Demography, extinction and genetics

Camille Coron

Université Paris-Sud

Luminy
June 2018

Motivations

Joint works with:

- Denis Villemonais and Sylvie Méléard
- Diala Abu Awad

We aim at studying:

- Extinction of populations
    - Evolution of populations near extinction
    - Joint dynamics of demography and genetics
- Genetic composition of populations conditioned on survival

Microscopic model

Features:

- Diploid individuals, 1 gene, L alleles
- Competition and sexual Mendelian reproduction
- Individual-based model

Model:

- Multi-type non-linear birth-and-death process
- Rescaling: Large population, frequent reproduction and death events

Jump rates

n = number of individuals
x_{ij} = proportion of genotype ij
$\mathbf{x} = (n, (x_{ij})_{i \leq j})$ = state of the population
x_i = proportion of allele i

$$\mu_{ij}(\mathbf{x}) = \left(d_{ij} + \sum_{1 \leq k,l \leq L} c_{ij,kl} n x_{kl} \right) n x_{ij},$$

$$\lambda_{ij}(\mathbf{x}) = b_{ij} n \times 2 x_i x_j, \qquad \lambda_{ii}(\mathbf{x}) = b_{ii} n x_i^2.$$

Rescaling

Large population, frequent reproduction and death events

$$\mathbf{Z}_t^K = \left(\frac{N^K(t) X_{ij}^K(t)}{K} \right)_{i \leq j}$$

$$\mathbf{Z}_0^K \Longrightarrow \mathbf{Z}_0$$

$$\begin{aligned} b_{ij}^K &= \gamma K + \beta_{ij}, \\ d_{ij}^K &= \gamma K + \delta_{ij}, \\ c_{ij,kl}^K &= \frac{\alpha_{ij,kl}}{K}, \end{aligned}$$

Slow-fast convergence

Fast convergence to Hardy-Weinberg structure (Ethier & Nagylaki (1980))

$$\sup_{t\leq u\leq t+s} \mathbb{E}((\epsilon_{ij}^K(u))^2) \underset{K\to\infty}{\longrightarrow} 0$$

Slow convergence to a diffusion process:

$$((n^K(t), x_2^K(t), ..., x_L^K(t)))_{t\leq T} \underset{K\to\infty}{\Longrightarrow} ((n(t), x_2(t), ..., x_L(t)))_{t\leq T}$$

Limiting diffusion process

$$f(N(t), X_2(t), ..., X_L(t)) = M_t + \int_0^t \mathcal{L} f(N(s), X_2(s), ..., X_L(s))ds$$

$$\begin{aligned}
\mathcal{L} f(n, x_2, ..., x_L) = {} & n\left(\rho - \alpha n + \sum_{i=2}^{L} s_i x_i\right) \frac{\partial f}{\partial n}(n, x_2, ..., x_L) \\
& + \gamma n \frac{\partial^2 f}{\partial n^2}(n, x_2, ..., x_L) \\
& + \sum_{i=2}^{L} x_i \Big(s_i - \sum_{j=1}^{L} x_j s_j \Big) \frac{\partial f}{\partial x_i}(n, x_2, ..., x_L) \\
& + \sum_{i=2}^{L} \gamma \, \frac{x_i(1-x_i)}{2n} \frac{\partial^2 f}{\partial x_i^2}(n, x_2, ..., x_L) \\
& - \sum_{i \neq j \in [\![2, N]\!]} \gamma \, \frac{x_i x_j}{2n} \frac{\partial^2 f}{\partial x_i \partial x_j}(n, x_2, ..., x_L).
\end{aligned}$$

Questions

- Behaviour of genetics at extinction
- Impact of adding demography

Wright-Fisher with demography

Theorem

(i) *The population gets extinct almost surely in finite time.*
(ii) *One of the allele will get fixed a.s. before extinction.*
(iii) *The population experiences successive allele extinctions.*

Extinction and fixation

$$\begin{cases} dN_t &= \sigma(N_t)\,dB_t + N_t(\rho - \alpha N_t)dt, \quad \alpha > 0 \\ dX_t &= \sqrt{\frac{X_t(1-X_t)}{f(N_t)}}\,dW_t \end{cases} \qquad t < T_{0+}^N, \tag{1}$$

Theorem

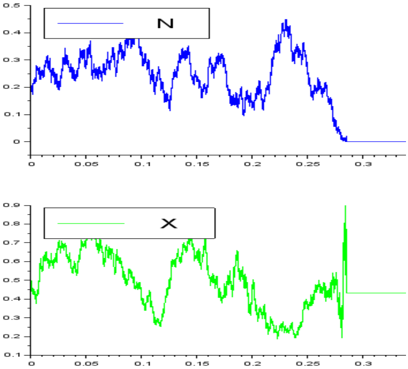
Fixation occurs before extinction with probability one if and only if

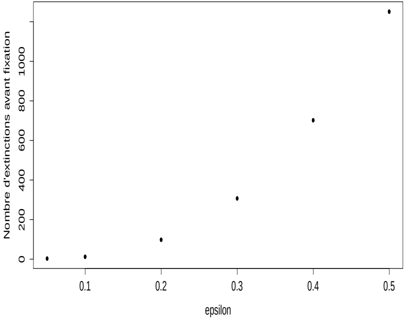
$$\int_{0+} \frac{y}{\sigma^2(y) f(y)}\,dy = +\infty. \tag{2}$$

Extinction before fixation

$$dN_t = \sqrt{N_t^{(1-\varepsilon)}}dB_t^1 + N_t(-1 - 0.1N_t)dt \tag{3}$$

$$dX_t = \sqrt{\frac{X_t(1-X_t)}{N_t}}dB_t^2 \tag{4}$$





Ideas of the proof

Theorem

(i) *The population gets extinct almost surely in finite time.*
Well-known (Ikeda-Watanabe, Chapter VI.3).

(ii) *One of the allele will get fixed a.s. before extinction.*
Girsanov+Time change+Path integrability argument.

(iii) *The population experiences successive allele extinctions.*
Girsanov+Rescaling+Time change+Path integrability argument.

1. Model and rescaling
2. Demography and allele fixation
3. Path integrability
4. Rescaling and time changes
5. Distance to the Wright-Fisher diffusion

Path integrability criterion

Theorem

- $(Z_t, 0 \leq t \leq T_0)$ *regular diffusion process on* $[0, +\infty)$
- *Scale function* s, *speed measure* m.
- $\mathbb{P}_z(T_0 < +\infty) = 1$ *for all* $z \in [0, +\infty)$
- $f : (0, +\infty) \to \mathbb{R}_+$ *locally bounded measurable function.*

$$\int_{0+} s(y)\, f(y)\, m(dy) < +\infty \iff \int_0^{T_0} f(Z_s)\, ds < +\infty \quad \mathbb{P}_z - a.s.$$

$$\int_{0+} s(y)\, f(y)\, m(dy) = +\infty \iff \int_0^{T_0} f(Z_s)\, ds = +\infty \quad \mathbb{P}_z - a.s.$$

Path integrability criterion: proof

- Engelbert & Tittel (2002), Khoshnevisan, Salminen & Yor (2006) Mijatovic & Urusov (2012)

- $\mathbb{P}(\int_0^{T_0} f(Z_s)ds < \infty) \in \{0,1\}$

- If $\int_0^{\infty} s(y)\, f(y)\, m(dy) = +\infty$ then $\mathbb{P}_z\left(\int_0^{T_0} f(Z_s)\, ds = +\infty\right) \geq \frac{1}{20}$.

- $\mathbb{E}_z\left[\left(\int_0^{T_0} f(Z_s)\, ds\right)^n\right] \leq n!\, \left(\int_0^{\infty} s(y)\, f(y)\, m(dy)\right)^n$

Path integrability, Feller diffusion

Lemma

Let N be solution of

$$dN_t = \sqrt{\gamma N_t}\, dB_t + N_t(\rho - \xi N_t)dt.$$

Let $T_0^N = \inf\{t \geq 0, N_t = 0\}$. *For any* $x \in \mathbb{R}_+$,

$$\mathbb{P}_x\Big(\int_0^{T_0^N} \frac{1}{N_s}\, ds = +\infty \Big) = 1.$$

Path integrability, Wright-Fisher diffusion

Lemma

Let Y be solution of

$$dY_t = \sqrt{Y_t(1-Y_t)}\,dB_t, \qquad Y_0 \in [0,1).$$

Let $T_1 = \inf\{t \geq 0, Y_t = 1\}$. *For any* $y \in (0,1)$,

$$\mathbb{P}_y\Big(\int_0^{T_1} \frac{1}{1-Y_s}\,ds = +\infty \Big) = 1.$$

1. Model and rescaling
2. Demography and allele fixation
3. Path integrability
4. Rescaling and time changes
5. Distance to the Wright-Fisher diffusion

Wright-Fisher diffusion behaviour

Proposition

Let $(X^1, ..., X^{L-1})$ be an L-type Wright-Fisher neutral diffusion process.

- *One of the L alleles is fixed a.s. in finite time.*
  By induction on L.
- *The population experiences successive allele extinctions.*
  By induction on L: Time change+Path integrability

Proof: Time change+Path integrability

- $\int_0^{T_1^{X^L}} \frac{1}{1-X_s^L}\,ds = +\infty$
- Define τ on $[0,+\infty)$ such that $\int_0^{\tau(t)} \frac{1}{1-X^L(s)}ds = t \quad$ for all $t \geq 0$.
- Let

$$(Y_t^1, Y_t^2, ..., Y_t^{L-2})_{t\geq 0} = \left(\frac{X^1}{1-X^L}(\tau(t)), ..., \frac{X^{L-2}}{1-X^L}(\tau(t))\right)_{t\geq 0}.$$

Lemma

$(Y_t^1, Y_t^2, ..., Y_t^{L-2})_{t\geq 0}$ *is a* $L-1$*-type Wright-Fisher diffusion process.*

- Successive allele extinctions at time $S_1^Y < ... < S_{L-2}^Y < +\infty$
- Successive allele extinctions for $(X^1, X^2, ..., X^L)$ at times $\tau(S_1^Y) < ... < \tau(S_{L-2}^Y) < \tau(+\infty) = T_1^{X^L}$ if $T_1^{X^L} < \infty$

Demographic Wright-Fisher diffusion

- L-dimensional Girsanov transformation->neutral case
- $\int_0^{T_0^N} \frac{\gamma}{2N_s}\, ds = +\infty$ a.s.
- $\int_0^{\tau(t)} \frac{\gamma}{2N_s}\, ds = t$ for all $t \in \mathbb{R}_+$
- $\hat{X}_t = X_{\tau(t)}$ follows a neutral classical Wright-Fisher diffusion process.

Effective population size

- 2 neutral alleles
- (X, N) demographic Wright-Fisher diffusion with parameters ρ, α.
- X^{WF} classical Wright-Fisher diffusion with parameter N_e
- Calibration: we impose

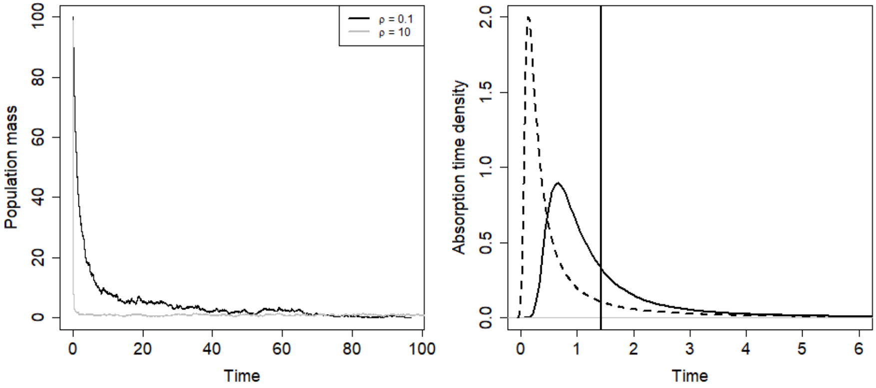
$$\mathbb{E}(T^{X}_{\{0,1\}}) = \mathbb{E}(T^{X^{WF}}_{\{0,1\}}),$$

which gives

$$N_e = \mathbb{E}\left(\frac{T^{X}_{\{0,1\}}}{\int_0^{T^{X}_{\{0,1\}}} \frac{1}{N_t} dt} \right).$$

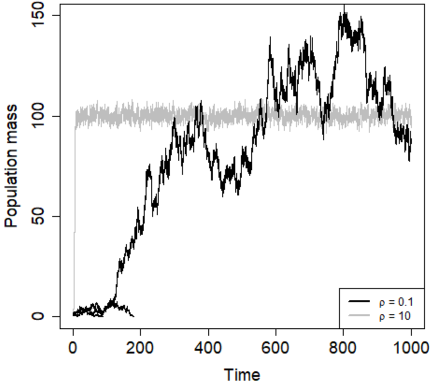
Law of absorption time

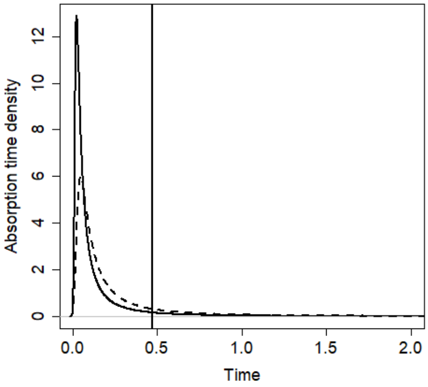
Decreasing population size



Law of absorption time

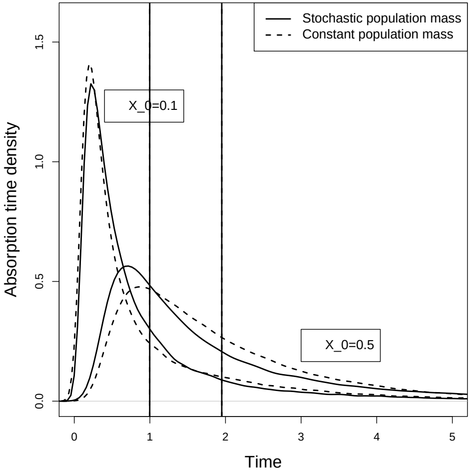
Increasing populations size





Law of absorption time

"Constant" population size



Perspectives

- Continuum of alleles: demographic Fleming-Viot process

- Quasi-stationary behaviour

Bibliography

- C. & Abu Awad (2017): *Effects of demographic stochasticity and life-history strategies on times and probabilities to fixation*. To appear in Heredity.
- C., Méléard, Villemonais (2017): Perpetual integrals convergence and extinctions in population dynamics. ArXiv.
- C. (2016): Slow-fast stochastic diffusion dynamics and quasi-stationary distributions for diploid populations. J. Math. Biol.
- Ethier & Nagylaki (1980): Diffusion approximations of markov chains with two time scales and applications to population genetics. Adv. in App. Probab.
- Engelbert & Tittel (2002): Integral functionals of strong Markov continuous local martingale. In Stochastic Processes and Related Topics: Proceedings of the 12th Winter School Siegmundsburg, Germany, ed. by Buckdahn, Engelbert and Yor. Taylor & Francis.
- Khoshnevisan, Salminen & Yor (2006): A note on a.s. finiteness of perpetual integral functionals of diffusions. ECP 11.
- Mijatovic & Urusov (2012): Convergence of integral functionals of one-dimensional diffusions. ECP 17