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

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Population genetic models

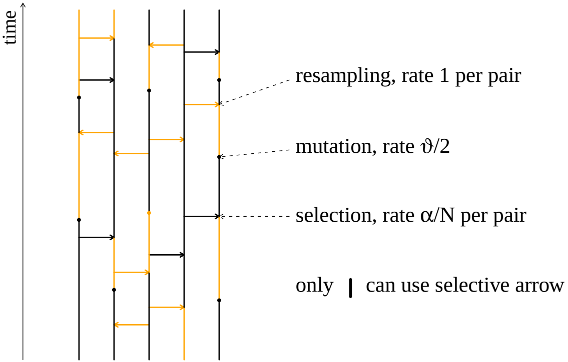
Populations of constant size have been **modelled** by

- **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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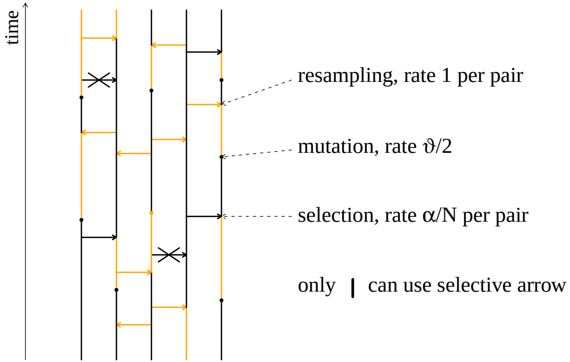

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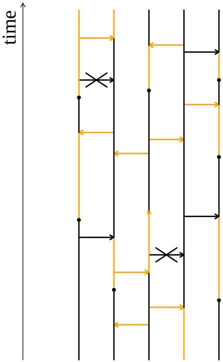

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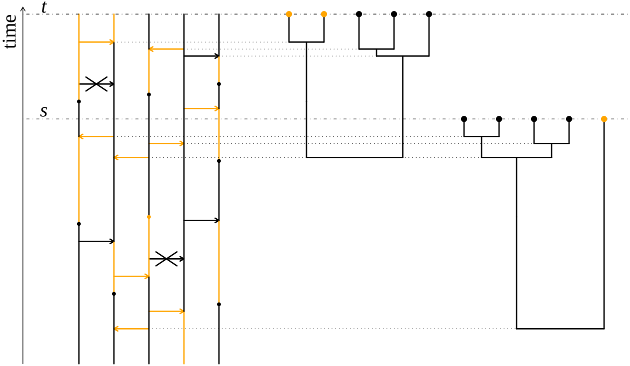

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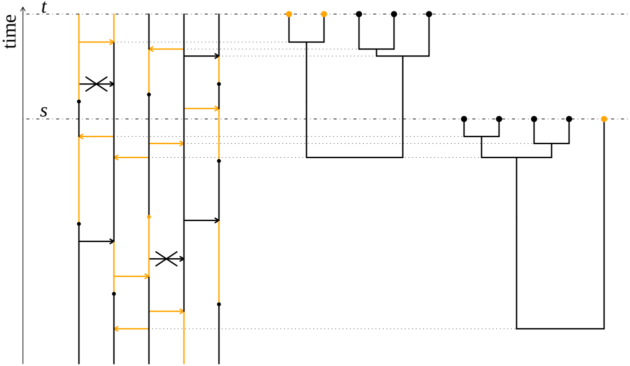

Goal: construct a tree-valued stochastic process $\mathcal{U} = (\mathcal{U}_t)_{t \geq 0}$

- 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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State space of $\mathcal{U}$:

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

- $r(x_1, x_2)$ 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

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

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

- Π **separates points** in $\mathbb{X}$

Generator for the Fleming-Viot process: measure-valued

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

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

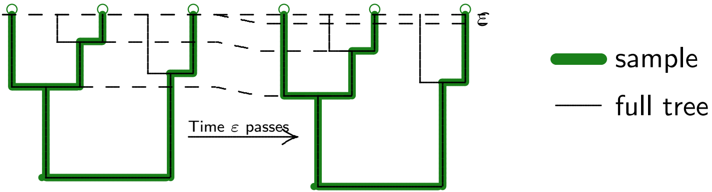
Generator for the Fleming-Viot process: tree-valued

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

- 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

$$\Omega^{\text{grow}}\Phi(X,r,\mu) = \langle \mu^{\mathbb{N}}, \text{div}\phi \rangle$$

with

$$\text{div}\phi := 2\sum_{i<j} \frac{\partial}{\partial r(x_i,x_j)} \phi\big(r(\underline{x},\underline{x}),\underline{u}\big)$$

Resampling: measure-valued

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

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

$$\boldsymbol{\Omega^{\mathrm{mut}}\Phi(\quad \mu) = \vartheta \cdot \sum_{k} \langle \mu^{\mathbb{N}}, \beta_{k}\phi - \phi \rangle}$$

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

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

Selection: measure-valued

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

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

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

Selection: tree-valued

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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 $\mathbf{n} \ll \mathbf{N}$ 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 $\mathcal{X} = (\mathcal{X}_t)_{\geq 0}$, $\mathcal{X}_t = (X_t, r_t, \mu_t)$ – 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**,

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

and

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

Then, $\mathbf{Q}$, defined by

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

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

Girsanov transform: tree-valued

Theorem: Let $\alpha, \alpha' \in \mathbb{R}$,
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$$\boldsymbol{\Psi(X, r, \mu) := (\alpha' - \alpha) \cdot \langle \mu^{\mathbb{N}}, \chi_1 \rangle}$$

and

$$\mathcal{M} = \Big(\Psi(X_t, r_t, \mu_t) - \Psi(X_0, r_0, \mu_0) - \int_0^t \Omega\Psi(X_s, r_s, \mu_s) ds \Big)_{t \geq 0}.$$

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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:**
  - $I = \{\bullet, \bullet\}$, $\chi(u) = 1_{\{u=\bullet\}}$ ($\bullet$ is fit, $\bullet$ is unfit)
  - $\frac{\vartheta}{2}$: mutation rate $\bullet \to \bullet$ and $\bullet \to \bullet$
  - 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**