Dynamics of Dirac distributions in the evolution of quantitative alleles with sexual reproduction

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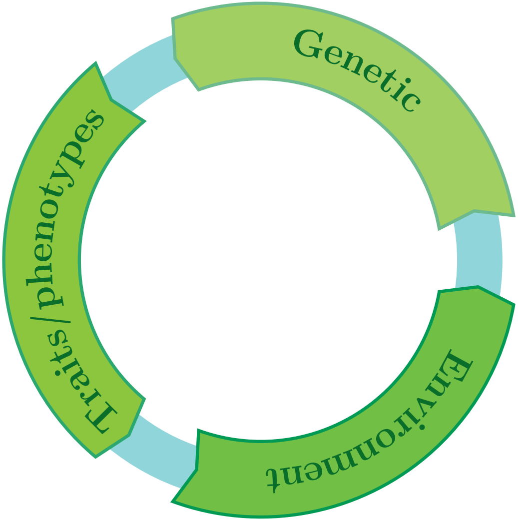
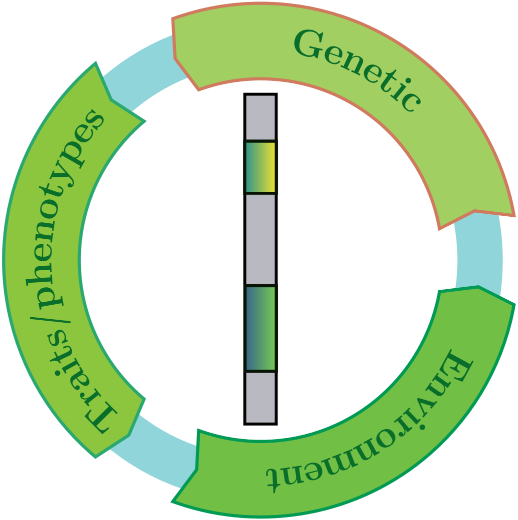
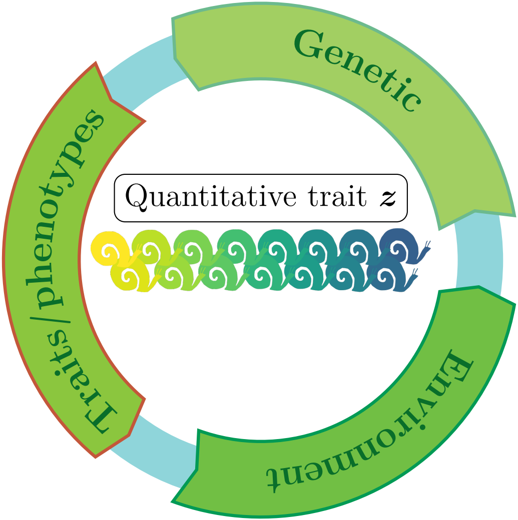
Modelling evolution and ecology



Modelling evolution and ecology

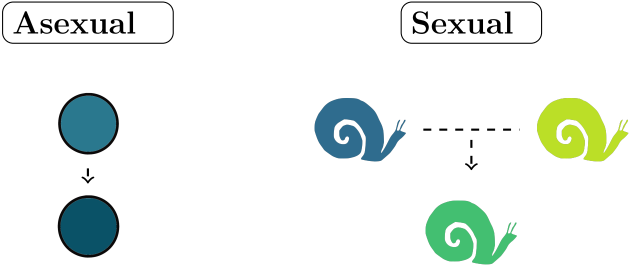


Modelling evolution and ecology



Modelling evolution and ecology

- **Mode of reproduction**
- **Genetic architecture of the trait**



- **Mode of reproduction**
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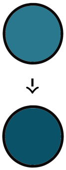
Asexual

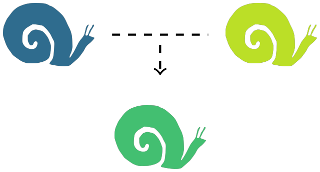


Mutations

Linear, (non-)local:

$n \mapsto K_{\sigma_M^2} * n - n, \; n \mapsto \sigma_M^2 \Delta_z n$

Sexual



Genetic shuffling

Non-linear, non-local:

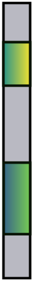
$n \mapsto \mathcal{B}_{\mathrm{sex}}[n] - n$

Transmission of traits across generations

- ◇ Mode of reproduction
- ◇ **Genetic architecture of the trait**

L loci, diallelic, discrete effects

2 loci, continuum of alleles



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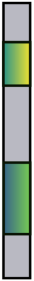
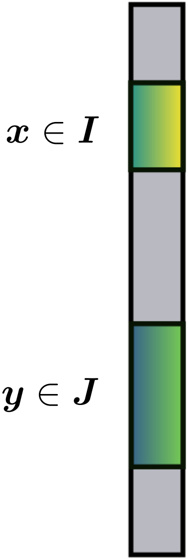


Continuum-of-alleles models (Burger (2000))



Kimura (1965) and Lande (1975)

- **Additive effects** of loci on the trait,
- **Gaussian selection functions** $\rightsquigarrow$ Gaussian distribution of allelic effects.

Continuum-of-alleles models (Burger (2000))

$\boldsymbol{x} \in \boldsymbol{I}$

$\boldsymbol{y} \in \boldsymbol{J}$

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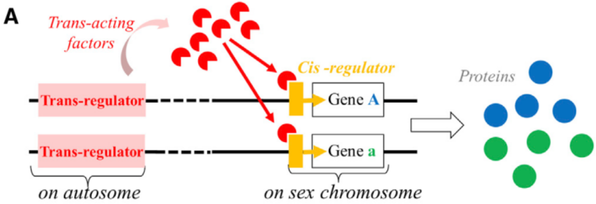
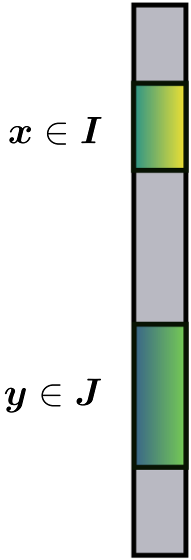


Multiplicative gene interactions
Lenormand et al. (2020)

Continuum-of-alleles models (Burger (2000))



Kimura (1965) and Lande (1975)

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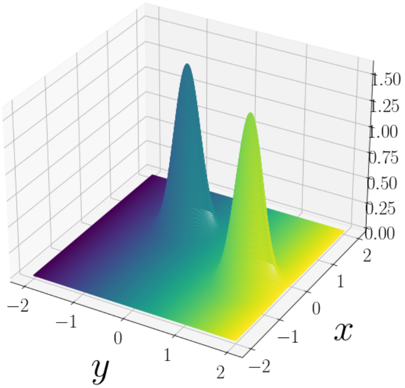
Motivation

What are the **long-term dynamics** of the allelic distribution with:

- **General gene interactions** (*e.g. regulation of gene expression*, Lenormand et al. (2020)),
- **general selection functions** $\boldsymbol{m(x, y)}$.

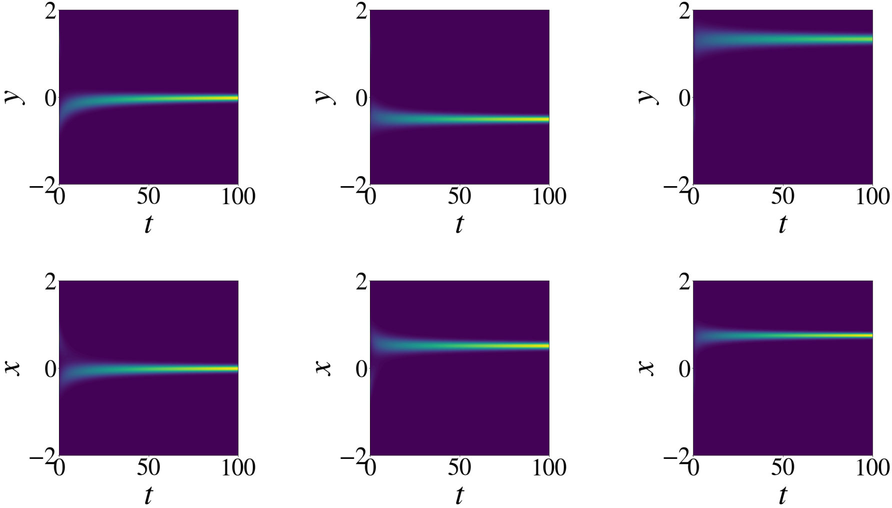
Motivation



Bimodal initial state

Motivation

$m(x, y) = x^2 + y^2$ $\quad$ $m(x, y) = (x + y)^2$ $\quad$ $m(x, y) = (1 - xy)^2$



Generic two-locus model for haploid populations.

Dynamics of the allelic distribution $\boldsymbol{n}$,
$(t, x, y) \in [0, T] \times I \times J$

$$\begin{cases} \partial_{\boldsymbol{t}} \boldsymbol{n}(\boldsymbol{t}, x, y) = \overbrace{r\, \mathcal{B}[\boldsymbol{n}](\boldsymbol{t}, x, y)}^{\text{reproduction}} - \overbrace{\kappa\, \boldsymbol{\rho}(\boldsymbol{t})\, \boldsymbol{n}(\boldsymbol{t}, x, y)}^{\text{competition}} - \overbrace{m(x, y)\, \boldsymbol{n}(\boldsymbol{t}, x, y)}^{\text{natural selection}}, \\ \boldsymbol{\rho}(t) = \int_{I \times J} \boldsymbol{n}(\boldsymbol{t}, x', y')\, dx'\, dy', \\ \boldsymbol{n}(0, x, y) = \boldsymbol{n}^{\mathbf{0}}(x, y). \end{cases} \qquad (P\,(\boldsymbol{n}))$$

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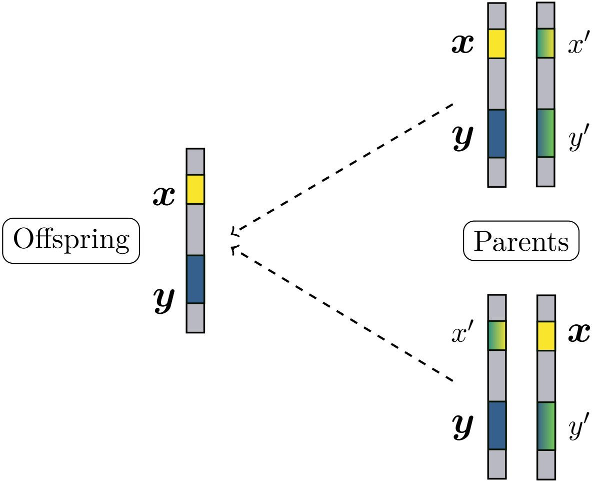
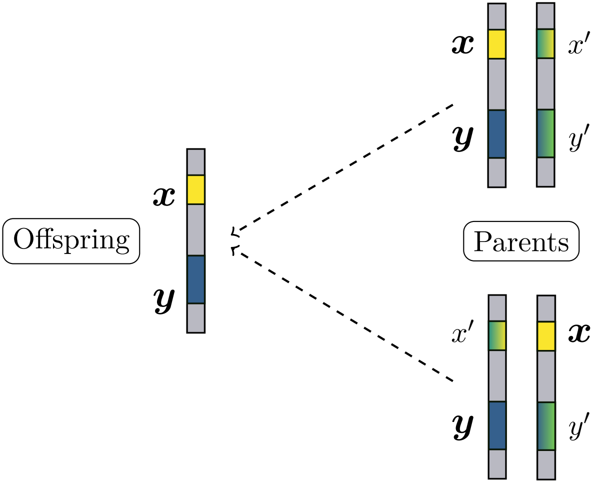
Generic two-locus model for haploid populations.

Reproduction: no mutation



Generic two-locus model for haploid populations: Mendelian inheritance.

Reproduction: no mutation



$\propto \boldsymbol{n}(\boldsymbol{x}, \boldsymbol{y}) \times \iint \boldsymbol{n}(x', y') dx' dy'$

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Two-locus model for haploid.

Integro-differential equation

$$
\begin{cases}
\partial_{\boldsymbol{t}} \boldsymbol{n}(\boldsymbol{t},x,y) = \frac{r}{2} \overbrace{\left[\frac{\boldsymbol{\rho}^{\boldsymbol{Y}}(\boldsymbol{t},x)\,\boldsymbol{\rho}^{\boldsymbol{X}}(\boldsymbol{t},y)}{\boldsymbol{\rho}(\boldsymbol{t})} + \boldsymbol{n}(\boldsymbol{t},x,y) \right]}^{\mathcal{B}[\boldsymbol{n}](\boldsymbol{t},x,y)} - \left(m(x,y) + \kappa\,\boldsymbol{\rho}(\boldsymbol{t})\right)\,\boldsymbol{n}(\boldsymbol{t},x,y), \\
\boldsymbol{\rho}^{\boldsymbol{X}}(\boldsymbol{t},y) = \int_I \boldsymbol{n}(\boldsymbol{t},x',y)\,dx', \quad \boldsymbol{\rho}^{\boldsymbol{Y}}(\boldsymbol{t},x) = \int_J \boldsymbol{n}(\boldsymbol{t},x,y')\,dy', \\
\boldsymbol{\rho}(t) = \int_{I\times J} \boldsymbol{n}(\boldsymbol{t},x',y')\,dx'\,dy', \\
\boldsymbol{n}(0,x,y) = \boldsymbol{n}^{\boldsymbol{0}}(x,y).
\end{cases}
$$

One-locus diploid model: Collet, Méléard, and Metz (2013)

Stochastic derivation of an equation similar to $(P(\boldsymbol{n}))$ with $\boldsymbol{n}^{\boldsymbol{0}}$ and $\boldsymbol{m}$ symmetrical $\rightsquigarrow$ $\boldsymbol{n}(\boldsymbol{t},\cdot,\cdot)$ symmetrical.

Two-locus model for haploid: preliminary result.

Integro-differential equation

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Theorem (Well-posedness)

Under suitable assumptions, there ***exists a unique solution*** $\boldsymbol{n} \in C^1([0,T]\times I\times J))$, *with a* ***bounded population size***

$$\exists(\rho^-,\rho^+),\ \forall \boldsymbol{t}\in\ [0,T], \qquad 0<\rho^-\le \boldsymbol{\rho}(\boldsymbol{t})\le\rho^+.$$

Specific question

What are the long-time dynamics with a small initial variance?

$$
\begin{cases}
\overbrace{\varepsilon \partial_t n_\varepsilon}^{\text{Long time}}(t,x,y) = \frac{r}{2}\left[\frac{\rho_\varepsilon^Y(t,x)\,\rho_\varepsilon^X(t,y)}{\rho_\varepsilon(t)} + n_\varepsilon(t,x,y)\right] - (m(x,y)+\kappa\rho_\varepsilon)\,n_\varepsilon, \\
\rho_\varepsilon^X(t,y) = \int_I n_\varepsilon(t,x',y)\,dx', \quad \rho_\varepsilon^Y(t,x) = \int_I n_\varepsilon(t,x,y')\,dy', \\
\rho_\varepsilon(t) = \int_{I\times J} n_\varepsilon(t,x',y')\,dx'\,dy', \\
n_\varepsilon(0,x,y) = n_\varepsilon^0(x,y) = \underbrace{\frac{1}{\varepsilon}\exp\left(\frac{u_\varepsilon^0}{\varepsilon}\right)}_{\text{Small initial variance}}.
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Weak convergence $n_\varepsilon \rightharpoonup n$

Uniformly bounded pop. size: $0 < \rho^- \leq \rho_\varepsilon(t) \leq \rho^+ \rightsquigarrow$ convergence toward **a measure** n. **Support?**

Asymptotic framework: Small variance methodology

Introduced by Diekmann et al. (2005) for quantitative genetic models[*] [†] [‡] :

$\boxed{\text{Diversity from reproduction}} \ll \boxed{\text{Selection pressure}}$

$\rightsquigarrow$ **Concentration** on the fittest traits.

$\rightsquigarrow$ Transform Dirac singularities: $u_\varepsilon := \varepsilon \log(\varepsilon\, n_\varepsilon)$.

---

[*] Geometric optics for reaction-diffusion (Freidlin 1986; Evans and Souganidis 1989)

[†] **Asexual**: ***constrained Hamilton-Jacobi eq.*** (Perthame and Barles 2008; Barles, Mirrahimi, and Perthame 2009; Lorz, Mirrahimi, and Perthame 2011; Mirrahimi 2017)

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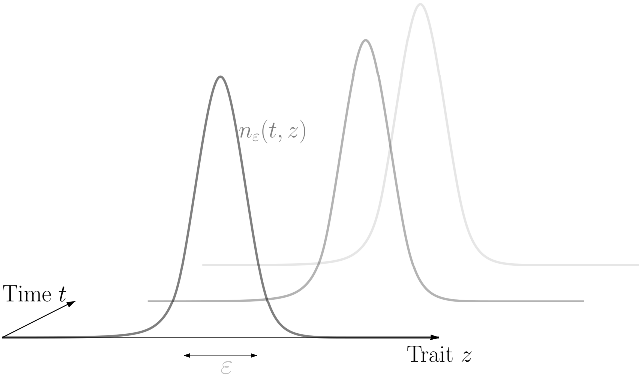
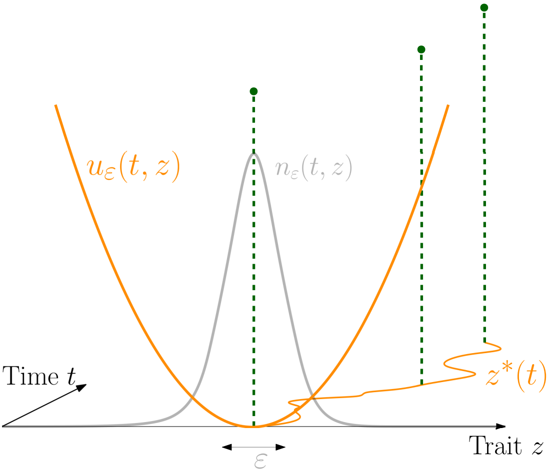


Moving concentrated distribution

Asymptotic framework: Small variance methodology



Transform: $n_\varepsilon = \frac{1}{\varepsilon}\,\exp\left(-\frac{u_\varepsilon(z)}{\varepsilon^2}\right)$.

Small variance method: $u_\varepsilon = \varepsilon \log(\varepsilon\, n_\varepsilon)$

Auxiliary integro-differential equation

$$
\begin{cases}
\partial_t\, u_\varepsilon(t,x,y) = \overbrace{\frac{r}{2\rho_\varepsilon(t)} \iint_{I\times J} \frac{1}{\varepsilon} \exp\left[\frac{u_\varepsilon(t,x,y') + u_\varepsilon(t,x',y) - u_\varepsilon(t,x,y)}{\varepsilon}\right] dx'\, dy'}^{\frac{r}{2}\frac{\rho_\varepsilon^X(t,y)\,\rho_\varepsilon^Y(t,x)}{\rho_\varepsilon(t)\, n_\varepsilon(t,x,y)}} \\
\qquad\qquad - \left(m(x,y) + \kappa\,\rho_\varepsilon(t) - \frac{r}{2}\right), \\
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u_\varepsilon(0,\cdot,\cdot) = u_\varepsilon^0.
\end{cases}
\tag{P_{u_ε}}
$$

$$
\partial_t u_\varepsilon = \frac{\varepsilon \partial_t n_\varepsilon}{n_\varepsilon}, \quad \varepsilon \partial_t n_\varepsilon(t,x,y) = \frac{r}{2}\left[\frac{\rho_\varepsilon^Y(t,x)\,\rho_\varepsilon^X(t,y)}{\rho_\varepsilon(t)} + n_\varepsilon(t,x,y)\right] - \left(m(x,y) + \kappa\rho_\varepsilon(t)\right) n_\varepsilon.
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Asymptotic analysis $(\varepsilon \to 0)$?

Convergence of u_ε and properties of the limit?

Main result

Theorem (D. and Mirrahimi (2022))

For all $T > 0$, $\boxed{u_\varepsilon \underset{\varepsilon\to 0}{\longrightarrow} u}$ *in* $C^0([0,T]\times I\times J)$ *(along subseq.),* $\boxed{\max u = 0}$.

(i) ***(Additivity of*** u***)***

$$\forall (t,x,y),\quad u(t,x,y) = u^Y(t,x) + u^X(t,y) := \max u(t,x,\cdot) + \max u(t,\cdot,y).$$

(ii) ***Limit equations on*** u^X, u^Y, *a.e.* $y, \forall t \in [0,T]$ *:*

$$u^X(t,y) = u^X(0,y) + r\,t - \kappa \int_0^t \rho(s)\,ds - \int_0^t \langle \phi^X(t,\cdot,y), m(\cdot,y)\rangle\,ds,$$

where ϕ^X *is the limit of* $\frac{n_\varepsilon}{\rho_\varepsilon^X}$ *in* $L^\infty\left(w^* - [0,T]\times I, M^1(I)\right)$.

(iii) ***(Support of*** $n \subset$ ***Zeros of*** u***)***

$$\begin{aligned}\operatorname{supp}(n(t,\cdot,\cdot)) &\subset \{(x,y)\in I\times J \mid u(t,x,y)=0\}\\ &= \{x\in I \mid u^Y(t,x)=0\}\times\{y\in J\mid u^X(t,y)=0\}.\end{aligned}$$

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Some elements of the proof

1. A priori **Lipschitz estimates**:
   - **Space** regularity: comparison principle on $\partial_x u_\varepsilon$ and $\partial_y u_\varepsilon$.
   - **Time** regularity: comparison principle on $\nu_\varepsilon(t,x,y) := \frac{\rho_\varepsilon^X(t,y)\,\rho_\varepsilon^Y(t,x)}{n_\varepsilon(t,x,y)\,\rho_\varepsilon(t)} \in [\nu_m, \nu_M]$.

$$\partial_t u_\varepsilon(t,x,y) = \frac{r}{2}\left[\overbrace{\frac{\rho_\varepsilon^X(t,y)\,\rho_\varepsilon^Y(t,x)}{n_\varepsilon(t,x,y)\,\rho_\varepsilon(t)}}^{\nu_\varepsilon(t,x,y)} + 1\right] - \kappa\rho_\varepsilon - m(x,y).$$

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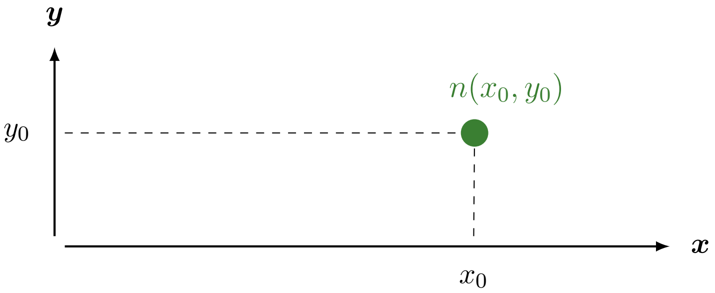
   ◇ **Time** regularity: comparison principle on $\nu_\varepsilon = \frac{\rho_\varepsilon^X(t,y)\,\rho_\varepsilon^Y(t,x)}{n_\varepsilon(t,x,y)\,\rho_\varepsilon(t)}$

Mendelian inheritance with sexual reproduction

$$\boxed{\nu_m \rho_\varepsilon(t)\, n_\varepsilon(t,x_0,y_0) \le \rho_\varepsilon^X(t,y_0)\,\rho_\varepsilon^Y(t,x_0) \le \nu_M n_\varepsilon(t,x_0,y_0)\rho_\varepsilon(t)}.$$



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Mendelian inheritance with sexual reproduction

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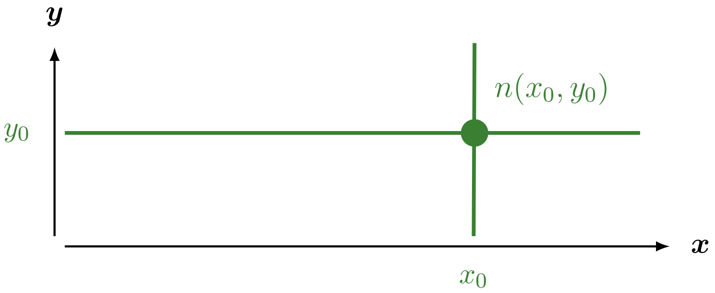

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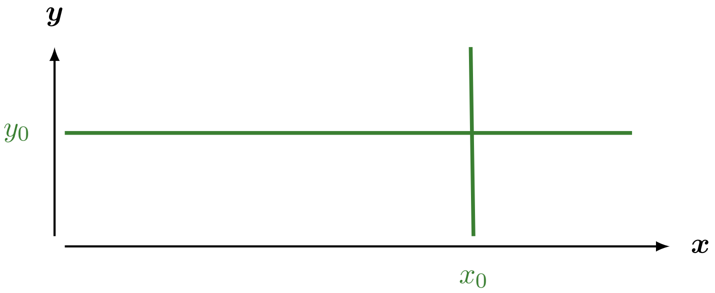

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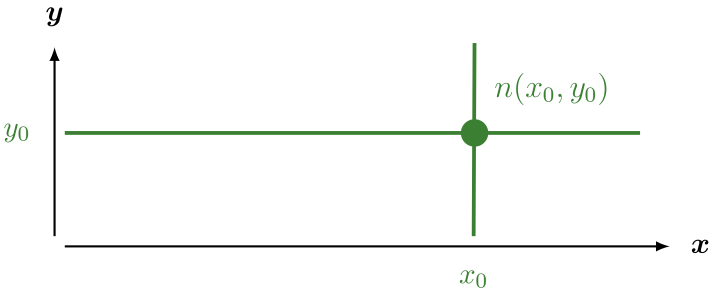

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Intuition of the asymptotic behaviour

Reproduction remains asymptotically bounded ≈

$$\forall (t,x,y), \quad \max_{(x',y')} \left[u(t,x,y') + u(t,x',y) - u(t,x,y)\right] = 0.$$

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3. **Limit equation** from the **marginals** ρ_ε^X and ρ_ε^Y (simple reproduction term):

$$\boxed{\partial_t u_\varepsilon^X(t,y) = \frac{\varepsilon \partial_t \rho_\varepsilon^X(t,y)}{\rho_\varepsilon^X(t,y)} = r - \kappa \rho_\varepsilon(t) - \int_I m(x',y) \frac{n_\varepsilon(t,x',y)}{\rho_\varepsilon^X(t,y)} dx'},$$

$$\partial_t u_\varepsilon(t,x,y) = \frac{\varepsilon \partial_t n_\varepsilon(t,x,y)}{n_\varepsilon(t,x,y)} = \frac{r}{2}\left[\frac{\rho_\varepsilon^X(t,y)\,\rho_\varepsilon^Y(t,x)}{n_\varepsilon(t,x,y)\,\rho_\varepsilon(t)} + 1\right] - \kappa\rho_\varepsilon - m(x,y).$$

Dynamics of dominant alleles under monomorphism

Assumptions:

(i) (**monomorphism**)
$\forall t \in [0,T] \quad , \exists! (\bar{x}(t), \bar{y}(t)), \quad u(t,\cdot,\cdot)^{-1}(\{0\}) = \{(\bar{x}(t), \bar{y}(t))\}.$

(ii) (**regularity**)

$$\begin{cases} \forall (t,y) \in [0,T] \times J, \quad \partial_t u^X(t,y) = r - \kappa\, \rho(t) - m(\bar{x}(t)), y), \\ \forall (t,x) \in [0,T] \times I, \quad \partial_t u^Y(t,x) = r - \kappa\, \rho(t) - m(x, \bar{y}(t)). \end{cases}$$

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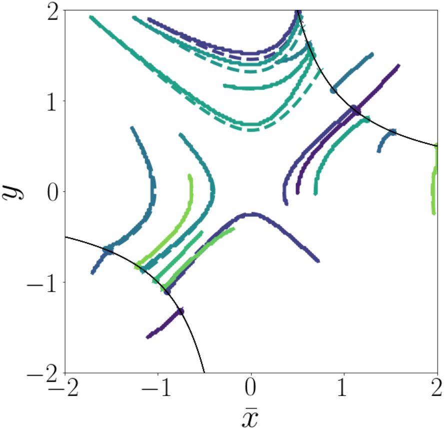
Proposition (Canonical equations)

Under suitable assumptions, the ***dynamics of the dominant alleles*** $(\bar{x}(t), \bar{y}(t))$ *read:*

$$\begin{cases} \frac{d\bar{x}}{dt} \times \overbrace{\partial_{xx} u^Y(\bar{x}(t))}^{1/Part.\ variance\ in\ pop} = \overbrace{\partial_x m(\bar{x}(t), \bar{y}(t))}^{Part.\ selection\ gradient}, \\ \frac{d\bar{y}}{dt} \times \partial_{yy} u^X(\bar{y}(t)) = \partial_y m(\bar{x}(t), \bar{y}(t)). \end{cases} \qquad (E_{\text{canonical}})$$

Comparison of ($E_{\text{canonical}}$) with the numerical resolution of ($P(n_{0.01})$).

Trajectories of the dominant alleles in a monomorphic system, $\boldsymbol{m(x,y) = (1 - xy)^2}$.



Conclusion

Quantitative alleles dynamics

Accurate description with our analysis with general selections

- **Convergence** of proxy $u_\varepsilon \to u$, $\mathrm{Supp.}(n(t,\cdot,\cdot)) \subset \mathrm{Zeros}(u(t,\cdot,\cdot))$.
- **Canonical equations** for dominant traits under monomorphism.

Broader perspective

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Suitable tools to study and predict evolutionary phenomena outside of classical frameworks.

What's next?

- Limits:
  1. Lack of regularity of limit objects ϕ^X, ϕ^Y.
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- All (some?) of your questions!

Acknowledgments

(a) Sepideh Mirrahimi*

(b) Vincent Calvez †

(c) Sally Otto ‡

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Questions?

Broader perspective

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