CEMRACS 2018: Horizontal Gene Transfer

Vincent Calvez [1] Susely Figueroa Iglesias [2] Hélène Hivert [3]
Sylvie Méléard[4] Anna Melnykova [5] Samuel Nordmann[6]

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[1] CNRS & Institut Camille Jordan, Lyon. `Vincent.Calvez@math.cnrs.fr`
[2] Univ. Toulouse, IMT, UPS. `Susely.Figueroa@math.univ-toulouse.fr`
[3] Univ. Lyon, École centrale de Lyon. `helene.hivert@ec-lyon.fr`
[4] Ecole Polytechnique, France. `sylvie.meleard@polytechnique.edu`
[5] Univ. Cergy-Pontoise & Univ. Grenoble Alpes. `anna.melnykova@u-cergy.fr`
[6] CAMS, EHESS, PSL Université, Paris. `samuel.nordmann@ehess.fr`

Motivation

Horizontal Gene Transfer (HGT) — exchange of genetic material between unicellular/multicellular organisms not through a vertical transmission.

- the evolution of organisms
- transmission of pathogenes
- resistance to antibiotics in bacteria

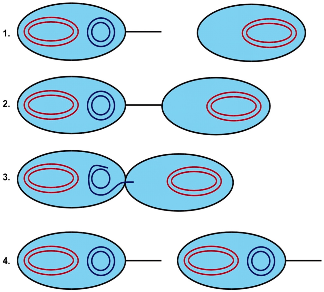
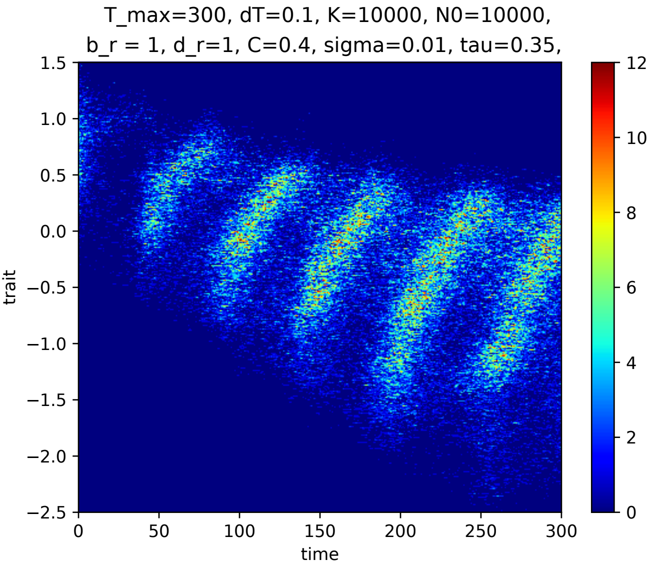


Figure 1: Unilateral HGT. Picture from Raz, Y. & Tannenbaum, E. (2010). The Influence of Horizontal Gene Transfer on the Mean Fitness of Unicellular Populations in Static Environments. Genetics, 185(1), 327–337.

Motivation: evolutionary rescue



Model

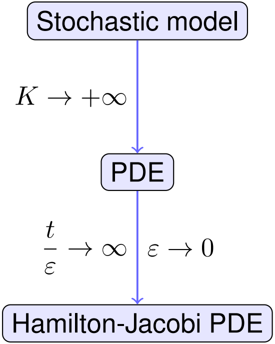
The demography of the population is regulated by:

- $X_i(t) \in \mathbb{R}^d$ is **the trait** of i-th individual living at t
- K: **scale parameter** (*carrying capacity*), N^t — size of the population at time t
- **Birth:** $b(x)$ with a mutation kernel **m(x,y).**
- **Death:** $d(x) + C\dfrac{N^t}{K}$**, where** C **is a competition rate**
- **Horizontal Gene Transfer (HGT):**

$$h_K(x, y, N^t) = \tau_0 \alpha(x - y)\frac{K}{N^t}$$

where α a smooth bounded function (for example: **heaviside**, **arctan**, etc..).

Structure of project



Stochastic model

$K \to +\infty$

PDE

$\frac{t}{\varepsilon} \to \infty$ $\varepsilon \to 0$

Hamilton-Jacobi PDE

Objective:

- Grasp the evolutionary rescue with the help of a deterministic model
- Develop a stable scheme to deal with asymptotically vanishing values
- Analyze the setting which leads to such a rescue both numerically and theoretically

Stochastic model

For a population described by point measure $\nu^t(dx) = \frac{1}{K}\sum_{i=0}^{N^t} \delta_{X_i(t)}(dx)$ the generator of the process is:

$$
\begin{aligned}
L^K F(\nu) = \sum_{i=1}^{N} b(x_i) \int_{\mathbb{R}^d} \left(F\left(\nu + \frac{1}{K}\delta_y\right) - F(\nu)\right) m(x_i, dy) \\
+ \sum_{i=1}^{N} \left(d(x_i) + C\frac{N}{K}\right) \left(F\left(\nu - \frac{1}{K}\delta_{x_i}\right) - F(\nu)\right) \\
+ \sum_{i,j=1}^{N} h_K(x_i, x_j, \nu) \left(F\left(\nu + \frac{1}{K}\delta_{x_i} - \frac{1}{K}\delta_{x_j}\right) - F(\nu)\right).
\end{aligned}
$$

Further reading:

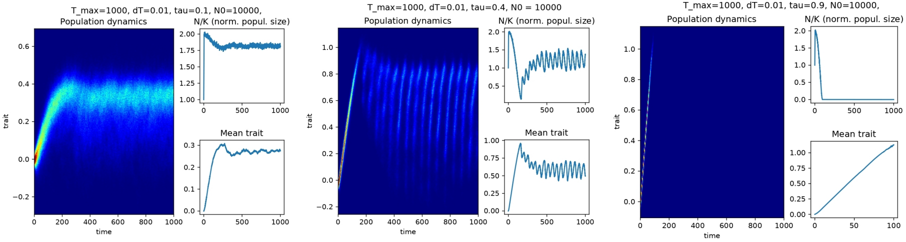
Billiard et al. (2016a, 2015)

Stochastic simulations: algorithm

Algorithm of simulation on $[0, \Delta, \dots, i\Delta, \dots, N\Delta = T]$:

```
0 Randomly initialize the population $X^0 := \mathcal{N}(x^0_{mean}, \sigma^0) \times N^0$
1 Set: $b \equiv const$, $d = d_r x^2 + C\frac{N^t}{K}$, $\alpha(x) = heav(x)$
2 For $i \in [1, N-1]$:
    (i) Copy $X_{i-1}$–th population to $X_i$
    (ii) Compute exponential arrival times for each individual:
        $$T_b := \lambda(b),\ T_d := \lambda(d),\ T_{HGT} := \lambda\left(\sum_{y \in X^i} h_K(x, y, N^{i-1})\right)$$
    (iii) $\forall x \in X_i$:
        * If $\mathbf{T_d \leq \Delta}$: remove $x$-th individual
        * If $\mathbf{T_b \leq \Delta}$: add a new individual with a trait from $\mathcal{N}(x, \sigma^2)$
        * If $\mathbf{T_{HGT} \leq \Delta}$: pick a trait $y \in X^i$ according to the law
              $$\frac{h_K(x, y, N^{i-1})}{\sum_{y \in X^i} h_K(x, y, N^{i-1})}$$
          then remove individual with trait $x$ and add a new individual with trait $y$.
    (iv) Return $X_i$
```

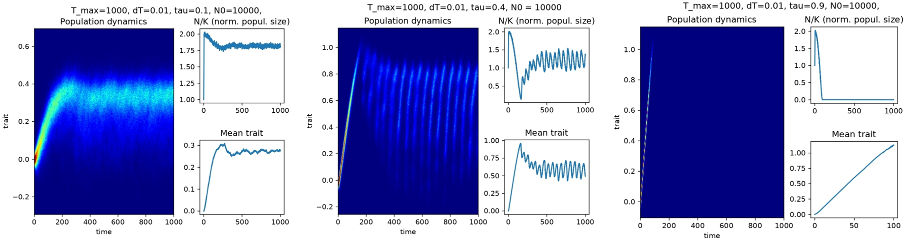
Stochastic simulations



(a) Stabilization: $\tau = 0.1$ (b) Cycles: $\tau = 0.4$ (c) Extinction: $\tau = 0.9$

Figure 2: Behavior of the population dynamics as the mutation rate τ is changing, $(b_r = d_r = 1, \sigma = 0.01, T_{max} = 1000, \Delta = 0.01)$.

Stochastic simulations



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All codes and more pictures:

`https://github.com/melnyashka/horizontal_gene_transfer`

PDE: Model and notations

The sequence of stochastic processes gives a macroscopic approximation when $K \to +\infty$.

$$\begin{cases} \partial_t f(t,x) = & -(d(x) + C\rho(t))f(t,x) + \int_{\mathbb{R}^d} m(x-y)b(y)f(t,y)dy \\ & +f(t,x)\int_{\mathbb{R}^d} \tau(x-y)\dfrac{f(t,y)}{\rho(t)}dy, \\ & \rho(t) = \int_{\mathbb{R}^d} f(t,x)dx, \qquad f(0,x) = f^0(x) > 0. \end{cases}$$

- $f(t,x) := \lim_{K\to+\infty} \nu^K$: density of the population at time t with trait x,
- $b(x), d(x), C$: birth, death and competition rate,
- $m(x-y)$: mutation kernel,
- $\tau(y-x) := \tau_0\left[\alpha(x-y) - \alpha(y-x)\right]$: HT kernel

Further reading:

Billiard et al. (2016b,a), Ferrière and Tran (2009)

PDE simulations

Explicit Euler scheme, (the integrals are computed with a left-point quadrature rule).

- Competition term: $\Delta x \sum_{j=0}^{N_x-1} f_j^n$

$$\frac{f_i^{n+1} - f_i^n}{\Delta t} = \left(- \rho^n - D_i + T_i^n \right) f_i^n + B_i^n$$

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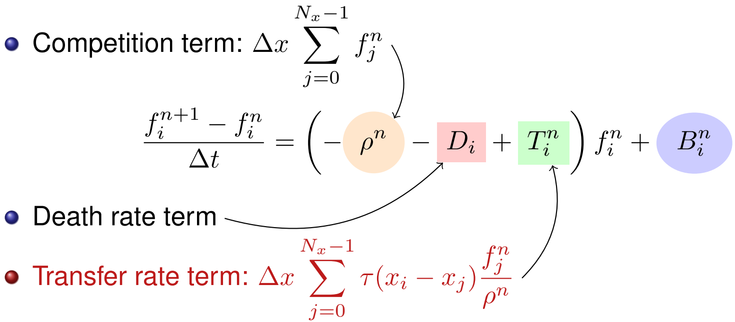

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- Transfer rate term: $\Delta x \sum_{j=0}^{N_x-1} \tau(x_i - x_j)\frac{f_j^n}{\rho^n}$

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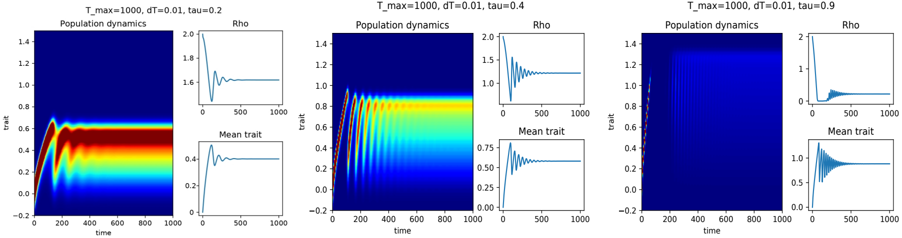
- Transfer rate term: $\Delta x \sum_{j=0}^{N_x-1} \tau(x_i - x_j) \frac{f_j^n}{\rho^n}$
- Birth rate term: $[m * (bf)]_i^n = \Delta z \sum_{k=0}^{N_z-1} m(z_k) b(x_i + z_k) f^n(x_i + z_k).$

PDE simulations



(a) Stabilization: $\tau = 0.2$ (b) Cycles: $\tau = 0.4$ (c) Regrowth: $\tau = 0.9$

Figure 3: Behavior of the population dynamics as the mutation rate τ is changing.

Shape of solutions

- Competition ⟶ Saturation: total population $\rho(t)$ is bounded.

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- Selection of the fittest : $\bar{x} = \operatorname{argmax}\,[b(\cdot) - d(\cdot)]$.

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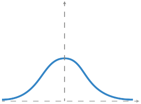
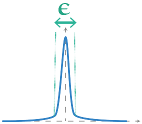
- **Small** Mutations. Rescaling parameter: $\varepsilon > 0$.

$m(y-y')$:



$\longleftrightarrow$ $\frac{1}{\varepsilon} m\left(\frac{y-y'}{\varepsilon}\right)$:



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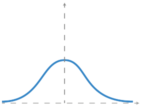

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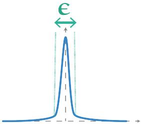

- Counterpart: **large** time

$t \longleftrightarrow \frac{t}{\varepsilon}$

Ecological scale — Evolutionary scale

$\partial_t \longleftrightarrow \varepsilon\partial_t$

PDE: The rescaled model

$$\begin{cases} \varepsilon\partial_t f_\varepsilon(t,x) & = & -(d(x)+C\rho_\varepsilon(t))f_\varepsilon(t,x) + \displaystyle\int_{\mathbb{R}} \overbrace{m(z)b(x+\varepsilon z)f_\varepsilon(t,x+\varepsilon z)dz}^{z=\frac{x-y}{\varepsilon}} \\ & & +f_\varepsilon(t,x)\displaystyle\int_{\mathbb{R}}\tau(x-y)\frac{f_\varepsilon(t,y)}{\rho_\varepsilon(t)}dy, \\ & & \\ \rho_\varepsilon(t) & = & \displaystyle\int_{\mathbb{R}} f_\varepsilon(t,x)dx, \qquad \text{+ init. conditions.} \end{cases}$$

Hopf-Cole transformation

$f_\varepsilon \approx$ Gaussian of variance ε.

$\Longrightarrow$ Hopf-Cole transformation:

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$$\Downarrow$$

$$\partial_t u_\varepsilon = -(d(x) + \rho_\varepsilon(t)) + \int_{\mathbb{R}^d} m(z) b(x+\varepsilon z) e^{\frac{u_\varepsilon(t,x+\varepsilon z) - u_\varepsilon(t,x)}{\varepsilon}} dz$$
$$+ \int_{\mathbb{R}} \tau(x-y) \frac{f_\varepsilon(t,y)}{\rho_\varepsilon(t)} dy.$$

The limiting Hamilton-Jacobi equation

- $\boxed{f_\varepsilon(t,x) = e^{\frac{u_\varepsilon(t,x)}{\varepsilon}}.}$
- (Formally) $u_\varepsilon \underset{\varepsilon\to 0}{\longrightarrow} u$ (viscosity) solution of:

$$\partial_t u = -(d(x)+\rho(t)) + b(x)\int_{\mathbb{R}} M(z)e^{z\cdot\nabla_x u}dz + \tau(x-\overline{x}(t))$$

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- Non-standard drift term

Hamilton-Jacobi: convenient framework for concentration phenomenon.
Formally :

- $\rho(t) = \max(0, b - d\bar{x}(t)^2)$.
- Adaptative dynamics:

$$\frac{\mathrm{d}}{\mathrm{d}t}\bar{x}(t) = \frac{1}{-\partial_x^2 u(t, \bar{x}(t))} \left[b - d\bar{x}(t)^2\right] \quad \text{+ possible jumps}$$

- Evolutionary Equilibrium:

$$\bar{x}_\star = \frac{\tau'(0)}{2d}.$$

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$$\bar{x}_\star = \frac{\tau'(0)}{2d}.$$

- Threshold:

$$\text{Oscillations} \quad \text{iff} \quad \frac{\tau'(0)^2}{\|\tau\|_\infty} \geq 4d.$$

- Threshold:

$$\text{Extinction} \quad \text{"iff"} \quad \|\tau\|_\infty \geq 2\sqrt{bd}.$$

Hamilton-Jacobi simulations

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PDE scheme not consistent

Asymptotic Preserving (AP) scheme (Jin, 1999, Klar, 1998, 1999)

- avoid the increase of computational cost,
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$$\begin{tikzcd}
P_\varepsilon \arrow[r, "\varepsilon\to 0"] & P_0 \\
S_\varepsilon^h \arrow[u, "h\to 0"] \arrow[r, "\varepsilon\to 0"] & S_0^h \arrow[u, "h\to 0"]
\end{tikzcd}$$

Hamilton-Jacobi simulations: numerical AP scheme

For $u(t,x) = \varepsilon \ln f(t,x)$ we compute:

- Competition term (Implicit). Recall: $\rho^{n+1} = \sum_i e^{\frac{u_i^{n+1}}{\varepsilon}}$.

$$\frac{u_i^{n+1} - u_i^n}{\Delta t} = -\rho^{n+1} - D_i + B_i^n + T_i^n$$

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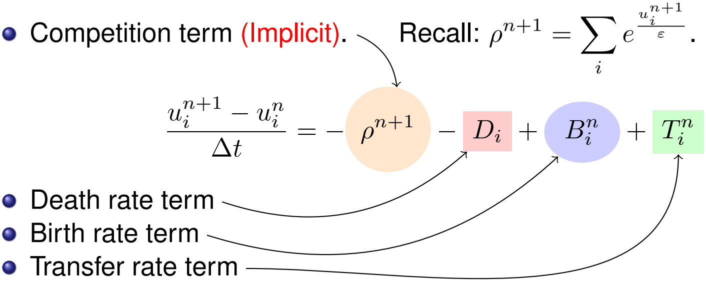

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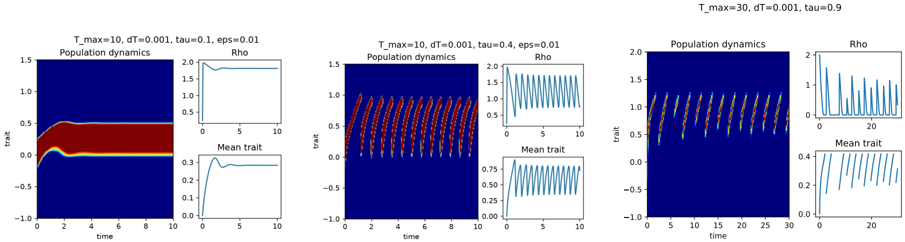
- Death rate term
- Birth rate term
- Transfer rate term

Remarking that for the exponential computations we make

$$\frac{f^\varepsilon(t^n,y)}{\rho^\varepsilon(t^n)} = \frac{\mathrm{e}^{u^\varepsilon(t^n,y)/\varepsilon}}{\int_{\mathbb{R}} \mathrm{e}^{u^\varepsilon(t^n,z)/\varepsilon} \mathrm{d}z} = \frac{\mathrm{e}^{(u^\varepsilon(t^n,y) - \max_x u^\varepsilon(t^n,x))/\varepsilon}}{\int_{\mathbb{R}} \mathrm{e}^{(u^\varepsilon(t^n,z) - \max_x u^\varepsilon(t^n,x))/\varepsilon} \mathrm{d}z},$$

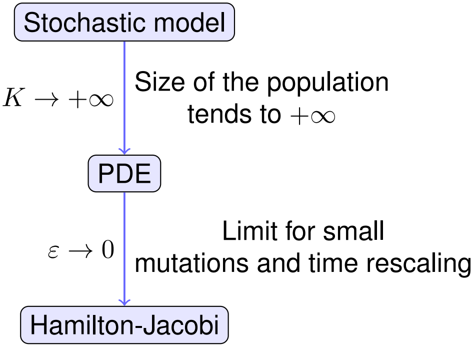
Hamilton-Jacobi simulations (PDE for $\varepsilon << 1$):



(a) Stabilization: $\tau = 0.1$ (b) Cycles: $\tau = 0.4$ (c) Extinction: $\tau = 0.9$

Figure 4: Behavior of the population dynamics as the mutation rate τ is changing.

Conclusion



Stochastic model

$K \to +\infty$ Size of the population tends to $+\infty$

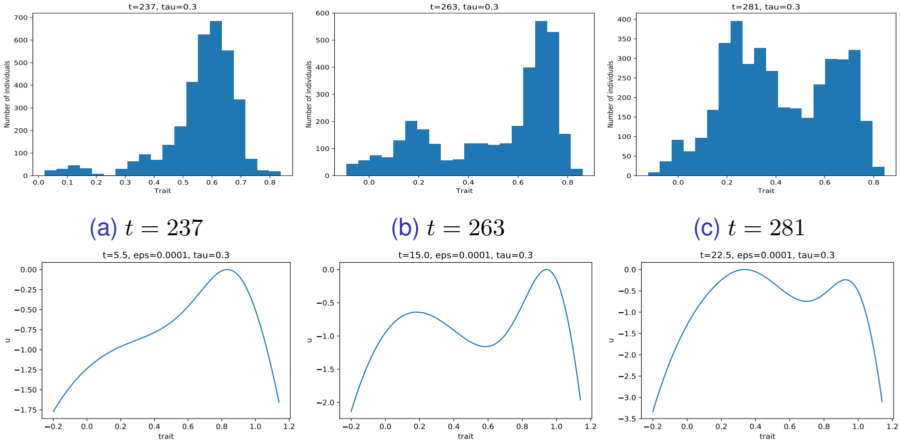
PDE

$\varepsilon \to 0$ Limit for small mutations and time rescaling

Hamilton-Jacobi

- After two limiting procedures, Hamilton-Jacobi model is still able to grasp the qualitative properties of the stochastic model.
- H-J is convenient to describe where the population concentrates. Our numerics shows that it is also able to describe *small population*.
- H-J framework allows a rigorous and rich description.

Evolutionary rescue


t=237, tau=0.3

t=263, tau=0.3

t=281, tau=0.3

t=5.5, eps=0.0001, tau=0.3

t=15.0, eps=0.0001, tau=0.3

t=22.5, eps=0.0001, tau=0.3

(a) $t = 237$ (b) $t = 263$ (c) $t = 281$

(d) $t = 5.5$ (e) $t = 15.0$ (f) $t = 22.5$

Figure 5: Stochastic/HJ. $\varepsilon = 10^{-4}$ and $\tau = 0.3$

Open questions

1. Rigorous proofs.
2. Formula for the period of oscillations.

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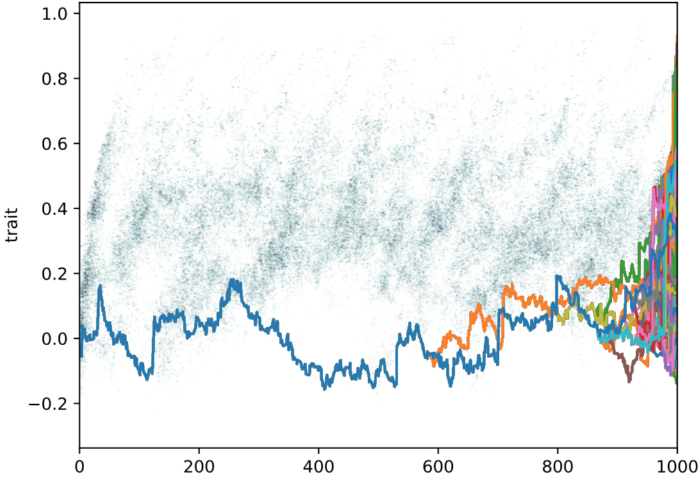
3. Reconstruction of lineages with the characteristics of Hamilton-Jacobi.



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