Evolving genealogies in neutral populations

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Neutral models of constant size

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

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

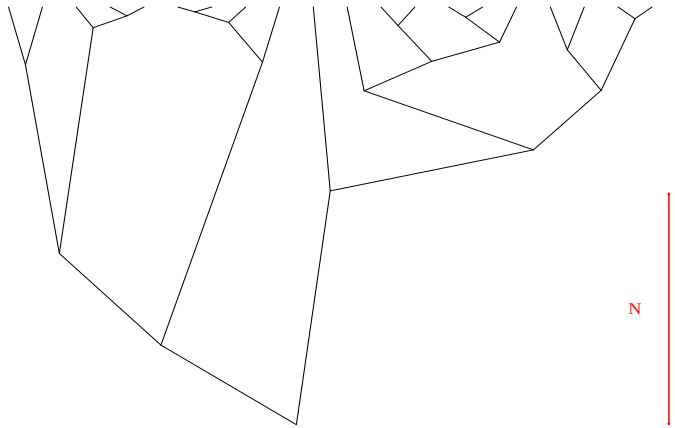
$$dX = \sqrt{X(1-X)}dW.$$

- **Measure-valued diffusions** (Fleming-Viot superprocess)
  Process $(\mu_t)_{t\geq 0}$ with state space $\mathcal{P}(K)$ such that $(\mu_t(A))_{t\geq 0}$ follows a Wright-Fisher diffusion.

Kingman's coalescent

Genealogies relating individuals are known to be distributed according to **Kingman's coalescent**:

- start with n lines
- if there are k lines the coalescence rate is $\binom{k}{2}$.
- stop when reaching one line.

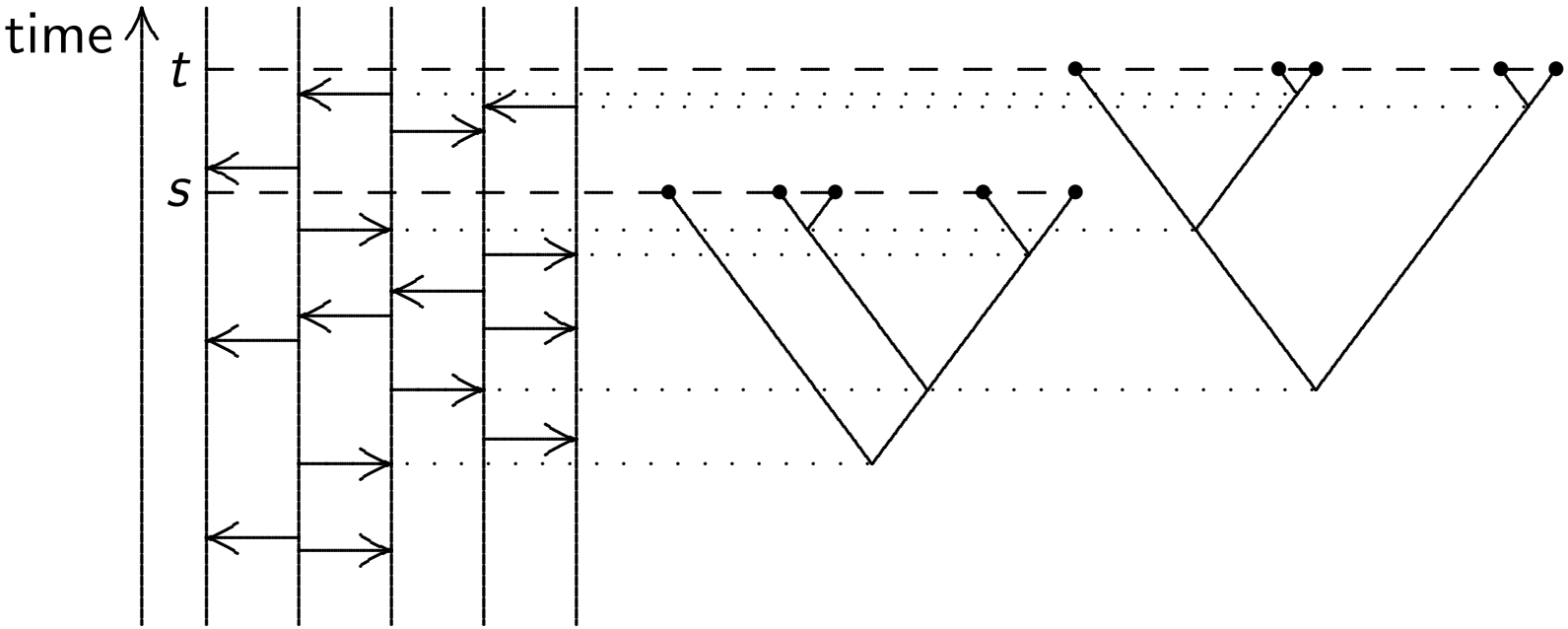


Example: Allelic distribution of a sample of size n at time t is uniquely given by the allelic distribution of ancestors at time 0

Evolving coalescents

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

- describes genealogical relationships **dynamically**
- makes **forward** and **coalescent** picture implicit



Formalizing genealogical trees

- **Leaves in Kingman's coalescent** form an ultrametric space.

State space of $\mathcal{U}$:

$\mathbb{U} :=$ {isometry class of (U, r, μ) :
(U, r) complete and separable **ultrametric** space, $\mu \in \mathcal{P}(U)$}.

- $r(u, v)$ defines the genealogical distance of individuals u and v
- μ marks currently living individuals

The Gromov-weak topology on $\mathbb{U}$

- Π: Algebra generated by functions on $\mathbb{U}$ of the form

$$\Phi(U, r, \mu) := \int \varphi(r(\underline{u}, \underline{u}))\mu^{\otimes n}(\mathrm{d}\underline{u})$$

for $\underline{u} = (u_1, \ldots, u_n), \varphi \in \mathcal{C}_b(\mathbb{R}^{\binom{n}{2}})$

Π **separates points** in $\mathbb{U}$.

- **Gromov-weak topology**:

$$(U_n, r_n, \mu_n) \to (U, r, \mu) \iff \forall \Phi \in \Pi : \Phi(U_n, r_n, \mu_n) \to \Phi(U, r, \mu)$$

- **Proposition** (Gromov; Vershik; Greven, P, Winter)
  - The space $(\mathbb{U}, \mathcal{O}_{\mathbb{U}})$ is **Polish**.

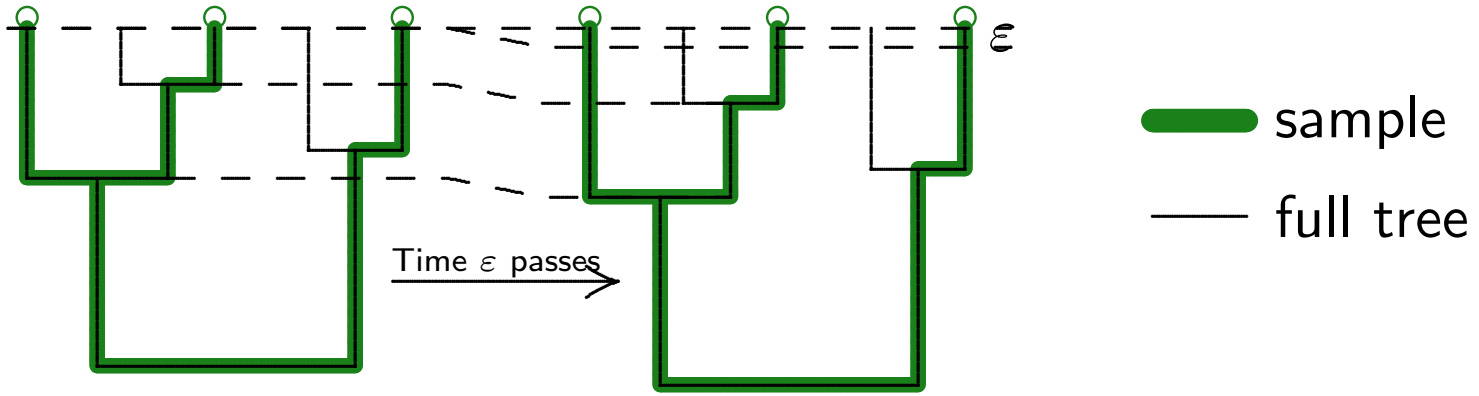
Martingale Problem

- Given: operator Ω on Π
  $\mathcal{U} = (\mathcal{U}_t)_{t\geq 0}$ solution of the (Ω, Π)-**martingale problem** if for all $\Phi \in \Pi$,
  $$\left(\Phi(U_t) - \int_0^t \mathrm{d}s\, \Omega\Phi(U_s)\right)_{t\geq 0}$$
  is a martingale. It is **well-posed** if there is exactly one such process.

- **Program**:
  - Define pregenerator for finite populations.
  - Establish **existence** by generator convergence and tightness.
  - Establish **uniqueness** by duality.

Tree Growth

When no resampling occurs the tree **grows**



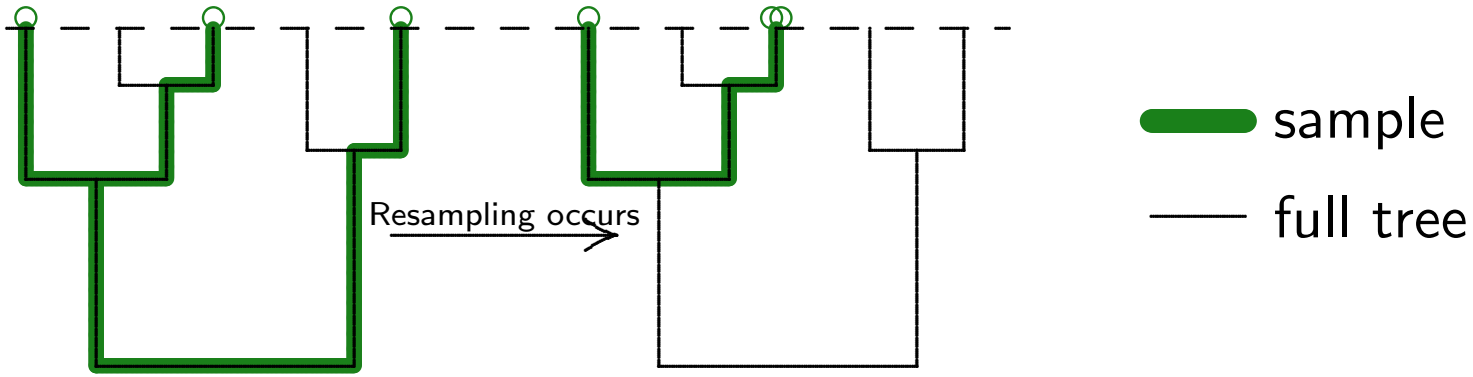
Distances in the sample grow

$$\Omega^N_{\text{grow}}\Phi(U,r,\mu) = \sum_{i,j}\int \frac{\partial\varphi}{\partial r_{ij}}\big(r(\underline{u},\underline{u})\big)\mu^{\otimes n}(d\underline{u}) + \mathcal{O}\big(\tfrac{1}{N}\big)$$

- $\frac{\partial\varphi}{\partial r_{ij}}$: measures the **change of** φ when $r(u_i,u_j)$ grows
- $\mathcal{O}\big(\frac{1}{N}\big)$: due to double sampling of the same individual

Resampling

Resampling does not change the tree



By resampling μ changes, so **different samples are picked**.

$$\Omega_{\text{res}}^N \Phi(U, r, \mu) = \tfrac{1}{2} \sum_{k,l} \int \left(\varphi\left(\theta_{kl} r(\underline{u}, \underline{u})\right) - \varphi\left(r(\underline{u}, \underline{u})\right)\right) \mu^{\otimes n}(d\underline{u}) + \mathcal{O}\left(\tfrac{1}{N}\right)$$

where $$\theta_{kl} r(u_i, u_j) = \begin{cases} r(u_k, u_j), & i = l \\ r(u_i, u_k), & j = l \\ r(u_i, u_j), & \text{else} \end{cases}$$

Martingale Problem

- **Pregenerator** for infinite system:

$$\Omega\Phi(U,r,\mu) = \sum_{i,j} \int \frac{\partial \varphi}{\partial r_{i,j}}\big(r(\underline{u},\underline{u})\big)\mu^{\otimes n}(d\underline{u})$$
$$+ \tfrac{1}{2}\sum_{k,l} \int \big(\varphi\big(\theta_{kl} r(\underline{u},\underline{u})\big) - \varphi\big(r(\underline{u},\underline{u})\big)\big)\mu^{\otimes n}(d\underline{u})$$

- Existence: **Approximation** by finite systems
- Uniqueness: **Duality** to Kingman's coalescent

The tree-valued Fleming-Viot dynamics

Theorem

- Solution $\mathcal{U} = (\mathcal{U}_t)$ of (Ω, Π)-mp exists as limit of tree-valued Moran models and is unique
- Almost surely,
  - $\mathcal{U}$ has **continuous** sample paths
  - $\mathcal{U}_t$ **compact** for all $t > 0$
  - **Quadratic variation** of $\Phi(\mathcal{U})$:

$$\mathrm{d}\langle \Phi(\mathcal{U}) \rangle_t = n^2 \langle \mu_t, \left(\rho - \langle \mu_t, \rho \rangle\right)^2 \rangle \mathrm{d}t,$$

where

$$\rho(u_1) := \int \mu_t^{\otimes(n-1)} \left(\mathrm{d}(u_2, \ldots, u_n) \phi((r(u_i, u_j))_{1 \le i < j \le n}\right)$$

The tree-length process

- Given (U, r, μ) and $u_1, u_2, \ldots$,

$$L_n(\underline{u}) := \text{length of tree spanned by } u_1, \ldots, u_n$$

- **Tree length distribution** of subsequentially sampled points:

$$\Lambda(U, r, \mu) := (L_2, L_3, \ldots)_* \mu^{\otimes \mathbb{N}} \in \mathcal{P}\left(\mathbb{R}_+^{\mathbb{N}}\right)$$

- **Theorem**: The process $(\Lambda(\mathcal{U}_t))_{t \geq 0}$ is **Markov**

Application: number of mutations on the tree

- Real data: **number of mutations** $S_n(t)$ of a sample at time t can be observed
- Length of sample tree $L_n(\underline{u}) \Rightarrow S_n \sim \textbf{Pois}\big(\frac{\theta}{2} L_n(\underline{u})\big)$
- So,

$$\mathbb{E}\big[e^{-\lambda S_n(t)}\big] = g^n\big(t; \theta(1 - e^{-\lambda})\big).$$

for

$$g^n(t;\theta) := \mathbb{E}\Big[\int \mu_t^{\otimes n}(d\underline{u}) \exp\big(-\theta L_n(\underline{u})\big)\Big]$$

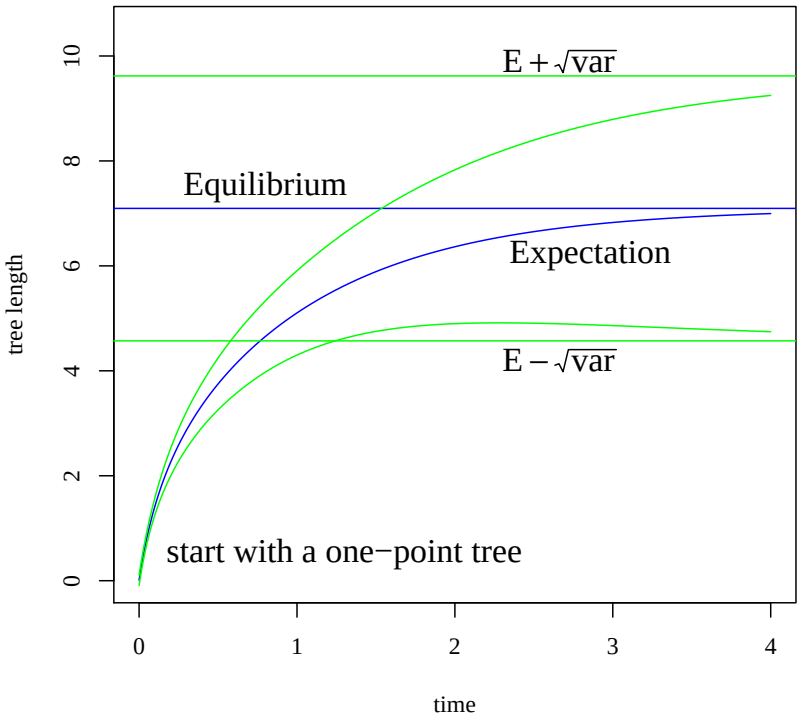
- $(g^2, g^3, \ldots)$ is solution of

$$\frac{d}{dt} g^n = -n\theta g^n + \binom{n}{2} \left(g^{n-1} - g^n \right)$$

- $(g^2, g^3, \ldots)$ given by

$$g^n(t;\theta) = \Gamma(n) \sum_{k=2}^{n} \frac{\binom{n}{k}(-1)^k(\theta+2k-1)}{\Gamma(\theta+n+k)} \cdot$$
$$\cdot \Big\{ e^{-k(\theta+(k-1))t} \sum_{m=2}^{k} \frac{\binom{k}{m}(-1)^m \Gamma(\theta+k+m-1)}{\Gamma(m)} g^m(0;\theta)$$
$$+ \big(1 - e^{-k(\theta+(k-1))t}\big)(k-1)(\theta+k)\Gamma(\theta+k-1) \Big\}.$$

Application: tree lengths



Example: consider a sample of $n = 20$ which starts in $(\{\bullet\}, \delta_\bullet)$. Moments of tree lengths can be calculated.

Outlook

Further questions

- Is it possible to include **mutation**, **selection**, **recombination**?
- What does the mp for tree-valued **branching** processes look like?
- Which tree-evolutions can be defined via **sample evolution**?