Stochastic modeling and eco-evolution of a diploid population

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Outline of the presentation

0. A diploid Mendelian population model

1. Stochastic modeling of the mutational meltdown
   - Motivations and references
   - Fixation probability of a slightly non-neutral allele
   - Existence of a mutational meltdown
   - Numerical results and biological interpretations

2. Slow-fast dynamics, quasi-stationarity and measure-valued processes
   - Slow-fast dynamics
   - Quasi-stationary behavior of a diploid population
   - Numerical results
   - Multi-allelic model, measure-valued processes, allele continuum
0 A diploid Mendelian population model

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Model

- 1 gene, 2 alleles: \( A \) and \( a \).
- Diploid individuals: genotypes \( AA \), \( Aa \) and \( aa \).
- Population at time \( t \):
  \[
  (Z_t, t \geq 0) = ((Z^1_t, Z^2_t, Z^3_t), t \geq 0).
  \]
- \((Z_t, t \geq 0)\) is a birth-and-death process with Mendelian reproduction and competition.
For any \((k, m, n) \in (\mathbb{Z}_+)^3\) such that \(N = k + m + n\),

\[
\begin{align*}
\lambda_1(k, m, n) &= \frac{b_1}{N-1} \left[ k(k - 1) + km + \frac{m(m - 1)}{4} \right] \\
\lambda_2(k, m, n) &= \frac{b_2}{N-1} \left[ km + mn + \frac{m(m - 1)}{2} + 2kn \right] \\
\lambda_3(k, m, n) &= \frac{b_3}{N-1} \left[ n(n - 1) + mn + \frac{m(m - 1)}{2} \right]
\end{align*}
\]

\[
\begin{align*}
\mu_1(k, m, n) &= k(d_1 + c_{11}(k - 1) + c_{12}m + c_{13}n) \\
\mu_2(k, m, n) &= m(d_2 + c_{21}k + c_{22}(m - 1) + c_{23}n) \\
\mu_3(k, m, n) &= n(d_3 + c_{31}k + c_{32}m + c_{33}(n - 1))
\end{align*}
\]

Demographic parameters: \(b_i > 0, d_i \geq 0, c_{ij} > 0\), for \(i, j \in \{1, 2, 3\}\).
A diploid Mendelian population model

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1. Stochastic modeling of the mutational meltdown

# Motivations

Mutational meltdown:
- Observed in small populations.
- Combination of two phenomena that reinforce each other.

Small population size

Demography

Frequent deleterious mutation fixations

Genetics
1. Stochastic modeling of the mutational meltdown

1.1. Motivations and references

Motivations

Mutational meltdown:

- Observed in small populations.
- Combination of two phenomena that reinforce each other.

Small population size $\implies$ Frequent deleterious mutation fixations

Demography

Genetics
Motivations

Mutational meltdown:

- Observed in small populations.
- Combination of two phenomena that reinforce each other.

Small population size \(\iff\) Frequent deleterious mutation fixations

Demography \hspace{2cm} Genetics
Hypotheses for this work

- \( b_i = b > 0 \) and \( c_{ij} = c > 0 \) for all \( i, j \in \{1, 2, 3\} \).
- \( d_1 = d \geq 0, \ d_2 = d + \delta \) and \( d_3 = d + \delta' \).
- No death when there are only 2 individuals left.

\[
\implies Z_t \in (\mathbb{Z}_+)^3 = (\mathbb{Z}_+)^3 \setminus \{(0, 0, 0), (1, 0, 0), (0, 1, 0), (0, 0, 1)\}.
\]

\((Z_t, t \geq 0)\) is a Markov process with 2 absorbing sets:

- \( \Gamma_A = \{(k, 0, 0) : k \geq 2\} \): fixation of allele \( A \),
- \( \Gamma_a = \{(0, 0, n) : n \geq 2\} \): fixation of allele \( a \).
Fixation probability of allele $a$

- **Aim:** Study the fixation probability of allele $a$ if the population starts from the state $(k, m, n) \in \left(\mathbb{Z}_+\right)^3$: 

$$u_{k,m,n}^{\delta,\delta'}$$

- **Champagnat & Lambert (2007):** haploid case.

- **Neutral case** ($\delta = \delta' = 0$): 
  $$X_t = \frac{Z_t^2 + 2Z_t^3}{2(Z_t^1 + Z_t^2 + Z_t^3)}, \quad t \geq 0$$
  is a martingale.

$$\Rightarrow u_{0,0,k,m,n}^{0,0} = \frac{m + 2n}{2(k + m + n)}.$$
Taylor expansion of $u_{k,m,n}^{\delta,\delta'}$

- Decomposition of $u$:
  \[ u_{k,m,n}^{\delta,\delta'} = \sum_{n'} \sum_{(i_1,\ldots,i_l) \in C_{(k,m,n)} \rightarrow (0,0,n')} \pi_{i_1} \pi_{i_2} \ldots \pi_{i_{l-1}} \pi_{i_l}. \]

- For all $(k, m, n) \in (\mathbb{Z}_+)^3$, $u_{k,m,n}^{\delta,\delta'}$ is a differentiable function of $(\delta, \delta')$ in $(0,0)$:
  \[ u_{k,m,n}^{\delta,\delta'} = \frac{m + 2n}{2(k + m + n)} - \delta v_{k,m,n} - \delta' w_{k,m,n} + o(|\delta| + |\delta'|). \]

- $|v_{k,m,n}| \leq C(k + m + n)$ and $|w_{k,m,n}| \leq C(k + m + n)$ for all $(k, m, n) \in (\mathbb{Z}_+)^3$. 
Kolmogorov-forward equation

\[
\begin{align*}
(L^{\delta,\delta'} u(., \delta, \delta'))(k, m, n) &= 0 \quad \forall (k, m, n) | N = k + m + n \geq 2 \\
u((0, 0, n), \delta, \delta') &= 1 \quad \forall n \geq 2 \\
u((k, 0, 0), \delta, \delta') &= 0 \quad \forall k \geq 2
\end{align*}
\]

\[
u_{k,m,n} = \frac{2n + m}{2(k + m + n)} - \delta v_{k,m,n} - \delta' w_{k,m,n} + o(|\delta| + |\delta'|).
\]

\[
\begin{align*}
(L^{0,0} v)(k, m, n) &= \frac{m(n-k)}{2N(N-1)} \quad \forall (k, m, n) | k + m + n \geq 3 \\
v(2, 0, 0) &= v(0, 0, 2) = 0
\end{align*}
\]
The formula of $v_{k,m,n}$

**Proposition (1.3.6)**

For all $(k, m, n)$ such that $N = k + m + n \geq 2$,

$$v(k, m, n) = (k - n) \left[ \frac{m}{N} x_N + \frac{N^2 - (k - n)^2}{N^2} y_N \right]$$  \hspace{1cm} (1)

where the sequence of vectors $(z_N)_{N \geq 3} = \begin{pmatrix} x_N \\ y_N \end{pmatrix}_{N \geq 3}$ is the unique bounded solution of the following system of equations:

$$\begin{cases} B_N z_{N+1} = C_N z_N + D_N z_{N-1} + f_N & \text{for all } N \geq 4 \\ B_3 z_4 = \tilde{C}_3 z_3 + f_3, \end{cases}$$  \hspace{1cm} (S2)

where the matrices $B_N$, $C_N$, $\tilde{C}_3$, $D_N$ and the vectors $f_N$ are known.
Sketch of the proof

Proof.

- If (1) is true then (S2) implies (S1).
- (S2) has a bounded solution \((z_N)_{N \geq 3}\) if \(b\) is small: for \(N \geq 3\),

\[
B_N z_{N+1} = (C_N + K_N) z_N + \sum_{k=3}^{N} (-1)^{N-k} E(k, N) f_k, \quad \text{if } (S2')
\]

\[
\begin{align*}
K_3 &= \tilde{C}_3 - C_3 \\
K_N &= D_N (C_{N-1} + K_{N-1})^{-1} B_{N-1} \quad \forall N \geq 4 \\
E(k, k) &= I_2 \quad \forall k \geq 3 \\
E(k, N) &= D_N (C_{N-1} + K_{N-1})^{-1} E(k, N-1) \quad \forall k \in [3, N-1].
\end{align*}
\]

- For all \((k, m, n) \in (\mathbb{Z}_+)^3\), \(v_{k,m,n}\) is an analytic function of \(b\).
Mutations and mutational time scale

- Each individual mutates at rate $\mu_K = \frac{2\mu}{K}, K \to +\infty$.
- Each individual is characterized by its genotype $g = (x, x') \in \mathcal{G}$.
- $M(x_1, x_2)$ is the probability that a DNA strand $x_1$ mutates to $x_2$.
- Population at time $t$:

$$Z^K_t = \sum_{i=1}^{N^K_t} \delta_{g_i,K}$$

**Theorem (1.5.1), Convergence towards the TSS)**

For all $0 < t_1 < \ldots < t_n$,

$$(Z^K_{Kt_1}, \ldots, Z^K_{Kt_n}) \rightarrow (\tilde{N}_{t_1} \delta_{G_{t_1}}, \ldots, \tilde{N}_{t_n} \delta_{G_{t_n}}) \text{ in law, when } K \to \infty.$$
Trait Substitution Sequence

- Conditionally to \((G_{t_1}, \ldots, G_{t_n}) = (g_1, \ldots, g_n)\), the random variables \(\tilde{N}_{t_1}, \ldots, \tilde{N}_{t_n}\) are independent and \(\tilde{N}_{t_i}\) has law 
  \(l(., b(g_i), d(g_i), c(g_i, g_i))\), with

  \[
  l(N, b, d, c) := \frac{C}{N} \prod_{k=2}^{N-1} \frac{b}{d + kc}.
  \]

- \((G_t)_{t>0}\) jumps from genotype \(g_1 = (x_1, x_1)\) to \(g_2 = (x_2, x_2)\) at rate

  \[
  2\mu M(x_1, x_2) \sum_{N=2}^{\infty} Nl(N, b(g_1), d(g_1), c(g_1, g_1)) f((N - 1, 1, 0), x_1, x_2).
  \]

- If \(d(x_1, x_2) = d(g_1) + \delta\) and \(d(g_2) = d(g_1) + \delta'\),

  \[
  f((N - 1, 1, 0), x_1, x_2) = u^{\delta, \delta'}_{N-1, 1, 0}.
  \]
Existence of a mutational meltdown

Jump rate of the process $G$: $\tau(b, d, c, \delta, \delta')$.

- Small population size $\iff$ Frequent deleterious mutation fixations.
- More and more frequent fixations of deleterious mutations.

**Theorem (1.5.2)**

If $\delta > 0$ and $\delta' > \delta$, and if $b$ is small enough, the mean time $T(b, d, c, \delta, \delta') = 1/\tau(b, d, c, \delta, \delta')$ is a decreasing function of $d$. 
1. Stochastic modeling of the mutational meltdown

1.4. Numerical results and biological interpretations

Distribution of the population size

**Figure:** Distribution of the population size under different intrinsic death rates $d$. In this figure, $b = 10$ and $c = 0.1$. 

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Stochastic modeling and eco-evolution of a diploid population
Existence of a mutational meltdown

Figure: Relationship between the mean time to fixation of a deleterious mutation $T$ and parameters $b$ and $d$. Each curve corresponds to a fixed value of $b$. Other parameters are $\delta = 0.05$, $\delta' = 0.1$, $c = 0.1$ and $m = 1$. 
Mean population size mean dynamics

**Figure:** Mean temporal decrease in the mean population size in additive and recessive cases. $b = 10$, $c = 0.1$, $m = 1$, $D_0 = 1$ and $\delta' = 0.2$. 

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Large population size and allometry

- Each individual has size $1/K$, $K \to +\infty$.
- $Z^K$ is a jump process with jump size equal to $1/K$.
- Demographic parameters depend on $K$. If $z = (z_1, z_2, z_3) \in (\mathbb{Z}_+)^3/K$ and $n = z_1 + z_2 + z_3$,

$$
\lambda^K_1(z) = \frac{Kb^K_1}{n} \left( z_1 + \frac{z_2}{2} \right)^2,
$$

$$
\lambda^K_2(z) = \frac{Kb^K_2}{n} 2 \left( z_1 + \frac{z_2}{2} \right) \left( z_3 + \frac{z_2}{2} \right),
$$

$$
\lambda^K_3(z) = \frac{Kb^K_3}{n} \left( z_3 + \frac{z_2}{2} \right)^2.
$$

$$
\mu^K_1(z) = K z_1 (d^K_1 + K (c^K_{11} z_1 + c^K_{21} z_2 + c^K_{31} z_3)),
$$

$$
\mu^K_2(z) = K z_2 (d^K_2 + K (c^K_{12} z_1 + c^K_{22} z_2 + c^K_{32} z_3)),
$$

$$
\mu^K_3(z) = K z_3 (d^K_3 + K (c^K_{13} z_1 + c^K_{23} z_2 + c^K_{33} z_3)).
$$
Demographic parameters scaling

Hypotheses:

\[ b_i^K = \gamma K + \beta_i \in [0, \infty], \]
\[ d_i^K = \gamma K + \delta_i \in [0, \infty], \]
\[ c_{ij}^K = \frac{\alpha_{ij}}{K} > 0, \]
\[ Z_0^K \xrightarrow{K \to \infty} Z_0 \quad \text{in law}, \]

there exists \( C \geq 0 \) such that for all \( K \in \mathbb{N}^*, \mathbb{E} \left( (N_0^K)^3 \right) \leq C, \)

where \( \gamma > 0 \) and \( Z_0 \) is a \((\mathbb{R}_+)^3\)-valued random variable.
Hardy-Weinberg deviation, new variables

\[ Y^K_t = \frac{4Z^1_t, K Z^3_t, K - (Z^2_t, K)^2}{4N^K_t} \]
\[ = N^K_t (p^{AA,K}_t - (p^{A,K}_t)^2) \]
\[ = N^K_t (2p^{A,K}_t p^{a,K}_t - p^{Aa,K}_t) \]
\[ = N^K_t (p^{aa,K}_t - (p^{a,K}_t)^2) \]

\[ X^K_t = \frac{2Z^1_t, K + Z^2_t, K}{2N^K_t} \]

\((Z^1_t, K, Z^2_t, K, Z^3_t, K) \leftrightarrow (N^K_t, X^K_t, Y^K_t)\)
Fast dynamics

Proposition (3.3.2)

For all $s,t > 0$, \( \sup_{t \leq u \leq t+s} \mathbb{E}((Y_u^K)^2) \rightarrow 0 \) when $K$ goes to infinity.

Proof.

By Kolmogorov-forward equation,

\[
\frac{d\mathbb{E} \left( (Y_t^K)^2 \right)}{dt} \leq -2\gamma K \mathbb{E} \left( (Y_t^K)^2 \right) + C_1.
\]

- $Y^K$ is a fast variable and the population converges to Hardy-Weinberg equilibrium.
Slow dynamics

Theorem (Theorem 3.3.3 and Corollary 3.3.4)

For all $\epsilon > 0$, $T^K_{\epsilon} = \inf\{t \in [0, T] : N^K_t \leq \epsilon\}$. \{$(N^K, X^K)_{\wedge T^K_{\epsilon}}$\}$K \geq 1$
converges in law in $\mathcal{D}([0, T], [\epsilon, \infty[ \times [0, 1])$ toward a stopped
continuous-time diffusion process $(N, X)_{\wedge T_{\epsilon}}$. In the neutral case where
$\beta_i = \beta$, $\delta_i = \delta$ and $\alpha_{ij} = \alpha$,

$$dN_t = (\beta - \delta - \alpha N_t) N_t dt + \sqrt{2\gamma N_t} dB^1_t$$

$$dX_t = \sqrt{\frac{\gamma X_t (1 - X_t)}{N_t}} dB^2_t$$
Diploid vs haploid (1)


\[ dN_t = (\beta - \delta - \alpha N_t) N_t \, dt + \sqrt{2\gamma N_t} \, dB_t^1 \]

\[ dX_t = \sqrt{\frac{\gamma X_t (1 - X_t)}{N_t}} \, dB_t^2 \]

\[ dN^h_t = (\beta - \delta - \alpha N^h_t) N^h_t \, dt + \sqrt{2\gamma N^h_t} \, d\tilde{B}_t^1 \]

\[ dX^h_t = \sqrt{\frac{2\gamma X^h_t (1 - X^h_t)}{N^h_t}} \, d\tilde{B}_t^2 \]
Diploid vs haploid (2)

\[ dN_t^A = N_t^A \left[ \beta - \delta - \alpha \frac{(N_t^A + N_t^a)}{2} \right] dt \]
\[ + \sqrt{\frac{4\gamma}{N_t^A + N_t^a}} N_t^A dW_t^1 + \sqrt{2\gamma \frac{N_t^A N_t^a}{N_t^A + N_t^a}} dW_t^2 \]
\[ dN_t^a = N_t^a \left[ \beta - \delta - \alpha \frac{(N_t^A + N_t^a)}{2} \right] dt \]
\[ + \sqrt{\frac{4\gamma}{N_t^A + N_t^a}} N_t^a dW_t^1 - \sqrt{2\gamma \frac{N_t^A N_t^a}{N_t^A + N_t^a}} dW_t^2 \]
\[ dN_t^{A,h} = (\beta - \delta - \alpha(N_t^{A,h} + N_t^{a,h}))N_t^{A,h} dt + \sqrt{2\gamma N_t^{A,h}} d\tilde{W}_t^1 \]
\[ dN_t^{a,h} = (\beta - \delta - \alpha(N_t^{A,h} + N_t^{a,h}))N_t^{a,h} dt + \sqrt{2\gamma N_t^{a,h}} d\tilde{W}_t^2 \]
2. Slow-fast dynamics and measure-valued processes

2.1. Slow-fast dynamics

Long-time population behavior

- **Extinction:** $\mathbb{P}^N_x(T_0 < +\infty) = 1$ (Cattiaux et al. (2009)).
- **Quasi-stationary behavior of the population?**

- **C.C.: From diploid populations to Wright-Fisher diffusions and quasi-stationary distributions. Arxiv 1309.3405, Submitted.**
Change of variables

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

If \( \alpha_{ij} = \alpha_{ji} \) for all \( i, j \in \{1, 2, 3\} \),

\[ dS_t^1 = dW_t^1 - q_1(S_t)dt \]
\[ dS_t^2 = dW_t^2 - q_2(S_t)dt , \]

\[ dS_t = dW_t - \nabla Q(S_t)dt \]
Absorption of the diffusion process $S$

Absorbing sets: $0$, $A \cup 0$, $a \cup 0$, $A \cup a \cup 0$.

**Theorem (3.4.7)**

- For all $s \in \mathcal{D} \setminus 0$, $\mathbb{P}_s^{S}(T_{A} \land T_{a} < T_{0}) = 1$.
- For all $s \in \mathcal{D} \setminus \partial \mathcal{D}$, $\mathbb{P}_s^{S}(T_{A} < T_{0}) > 0$, and $\mathbb{P}_s^{S}(T_{a} < T_{0}) > 0$. 

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2. Slow-fast dynamics and measure-valued processes

2.2. Quasi-stationary behavior of a diploid population

Quasi-stationary behavior of \((N, X)\)

<table>
<thead>
<tr>
<th>Theorem (Theorem 3.4.10 and Corollary 3.4.11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• There exists a (unique) probability measure (\nu_{N,X}^N ) on (\mathbb{R}<em>+^* \times [0, 1]) such that for all (F \subset \mathbb{R}</em>+^* \times [0, 1]) and all ((n, x) \in \mathbb{R}_+^* \times [0, 1]),</td>
</tr>
<tr>
<td>[ \lim_{t \to \infty} \mathbb{P}<em>{(n,x)}^N((N</em>{t}, X_{t}) \in F</td>
</tr>
<tr>
<td>• There exists a (unique) probability measure (\nu_{0,N,X} ) on (\mathbb{R}<em>+^* \times [0, 1]) such that for all (F \subset \mathbb{R}</em>+^* \times [0, 1]) and ((n, x) \in \mathbb{R}_+^* \times [0, 1]),</td>
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</tr>
</tbody>
</table>
Neutral case

**Figure:** Distribution of the proportion $X_t$ of allele $A$ in the neutral case, knowing that $N_t \neq 0$. $\beta_i = 1 = \delta_i$, and $\alpha_{ij} = 0.1$ for all $i, j$, and $t = 40$. 
Figure: Distribution of the proportion $X_t$ of allele $A$ in an overdominance case, knowing that $N_t \neq 0$, $\beta_i = 1$ for all $i \neq 2$, $\beta_2 = 5$, $\delta_i = 0$ for all $i$, $\alpha_{ij} = 0.1$ for all $(i, j)$, and $T = 100$. 

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Stochastic modeling and eco-evolution of a diploid population
Different niches

**Figure:** Distribution of the proportion $X_t$ of allele $A$ in a separate niches case, knowing that $N_t \neq 0$. $\beta_i = 1$, $\delta_i = 0$, $\alpha_{ii} = 0.1$ for all $i$, $\alpha_{ij} = 0$ for all $i \neq j$, and $T = 2500$. 
Finite number of alleles

- 1 gene, $L$ alleles $\in [1, L]$.
- Population at time $t$:
  \[ X^K(t) = (x^K_{ij}(t))_{1 \leq i, j \leq L} \in S_L(\mathbb{Z}_+/2K). \]
- $x^K_{ii}(t) \in \mathbb{Z}_+/K$ is the rescaled number of individuals with genotype $ii$ at time $t$.
- $x^K_{ij}(t) + x^K_{ji}(t) = 2x^K_{ij}(t) \in \mathbb{Z}_+/K$ is the rescaled number of individuals with genotype $ij$ at time $t$. 

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Stochastic modeling and eco-evolution of a diploid population
2. Slow-fast dynamics and measure-valued processes

2.4. Multi-allelic model and measure-valued processes

\textbf{Finite number of alleles}

- **Birth rates**: if the population \( x \) has rescaled size \( \phi_1(x) \in \mathbb{Z}_+/K \),

\[
\lambda_{ij}^K(x) = b_{ij}^K K \phi_1(x) 2p_i p_j = Kb_{ij}^K \frac{\left( \sum_{k=1}^{L} x_{ik} \right) \left( \sum_{l=1}^{L} x_{jl} \right)}{\phi_1(x)}
\]

\[
\lambda_{ii}^K(x) = b_{ii}^K K \phi_1(x) (p_i)^2 = Kb_{ii}^K \frac{\left( \sum_{k=1}^{L} x_{ik} \right)^2}{\phi_1(x)}.
\]

- **Death rates**:

\[
\mu_{ij}^K(x) = K x_{ij} \left( d_{ij}^K + K \sum_{1 \leq k,l \leq L} c_{ij,kl}^K x_{kl} \right),
\]

- **Scaling**:

\[
b_{ij}^K = \gamma K + \beta_{ij}, \quad d_{ij}^K = \gamma K + \delta_{ij} \quad \text{and} \quad c_{ij,kl}^K = \frac{\alpha_{ij,kl}}{K}.
\]
Slow-fast dynamics and measure-valued process

- Fast dynamics: convergence toward Hardy-Weinberg equilibrium.
- Slow dynamics:
  \( \{(N^K(t \wedge T^K_\epsilon), p_2^K(t \wedge T^K_\epsilon), p_3^K(t \wedge T^K_\epsilon), \ldots, p_L^K(t \wedge T^K_\epsilon))_{0 \leq t \leq T}\}_{K \geq 1} \)
  converges in law in \( \mathcal{D}([0, T], [\epsilon, \infty[ \times [0, 1]^{L-1}) \) toward a stopped diffusion process \( (N(t \wedge T_\epsilon), p_2(t \wedge T_\epsilon), \ldots, p_L(t \wedge T_\epsilon))_{0 \leq t \leq T} \).
- Measure-valued process:

  \[
  \eta^L_t = \sum_{i=1}^{L} x^L_i(t) \delta_{\frac{i}{L}} \in \mathcal{M}_F([0, 1]) \quad \text{with} \quad x^L_i(t) = N(t)p_i(t)
  \]

  \[
  \zeta^L_t = \left( \frac{\langle \eta^L_t, 1 \rangle}{2}, \frac{\eta^L_t}{\langle \eta^L_t, 1 \rangle} \right) \in \mathbb{R}^*_+ \times \mathcal{P}([0, 1]) \cup \{0\} \times \partial \mathcal{P}.
  \]
2. Slow-fast dynamics and measure-valued processes

2.4. Multi-allelic model and measure-valued processes

Allele continuum and convergence

**Theorem (4.4.1)**

The sequence $(\zeta_{t\wedge T_\epsilon}^L, t \geq 0)$ converges in law in $\mathbb{D}([0, T_\epsilon], [\epsilon, +\infty] \times \mathcal{P}([0, 1]))$ towards the unique continuous-time stopped process $(\zeta_{t\wedge T_\epsilon}, t \in [0, T]) = ((n_{t\wedge T_\epsilon}, p_{t\wedge T_\epsilon}), t \in [0, T])$ such that

$$\sup_{t \in [0, T_\epsilon]} \mathbb{E}(n_t^3) < +\infty,$$

and solution of the martingale problem: for all functions $f \in \mathcal{C}_b^2(\mathbb{R}^*_+ \times \mathbb{R}, \mathbb{R})$ and $G$ measurable on $[0, 1]$, if $H(n, p) = f(n, \langle p, G \rangle)$, then the process $(m_t^H, t \in [0, T])$ such that $t \in [0, T]$,

$$m_t^H = H(n_t, p_t) - H(n_0, p_0) - \int_0^{t\wedge T_\epsilon} \mathcal{L}^\zeta H(n_s, p_s) \, ds$$

is a continuous martingale.
\[
\mathcal{L}^\xi H(n, p) = n \int_0^1 \int_0^1 \beta_{xy} - \delta_{xy} - \left( \int_0^1 \int_0^1 \alpha_{xy,uv} ndp(u) dp(v) \right) dp(x) dp(y) \partial_1 f(n, \langle p, G \rangle) \\
+ \gamma n \partial_{11}^2 f(n, \langle p, G \rangle) \\
+ \int_0^1 G(x) \left[ \int_0^1 \int_0^1 \left( \beta_{xz} - \beta_{yz} \right) - \left( \delta_{xz} - \delta_{yz} \right) \\
- \int_0^1 \int_0^1 \alpha_{xz,uv} - \alpha_{yz,uv} ndp(u) dp(v) \right] dp(x) \partial_2 f(n, \langle p, G \rangle) \\
+ \frac{\gamma}{n} \left( \langle p, G^2 \rangle - \langle p, G \rangle^2 \right) \partial_{22}^2 f(n, \langle p, G \rangle).
\]