

The tree-valued Fleming-Viot process with mutation and selection

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Joint work with Andrej Depperschmidt and Andreas Greven

Population genetic models

Populations of constant size have been **modelled** by

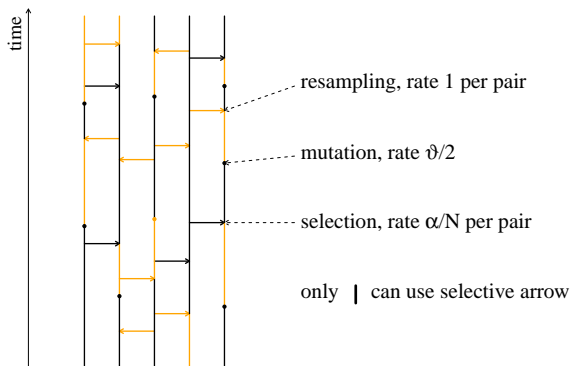
- ▶ **Markov Chains** (Wright-Fisher-model, **Moran model**)
- ▶ **Diffusion approximations** (Fisher-Wright diffusion)

$$dX = \alpha X(1 - X)dt + \sqrt{X(1 - X)}dW$$

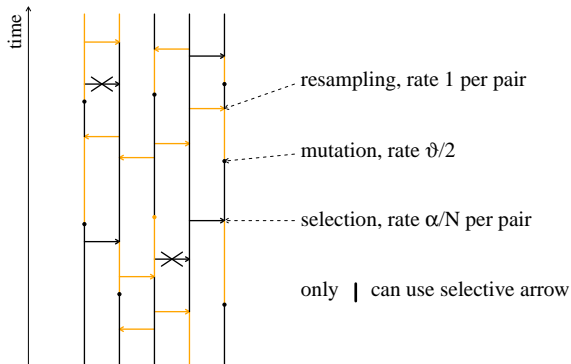
or **Measure-valued diffusions** (Fleming-Viot superprocess)

- ▶ **New:** Extend Fleming-Viot process by genealogical information → **Tree-valued Fleming-Viot process**

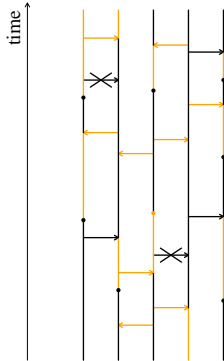
The Moran model with mutation and selection



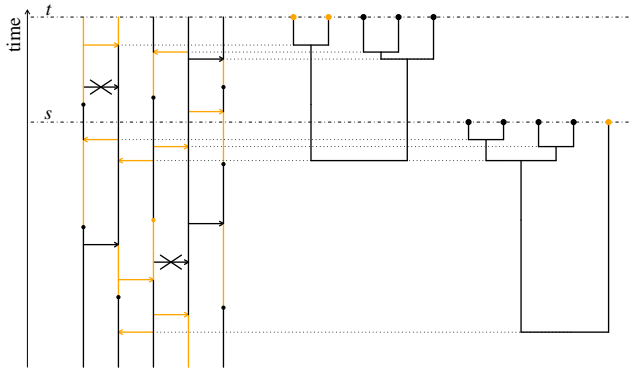
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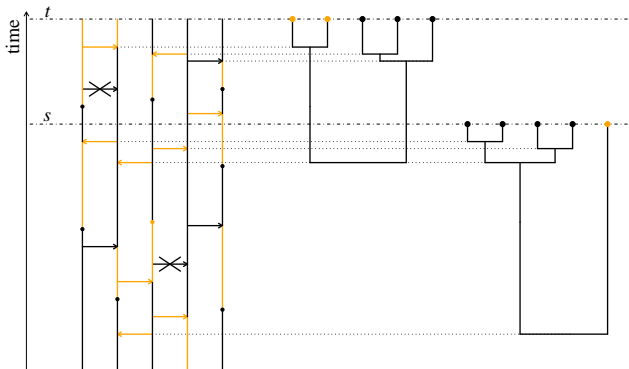
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The Moran model with mutation and selection



Goal: construct a tree-valued stochastic process $\mathcal{U} = (\mathcal{U}_t)_{t \geq 0}$

- ▶ describe genealogical relationships **dynamically**
- ▶ make **forward** and **backward** picture implicit

Summary: The tree-valued Fleming-Viot process

- ▶ **Theorem:** The (Ω, Π) -martingale problem is well-posed. Its solution – the **tree-valued Fleming-Viot process** – arises as weak limit of tree-valued Moran models.
- ▶ **Theorem:** Tree-valued processes for different α are **absolutely continuous** with respect to each other.
- ▶ **Theorem:** The **measure-valued** Fleming-Viot process is **ergodic** iff the **tree-valued** Fleming-Viot process is **ergodic**.
- ▶ **Theorem:** The distribution of R_{12}^α , the distance of **two randomly sampled points** in equilibrium, can be computed.

Formalizing genealogical trees

- ▶ **Leaves in genealogical trees** form a metric space; leaves are marked by elements of I (compact)

A tree is given by:

(X, r) complete and separable **metric** space

- ▶ $r(x_1, x_2)$ defines the genealogical distance of individuals x_1 and x_2

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Formalizing genealogical trees

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State space of \mathcal{U} :

$\mathbb{X} := \{\text{isometry class of } (X, r, \mu) : (X, r) \text{ complete and separable metric space, } \mu \in \mathcal{P}(X \times I)\}$

- ▶ $r(x_1, x_2)$ defines the genealogical distance of individuals x_1 and x_2
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Martingale Problem

- ▶ **Given: Markov process** $\mathcal{X} = (\mathcal{X}_t)_{t \geq 0}$. The **generator** is

$$\Omega\Phi(x) := \lim_{h \rightarrow 0} \frac{1}{h} \mathbf{E}_x[\Phi(\mathcal{X}_h) - \Phi(x)].$$

- ▶ **Given: Operator** Ω on Π . A solution of the (Ω, Π) -**martingale problem** is a process $\mathcal{X} = (\mathcal{X}_t)_{t \geq 0}$ if for all $\Phi \in \Pi$,

$$\left(\Phi(\mathcal{X}_t) - \int_0^t \Omega\Phi(\mathcal{X}_s) ds \right)_{t \geq 0}$$

is a martingale. The MP is **well-posed** if there is exactly one such process.

Polynomials on $\mathcal{P}(I)$

Π : functions of the form (polynomials)

$$\Phi(\mu) := \langle \mu^{\mathbb{N}}, \phi \rangle := \int \phi(\underline{u}) \mu^{\mathbb{N}}(d\underline{u})$$

for $\underline{u} = (u_1, u_2, \dots)$, $\phi \in \mathcal{C}_b(I^{\mathbb{N}})$ depending on finitely many coordinates

- ▶ Π separates points in $\mathcal{P}(I)$

Polynomials on \mathbb{U}

Π : functions on \mathbb{U} of the form (polynomials)

$$\Phi(X, r, \mu) := \langle \mu^{\mathbb{N}}, \phi \rangle := \int \phi(r(\underline{x}, \underline{x}), \underline{u}) \mu^{\mathbb{N}}(d(\underline{x}, \underline{u}))$$

for $(\underline{x}, \underline{u}) = ((x_1, u_1), (x_2, u_2), \dots)$, $\phi \in \mathcal{C}_b(\mathbb{R}^{\binom{\mathbb{N}}{2}} \times l^{\mathbb{N}})$ depending on finitely many coordinates

- ▶ Π separates points in \mathbb{X}

Generator for the Fleming-Viot process: measure-valued

$$\Omega := \Omega^{\text{res}} + \Omega^{\text{mut}} + \Omega^{\text{sel}}$$

- ▶ Ω^{res} : resampling
- ▶ Ω^{mut} : mutation
- ▶ Ω^{sel} : selection

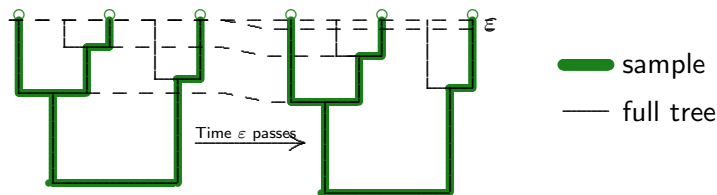
Generator for the Fleming-Viot process: tree-valued

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- ▶ Ω^{grow} : tree growth
- ▶ Ω^{res} : resampling
- ▶ Ω^{mut} : mutation
- ▶ Ω^{sel} : selection

Tree Growth

When no resampling occurs the tree **grows**



Distances in the sample grow at speed 2

$$\Omega^{\text{grow}} \Phi(X, r, \mu) = 2 \cdot \left\langle \mu^{\mathbb{N}}, \sum_{i < j} \frac{\partial}{\partial r_{ij}} \phi \right\rangle.$$

Resampling: measure-valued

$$\Omega^{\text{res}} \Phi(\mu) := \sum_{k < l} \langle \mu^{\mathbb{N}}, \phi \circ \theta_{k,l} - \phi \rangle$$

with

$$(\theta_{k,l}(\underline{u}))_i := \begin{cases} u_i, & i \neq l \\ u_k, & i = l \end{cases}$$

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In addition,

$$(\theta_{k,l} r(\underline{x}, \underline{x}))_{i,j} := \begin{cases} r(x_i, x_j), & \text{if } i, j \neq l, \\ r(x_i, x_k), & \text{if } j = l, \\ r(x_k, x_j), & \text{if } i = l, \end{cases}$$

Mutation: measure-valued

- ▶ ϑ : total mutation rate
- ▶ $\vartheta \cdot \beta(u, dv)$: mutation rate from u to v

$$\Omega^{\text{mut}} \Phi(\mu) = \vartheta \cdot \sum_k \langle \mu^{\mathbb{N}}, \beta_k \phi - \phi \rangle$$

with $\beta_k(\underline{u}, dv)$ acting on k th variable

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Selection: measure-valued

- ▶ α : selection coefficient
- ▶ $\chi(u) \in [0, 1]$: fitness of type u (continuous)

$$\Omega^{\text{sel}}\Phi(\mu) := \alpha \cdot \sum_{k=1}^n \langle \mu^{\mathbb{N}}, \chi_k \cdot \phi - \chi_{n+1} \cdot \phi \rangle$$

where ϕ only depends on sample of size n
with χ_k acting on k th variable

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Selection: tree-valued

- ▶ **Why is selection the same as for measure-valued case?**
- ▶ Ω_N^{sel} : generator for finite model of size N
- ▶ ϕ : only depends on first $n \ll N$ individuals

$$\begin{aligned}\Omega_N^{\text{sel}}\Phi(X, r, \mu) &\approx \frac{\alpha}{N} \sum_{k,l=1}^N \langle \mu^N, \chi_k(\phi \circ \theta_{k,l} - \phi) \rangle \\ &\approx \alpha \cdot \sum_{l=1}^n \langle \mu^N, \chi_{n+1}(\phi \circ \theta_{n+1,l} - \phi) \rangle \\ &= \alpha \cdot \sum_{l=1}^n \langle \mu^N, \chi_l \cdot \phi - \chi_{n+1} \cdot \phi \rangle\end{aligned}$$

The tree-valued Fleming-Viot process

- ▶ **Theorem:** The (Ω, Π) -martingale problem is well-posed. Its solution $\mathcal{X} = (\mathcal{X}_t)_{t \geq 0}$, $\mathcal{X}_t = (X_t, r_t, \mu_t)$ – the **tree-valued Fleming-Viot process** – arises as weak limit of tree-valued Moran models and satisfies:
 - ▶ $\mathbf{P}(t \mapsto \mathcal{X}_t \text{ is continuous}) = 1$,
 - ▶ $\mathbf{P}((X_t, r_t) \text{ is compact for all } t > 0) = 1$,
 - ▶ \mathcal{X} is Feller (hence strong Markov)

Girsanov transform: measure-valued

Theorem: Let $\alpha, \alpha' \in \mathbb{R}$,
 \mathcal{X} solution of (Ω, Π) -MP **for selection coefficient α** ,

$$\Psi(\mu) := (\alpha' - \alpha) \cdot \langle \mu^{\mathbb{N}}, \chi_1 \rangle$$

and

$$\mathcal{M} = \left(\Psi(\mu_t) - \Psi(\mu_0) - \int_0^t \Omega \Psi(\mu_s) ds \right)_{t \geq 0}.$$

Then, \mathbf{Q} , defined by

$$\left. \frac{d\mathbf{Q}}{d\mathbf{P}} \right|_{\mathcal{F}_t} = e^{\mathcal{M}_t - \frac{1}{2}[\mathcal{M}]_t}$$

solves (Ω, Π) -MP for selection coefficient α'

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Theorem: Let $\alpha, \alpha' \in \mathbb{R}$,
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and

$$\mathcal{M} = \left(\Psi(\mathbf{X}_t, \mathbf{r}_t, \mu_t) - \Psi(\mathbf{X}_0, \mathbf{r}_0, \mu_0) - \int_0^t \Omega \Psi(\mathbf{X}_s, \mathbf{r}_s, \mu_s) ds \right)_{t \geq 0}.$$

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Long-time behavior

Theorem:

The **tree-valued** Fleming-Viot process is **ergodic** iff the **measure-valued** Fleming-Viot process is **ergodic**

Application: distances is equilibrium

► Theorem:

- $I = \{\bullet, \circ\}$, $\chi(u) = 1_{\{u=\bullet\}}$ (\bullet is fit, \circ is unfit)
- $\frac{\vartheta}{2}$: mutation rate $\bullet \rightarrow \circ$ and $\circ \rightarrow \bullet$
- R_{12}^α : **distance of two randomly sampled points** in equilibrium

$$\mathbf{E}[e^{-\lambda R_{12}^\alpha/2}] = \frac{1}{1 + \lambda} + \frac{4\vartheta(2 + \lambda + 2\vartheta)\lambda}{(1 + \vartheta)(1 + \lambda + \vartheta)(6 + \lambda + \vartheta)(1 + \lambda)(6 + 2\lambda + \vartheta)}\alpha^2 + \mathcal{O}(\alpha^3)$$

► Proof: Use

$$\mathbf{E}[\Omega \langle \mu_\infty^{\mathbb{N}}, e^{-\lambda r(x_1, x_2)/2} \rangle] = 0$$

Summary and outlook

- ▶ Once the **right state-space** is chosen, construction of tree-valued Fleming-Viot process straight-forward
- ▶ Genealogical distances can be **computed** using generators
- ▶ Next step: Include **recombination**