Limiting diffusion and quasi-stationary behavior of a diploid population

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Motivation

- Consider a population of diploid individuals
- One gene, two alleles.
- In a long-time scale, conditionally to the surviving of the population, which allele will remain?
- Can we observe a long-time coexistence of the two alleles?

Understand the quasi-stationary behavior of a diploid population.

Model

- 2 alleles, A and a. Genotypes: AA, Aa and aa.
- 3-type birth-and-death process:

$$Z_t = (Z_t^1, Z_t^2, Z_t^3).$$

- Population size $N = Z^1 + Z^2 + Z^3$.
- $2Z^1 + Z^2 = A^1$ =number of alleles A,
  $2Z^3 + Z^2 = A^2$ =number of alleles a.
- Proportion of allele A:

$$X = \frac{2Z^1 + Z^2}{2N}$$

Birth-and-death rates

- Logistic model:

$$d^1(Z) = (d_1 + c_{11}Z^1 + c_{21}Z^2 + c_{31}Z^3)Z^1$$

- Diploid Mendelian reproduction:

$$b^1(Z) = \frac{bp_1}{N}\left[\left(Z^1\right)^2 + Z^1Z^2 + \frac{(Z^2)^2}{4}\right]$$

Change of scale

- Rescaling the size of individuals: $Z^K = Z/K \in (\mathbb{Z}_+)^3/K$, $K \longrightarrow +\infty$
- 2 birth and natural death scalings:
  - First scaling:

$$\begin{aligned} b_i^K &= \beta \\ d_i^K &= \delta \\ Kc_{ij}^K &= \alpha \end{aligned}$$

  - Second scaling:

$$\begin{aligned} b_i^K &= \gamma K + \beta_i \\ d_i^K &= \gamma K + \delta_i \\ Kc_{ij}^K &= \alpha_{ij} \end{aligned}$$

Deterministic limit in the first scaling

From Collet, P., Méléard, S., Metz, J.A.J. (2012), convergence toward a deterministic limit $(\mathcal{Z}_t)_{t\geq 0}$, if $Z_0^K \longrightarrow \mathcal{Z}_0$.

$$\begin{cases} \frac{d\mathcal{Z}_t^1}{dt} = b^{1,\infty}(\mathcal{Z}_t) - d^{1,\infty}(\mathcal{Z}_t) \\ \frac{d\mathcal{Z}_t^2}{dt} = b^{2,\infty}(\mathcal{Z}_t) - d^{2,\infty}(\mathcal{Z}_t) \\ \frac{d\mathcal{Z}_t^3}{dt} = b^{3,\infty}(\mathcal{Z}_t) - d^{3,\infty}(\mathcal{Z}_t). \end{cases}$$

$$Y_t = \frac{4\mathcal{Z}_t^1\mathcal{Z}_t^3 - (\mathcal{Z}_t^2)^2}{4\mathcal{N}_t} \Longrightarrow \frac{dY_t}{dt} = -\delta Y_t \quad \forall t \geq 0 \quad \text{if } \alpha = 0.$$

$$\Longrightarrow Y_t = Y_0 e^{-\delta t}.$$

$$\begin{cases} \mathcal{Z}_t^1 = Y_0 e^{-\delta t} + (\mathcal{Z}_0^1 - Y_0)e^{(\beta-\delta)t} \\ \mathcal{Z}_t^2 = -2Y_0 e^{-\delta t} + (\mathcal{Z}_0^2 + 2Y_0)e^{(\beta-\delta)t} \\ \mathcal{Z}_t^3 = Y_0 e^{-\delta t} + (\mathcal{Z}_0^3 - Y_0)e^{(\beta-\delta)t}. \end{cases}$$

Hardy-Weinberg equilibrium

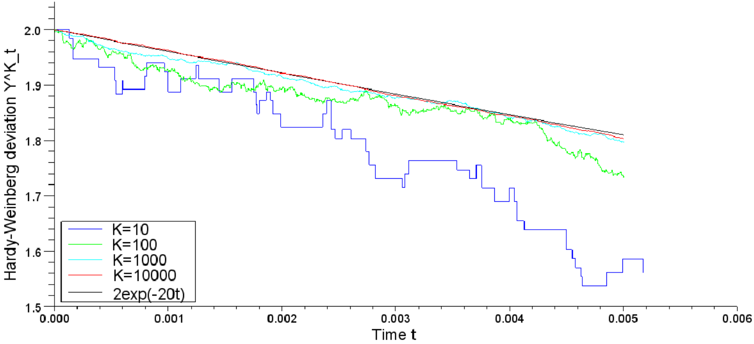

Figure : Convergence of the sequence of processes Y^K towards the deterministic function $t \mapsto Y_0 e^{-\delta t}$. Each curve corresponds to a different value of K. In this figure, $\beta = 10$, $\delta = 20$, $\alpha = 0$.

Second scaling and hypotheses

New scaling:

$$\begin{aligned} b^{i,K} &= \gamma K + \beta_i \\ d^{i,K} &= \gamma K + \delta_i \\ c_{ij}^K &= \frac{\alpha_{ij}}{K} \end{aligned}$$

Hypotheses: There exists a constant C such that for all $K \in \mathbb{N}$,

$$K\left(Y_0^K/N_0^K\right)^2 \leq C,$$

$$\mathbb{E}\left(\left(N_0^K\right)^2\right) \leq C.$$

Population size and Hardy-Weinberg deviation

Under these hypotheses:

- There exists a constant C_1 such that for all K, $\sup_{t \geqslant 0} \mathbb{E}\left(\left(N_t^K\right)^2\right) \leq C_1$,
- For all $t \geq 0$, Y_t^K converges in L^1 toward 0 when $K \to \infty$.

Sufficient confitions on α_{ij} in the cooperation case.

Convergence toward a diffusion process

- The sequence of processes $\left((A^{1,K},A^{2,K})\right)_{K\geq 0}$ is tight.
- This sequence converges toward a diffusion (A^1,A^2) such that in the neutral case:

$$dA^1_t=\sqrt{\frac{4\gamma}{A^1_t+A^2_t}A^1_t}dB^1_t+\sqrt{2\gamma\frac{A^1_tA^2_t}{A^1_t+A^2_t}}dB^2_t+\left(\beta-\delta-\alpha\frac{A^1_t+A^2_t}{2}\right)A^1_tdt$$

$$dA^2_t=\sqrt{\frac{4\gamma}{A^1_t+A^2_t}A^2_t}dB^1_t-\sqrt{2\gamma\frac{A^1_tA^2_t}{A^1_t+A^2_t}}dB^2_t+\left(\beta-\delta-\alpha\frac{A^1_t+A^2_t}{2}\right)A^2_tdt$$

Comparison with the haploid case 1

Diploid population:

$$dA_t^1 = \sqrt{\frac{4\gamma}{A_t^1 + A_t^2}} A_t^1 dB_t^1 + \sqrt{2\gamma \frac{A_t^1 A_t^2}{A_t^1 + A_t^2}} dB_t^2 + \left(\beta - \delta - \alpha \frac{A_t^1 + A_t^2}{2}\right) A_t^1 dt$$

$$dA_t^2 = \sqrt{\frac{4\gamma}{A_t^1 + A_t^2}} A_t^2 dB_t^1 - \sqrt{2\gamma \frac{A_t^1 A_t^2}{A_t^1 + A_t^2}} dB_t^2 + \left(\beta - \delta - \alpha \frac{A_t^1 + A_t^2}{2}\right) A_t^2 dt$$

Haploid Lotka-Volterra diffusion (Cattiaux, P., Méléard, S. (2009)):

$$dH_t^1 = \sqrt{2\gamma H_t^1} dB_t^1 + (\beta - \delta - \alpha(H_t^1 + H_t^2)) H_t^1 dt$$

$$dH_t^2 = \sqrt{2\gamma H_t^2} dB_t^2 + (\beta - \delta - \alpha(H_t^1 + H_t^2)) H_t^2 dt$$

Comparison with the haploid case 2

Diploid population:

$$\begin{aligned} dN_t &= (\beta - \delta - \alpha N_t)N_t dt + \sqrt{2\gamma N_t} dB^1_t \\ dX_t &= \sqrt{\frac{\gamma X_t(1-X_t)}{N_t}} dB^2_t. \end{aligned}$$

Haploid population (Cattiaux, P., Méléard, S. (2009)):

$$\begin{aligned} dN^h_t &= (\beta - \delta - \alpha N^h_t)N^h_t dt + \sqrt{2\gamma N^h_t} dW^1_t \\ dX^h_t &= \sqrt{\frac{2\gamma X^h_t(1-X^h_t)}{N^h_t}} dW^2_t. \end{aligned}$$

A change of variables

$$S_t^1 = \sqrt{\frac{\gamma N_t}{2}} \cos\left(\frac{\arccos(2X_t - 1)}{\sqrt{2}}\right)$$

$$S_t^2 = \sqrt{\frac{\gamma N_t}{2}} \sin\left(\frac{\arccos(2X_t - 1)}{\sqrt{2}}\right).$$

$S = (S^1, S^2)$ satisfies

$$dS_t = dW_t - \nabla Q(S_t) dt.$$

Diffusion coefficient

$$Q(S)=\begin{cases}\dfrac{\ln\left(\left(S^1\right)^2+\left(S^2\right)^2\right)}{2}+\frac{1}{2}\ln\left(\sin\left(\sqrt{2}\arctan\left(\frac{S^2}{S^1}\right)\right)\right)\\ \qquad -\left(\beta-\delta-\frac{\alpha\gamma}{4}\left(\left(S^1\right)^2+\left(S^2\right)^2\right)\right)\dfrac{\left(S^1\right)^2+\left(S^2\right)^2}{4}\\ \qquad \text{if } S^1\geqslant 0\\ \dfrac{\ln\left(\left(S^1\right)^2+\left(S^2\right)^2\right)}{2}+\frac{1}{2}\ln\left(\sin\left(\sqrt{2}\left(\arctan\left(\frac{S^2}{S^1}\right)+\pi\right)\right)\right)\\ \qquad -\left(\beta-\delta-\frac{\alpha\gamma}{4}\left(\left(S^1\right)^2+\left(S^2\right)^2\right)\right)\dfrac{\left(S^1\right)^2+\left(S^2\right)^2}{4}\\ \qquad \text{if } S^1\leqslant 0.\end{cases}$$

Definition space, absorbing sets

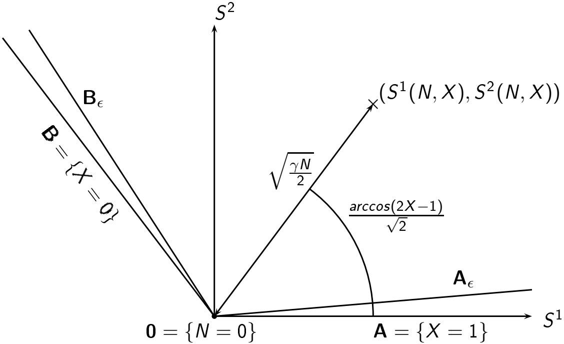

Figure : Definition space D for S.

Absorption: properties

Theorem

(i) *For all* $x \in D$, $\mathbb{P}_x(T_0 < \infty) = 1$ *and there exists* $\lambda > 0$ *such that* $sup_x \mathbb{E}_x(e^{\lambda T_0}) < +\infty$ *(Cattiaux et al. 2009).*

(ii) *For all* $x \in D \setminus \mathbf{0}$, $\mathbb{P}_x(T_{\mathbf{A}} \wedge T_{\mathbf{B}} < T_{\mathbf{0}}) = 1$.

- *True for the Brownian motion.*
- *Girsanov Theorem on* $D_\epsilon \Rightarrow \mathbb{P}_x(T_{\mathbf{A}_\epsilon} \wedge T_{\mathbf{B}_\epsilon} < T_{\mathbf{0}}) = 1$
- *Monotone convergence Theorem to conclude.*

(iii) *For all* $x \in D \setminus \partial D$, $\mathbb{P}_x(T_{\mathbf{A}} < T_{\mathbf{0}}) > 0$, *and* $\mathbb{P}_x(T_{\mathbf{B}} < T_{\mathbf{0}}) > 0$.

- *In the neutral case,* $\mathbb{P}_x(T_{\mathbf{B}} < T_{\mathbf{0}}) = 1/2$ *for all* $x \in \mathbf{B}_{\tan(\pi/(2\sqrt{2}))}$.
- *Markov property to conclude.*
- *Girsanov Theorem in the non-neutral case.*

Quasi-stationary behavior

Theorem

(Cattiaux, P. and Méléard, S. (2009))

(i) *There exists a unique distribution* ν_1 *on* $D \setminus \partial D$ *such that*
$$\lim_{t\to\infty} \mathbb{P}_x(S_t \in E | T_{\partial D} > t) = \nu_1(E) \quad \forall x \in D \setminus \partial D.$$

(ii) *There exists a unique distribution* ν *on* $D \setminus \mathbf{0}$ *such that*
$$\lim_{t\to\infty} \mathbb{P}_x(S_t \in E | T_0 > t) = \nu(E) \quad \forall x \in D \setminus \partial D.$$

Numerical results 1

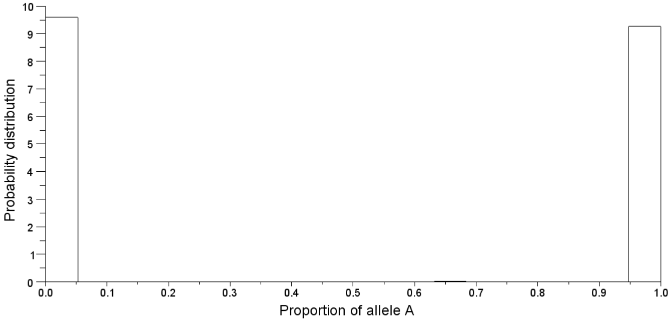

Figure : Distribution of the proportion X_t of allele A in a neutral case, knowing that $N_t \neq 0$. In this figure, $\beta_i = 1 = \delta_i$, and $\alpha_{ij} = 0.1$ for all i, j.

Numerical results 2

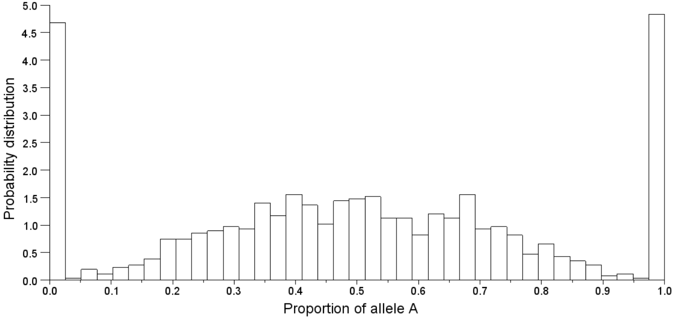

Figure : Distribution of the proportion X_t of allele A in an overdominance case, knowing that $N_t \neq 0$. In this figure, $\beta_i = 1$, $\delta_i = 0$, α is symmetric, $\alpha_{ii} = 0.1 = \alpha_{13}$ for all i, and $\alpha_{12} = \alpha_{23} = 0$.

Perspectives

- Which are the exact conditions for coexistence of the two alleles?
- 3-dimensional numerical results.
- More alleles.

Bibliography

- Cattiaux, P., Collet, P., Lambert, A., Martinez, S., Méléard, S,. and San Martín, J. (2009): Quasi-stationarity distributions and diffusion models in population dynamics. The Annals of Probability. 37:5:1926–1969
- Cattiaux, P., and Méléard, S. (2009): Competitive or weak competitive stochastic Lotka-Volterra systems conditioned on non-extinction. Journal of Mathematical Biology. 60:797–829.
- Collet, P., Méléard, S. and Metz, J.A.J. (2012): A rigorous model study of the adaptative dynamics of Mendelian diploids. Journal of Mathematical Biology. 205:1–39.
- C.C.: From diploid populations to Wright-Fisher diffusions and quasi-stationary distributions. Prepublication.
- Metz, J.A.J. and Redig, F. (2013): A birth and death process approach to selection in diploid populations. Prepublication.