, t \geq 0)$ *converge in law as* $\varepsilon \to 0$ *to* $(\bar{u}(x(t))\delta_{x(t)}, t \geq 0)$, *where* x *is solution of the ODE*

$$\frac{dx}{dt} = \int h^2 p(x)\bar{u}(x)\partial_1 f(x;x)m(x,h)dh.$$

This is the canonical equation of adaptive dynamics (Dieckmann and Law, 1996).

$\rightsquigarrow$ Evolutionary branching can only occur in the neighborhood of a stable evolutionary singularity and on a longer scale than t/ε^2.

A definition of evolutionary branching

Definition

For any $\eta > 0$, we say that there is η-branching at the evolutionary singularity x^* if

- *There exist $t > 0$ such that the support of Λ_t^ε is composed of a single trait in $(x^* - \eta, x^* + \eta)$.*
- *There exist $s > t$ such that the support of Λ_s^ε is composed of two traits distant of more than η.*
- *Between s and t, the support of Λ^ε is always a subset of $[x^* - \eta, x^* + \eta]$ composed of at most 2 traits.*

Branching criterion

- Assume $x^* = 0$. We have $\partial_1 f(0;0) = 0$.
- Let $a = \partial_{11} f(0;0)$ and $c = \partial_{22} f(0;0)$. Assume that $a \neq 0$ and $a + c \neq 0$.
- The evolutionary singularity $x^* = 0$ is stable for the canonical equation if

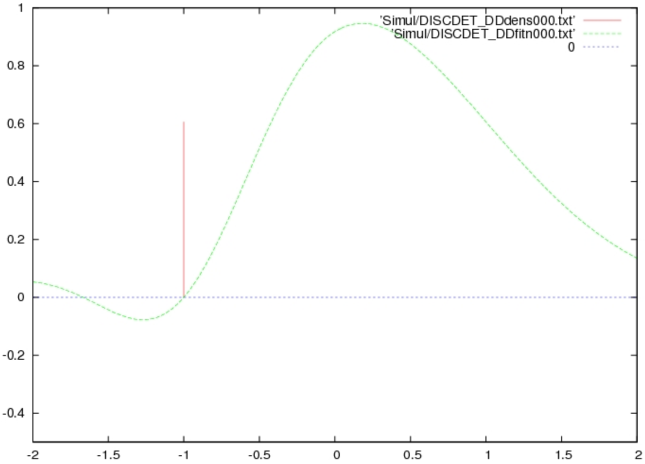
$$c > a.$$

Theorem

When $c > a$, for all sufficiently small $\eta > 0$, there exists $\varepsilon_0 > 0$ s.t. for all $\varepsilon < \varepsilon_0$,

- *If $a > 0$, then $\mathbb{P}^\varepsilon(\eta\text{-branching}) = 1$.*
- *If $a < 0$, then $\mathbb{P}^\varepsilon(\eta\text{-branching}) = 0$.*

Coevolution with the fitness landscape



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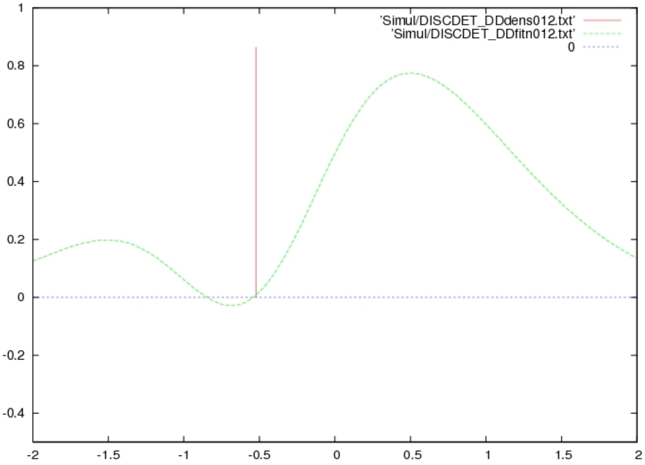

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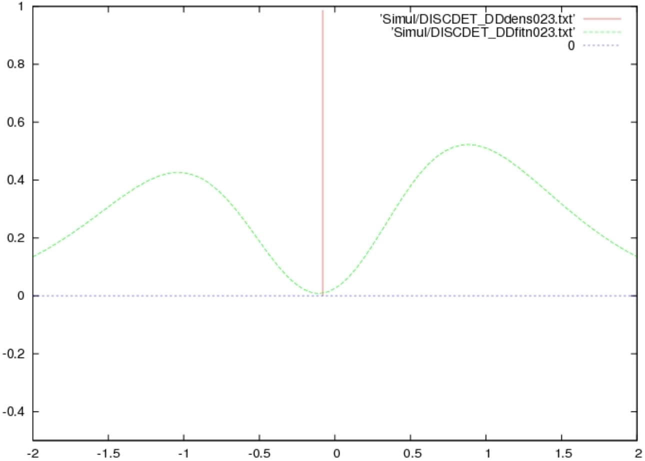

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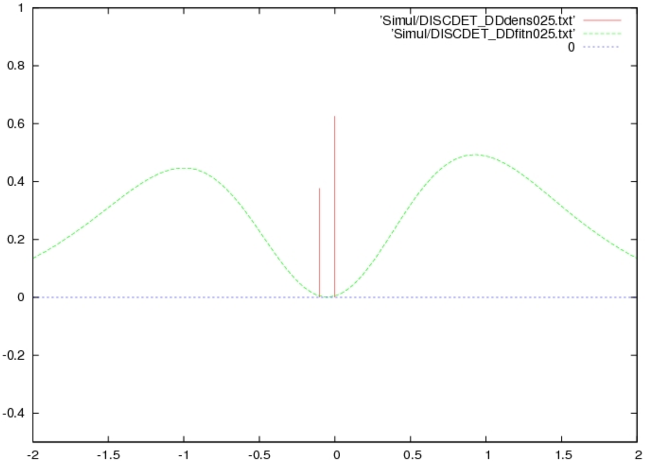

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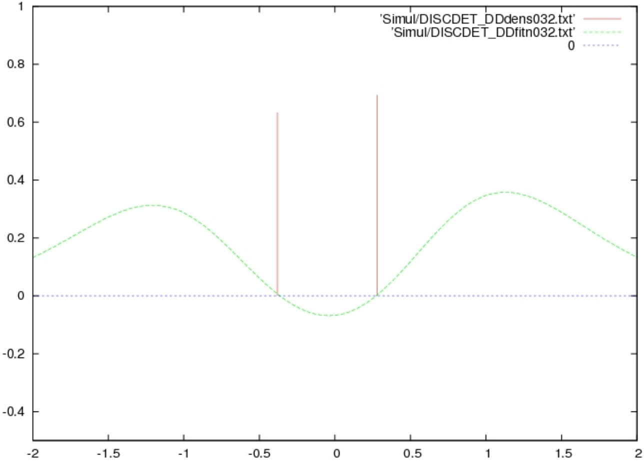

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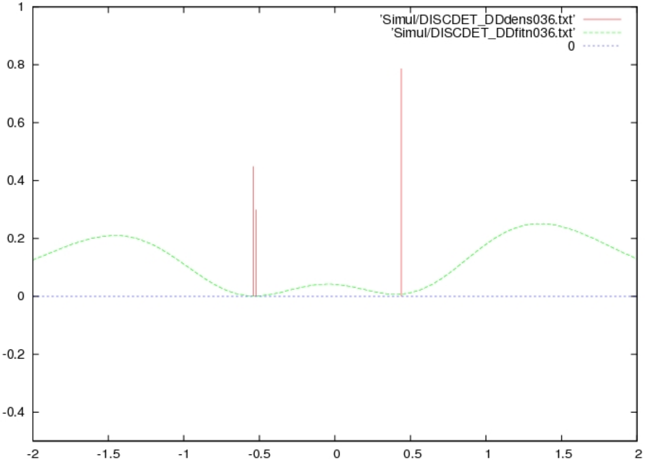

Coevolution with the fitness landscape