Some mathematical models from population genetics

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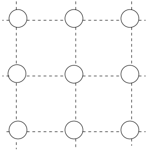
with thanks to numerous collaborators, especially Nick Barton, IST Austria

CMAP5, May 2023

Spatial models so far: subdivided populations

Kimura's stepping stone model

Special case $N_e(i) \equiv N_e$



$$dp_i = \sum_j m_{ji}(p_j - p_i)dt + \sqrt{\frac{1}{N_e} p_i(1-p_i)} dW_i$$

$\{W_i\}_{i \in I}$ independent Brownian motions

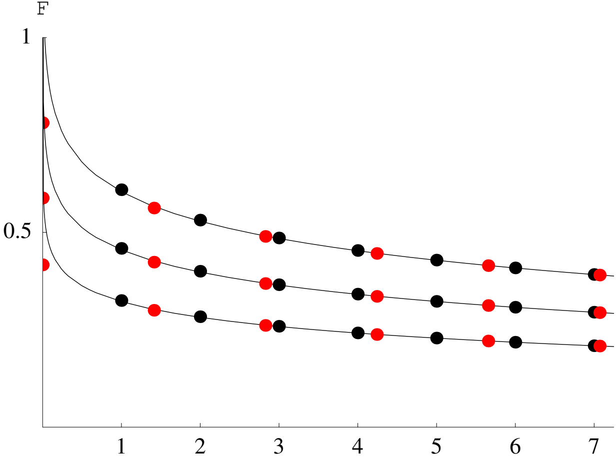
System of W-F diffusions coupled through migration

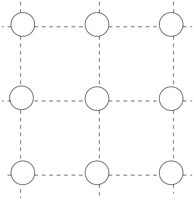
The structured coalescent $\underline{n}$:

- $\begin{cases} n_i \mapsto n_i - 1 \\ n_j \mapsto n_j + 1 \end{cases}$ at rate $n_i m_{ji}$
- $n_i \mapsto n_i - 1$ at rate $\frac{1}{2N_e} n_i (n_i - 1)$

Isolation by distance

Malécot-Wright approximation for the stepping stone model





$F = \mathbb{P}[\text{identity}]$

The unreasonable effectiveness of the Kingman coalescent

Common to use Kingman coalescent even for natural populations
Replace census population size by an effective population size

Sampling uniformly from the torus $\mathbb{T}(L) \subset \mathbb{Z}^2$
$T =$ time to MRCA two individuals sampled uniformly from $\mathbb{T}(L)$

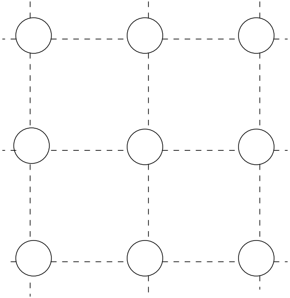
- $T_0 =$ time to first come into same deme
- $t_0 =$ time to coalesce started from same deme

$T = T_0 + t_0$
$t_0 \ll T_0$

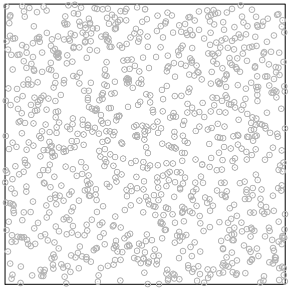
On timescale $L^2 \log L$ genealogy uniform sample from $\mathbb{T}(L) \rightarrow$ Kingman coalescent as $L \rightarrow \infty$ Zähle, Cox, Durrett (2005)

Census population size grows with L^2 so this does not explain the timescale seen in real populations

An obvious challenge

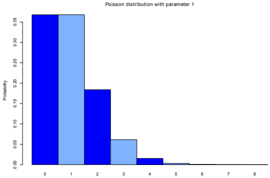


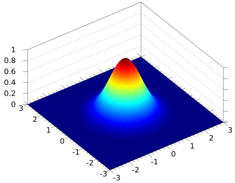
Modelling a spatial continuum: the Wright-Malécot model



$N = 1000$

- Individuals are scattered across a two-dimensional space.
- In each generation, each individual produces a Poisson number of offspring (average one).
- Offspring are scattered in a Gaussian distribution around their parent.



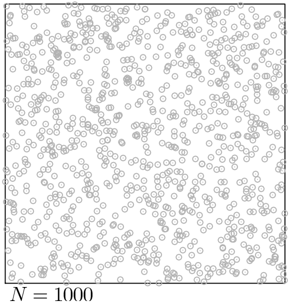


Mitch Gooding
Jerome Kelleher

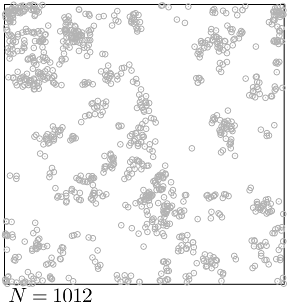
The pain in the torus (Felsenstein, 1975)

With thanks to Jerome Kelleher

$t = 0$



$t = 10$



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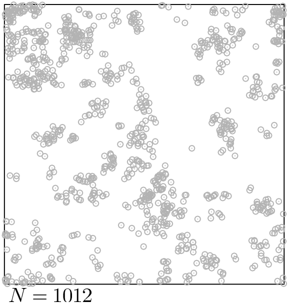

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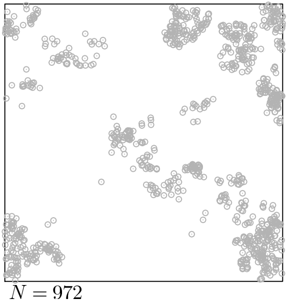

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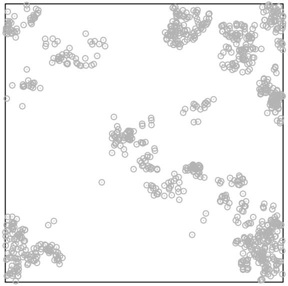
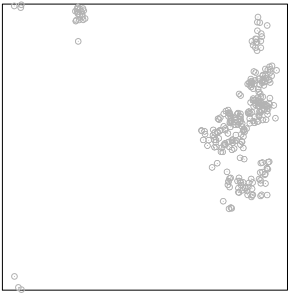


$t = 100$ $N = 972$



$t = 1000$ $N = 293$

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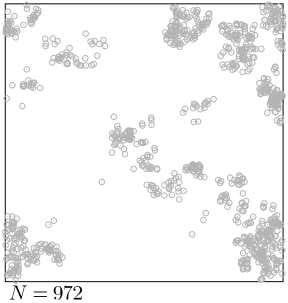

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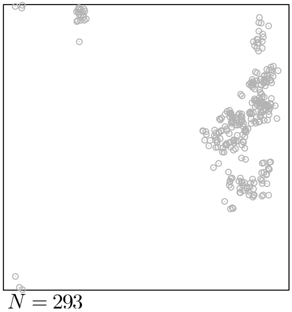

In $d = 1, 2$ population exhibits clumping/extinction

Mathematical problems

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What about modifying the stepping stone model?

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In 2D the diffusion limit fails over small scales ... and so does the obvious backwards model.

Biological problems

Genetic diversity much lower than expected from census numbers

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Allele frequencies correlated over long distances

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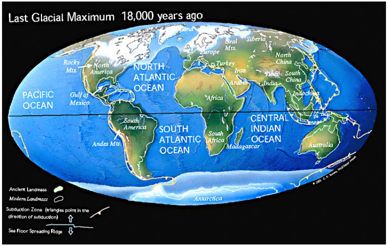
Demographic history of many species dominated by large scale extinction-recolonisation events

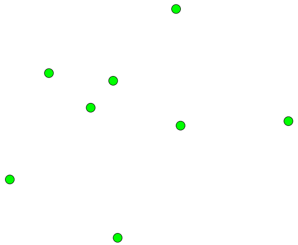


Small neighbourhood size

In a spatial continuum, a single individual can be parent to a significant proportion of the local population.

An individual based model

- Start with Poisson intensity λdx.
  Events rate $dt \otimes dx \otimes \xi(dr, du)$.
  Throw down ball $B(x, r)$.



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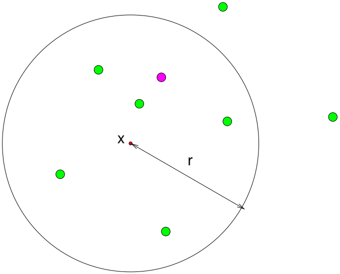

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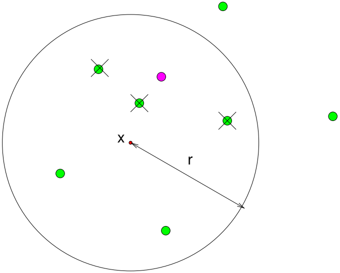

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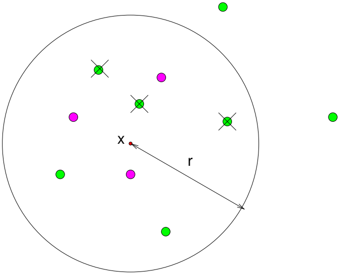

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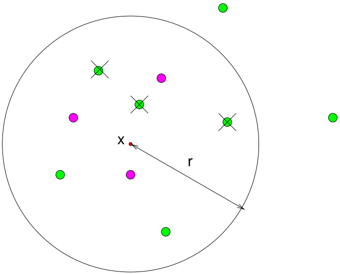
Offspring inherit type of parent



$\lambda \to \infty$ limit (no space)

Start from $\texttt{Poiss}(\lambda)$

If first reproduction event has 'impact' u

- $\texttt{Poiss}((1-u)\lambda)$ 'survivors';
- $\texttt{Poiss}(u\lambda)$ offspring.

As $\lambda \to \infty$ proportion u of individuals die and are replaced by offspring of the type of the parent.

The Λ-Fleming-Viot process

State $\{\rho(t, \cdot) \in \mathcal{M}_1(K), t \geq 0\}$. K space of genetic types.

- Poisson Point Process Π intensity $dt \otimes F(du)$
- if $(t, u) \in \Pi$, individual sampled at random from population at time $t-$ (i.e. choose $k \sim \rho(t-)$)
- proportion u of population replaced by offspring of chosen individual

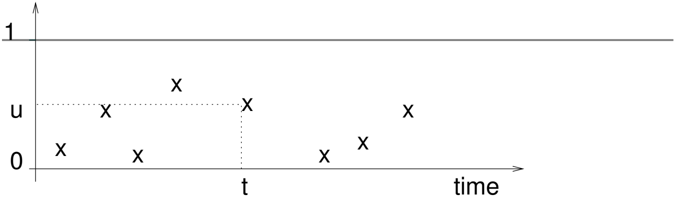
$$\rho(t, \cdot) = (1-u)\rho(t-, \cdot) + u\delta_k.$$

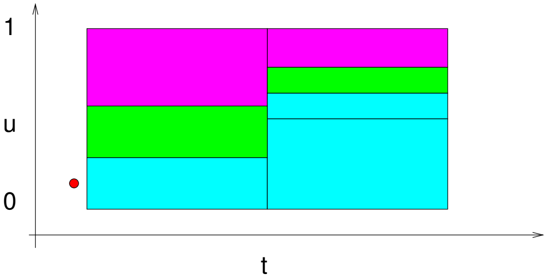
$F(du) = \frac{\Lambda(du)}{u^2}$, Λ finite measure on $[0, 1]$.

Donnelly & Kurtz (1999)

('Generalised Fleming-Viot process', Bertoin & Le Gall 2003)

The Λ-Fleming-Viot process





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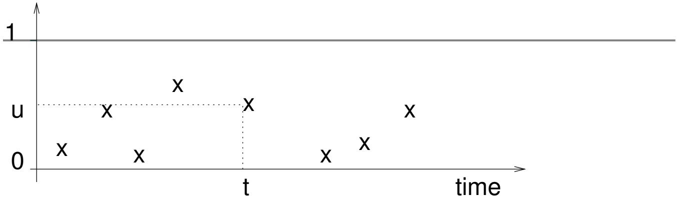

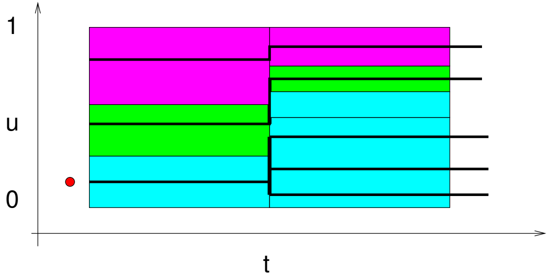

Λ-coalescents

Donnelly & Kurtz (1999), Pitman (1999), Sagitov (1999)

If there are currently n ancestral lineages, each transition involving j of them merging happens at rate

$$\beta_{n,j} = \int_0^1 u^j (1-u)^{n-j} \, \frac{\Lambda(du)}{u^2}$$

- Λ a finite measure on $[0,1]$
- Kingman's coalescent, $\Lambda = \delta_0$

The spatial Λ-Fleming-Viot process

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Barton - E - Véber and friends

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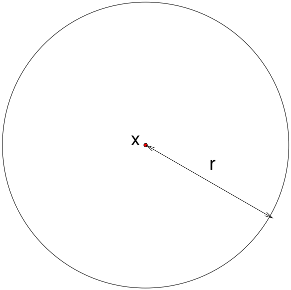

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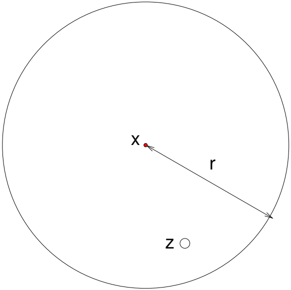

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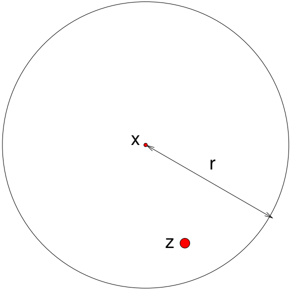

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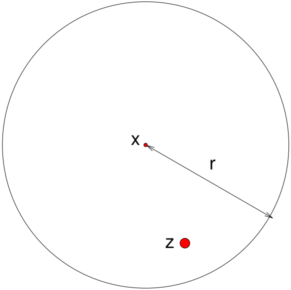
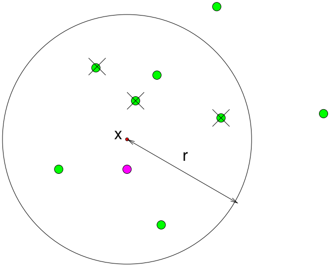


Backwards in time

- A *single* ancestral lineage evolves in series of jumps with intensity

$$dt \otimes \int_{(|x|/2,\infty)} \int_{[0,1]} \frac{L_r(x)}{\pi r^2}\, u\, \xi(dr, du) dx$$

on $\mathbb{R}_+ \times \mathbb{R}^2$ where $L_r(x) = |B_r(0) \cap B_r(x)|$.



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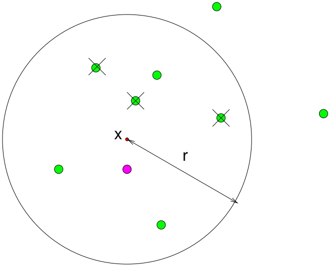

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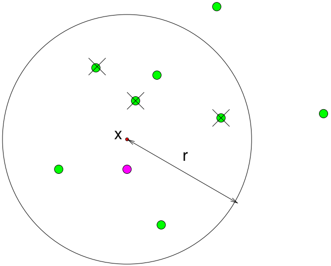
Note: If $\xi(dr, du) = \mu(dr) \otimes \delta_u$, rate of jumps $\propto u$.



Duality

Suppose $K = \{a, A\}$. Define $w(t, x) = \rho(t, x, \{a\})$ to be the proportion of the population at site x at time t that are of type a.

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(actually have to sample from random positions and integrate to circumvent issues with sets of Lebesgue measure zero)

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A framework for modelling

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- Different shapes of event,
- Non-uniform replacement,
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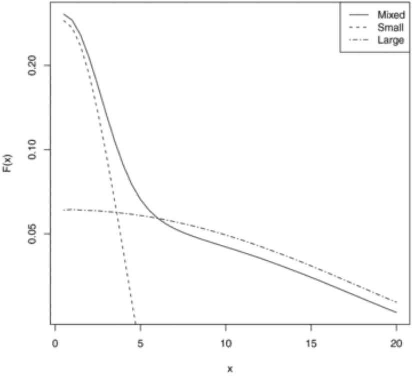
Robust results? $\rightsquigarrow$ Scaling limits.

Example: Wright and Malécot again

The effect of mixed events on F(x, μ). A mixture of rare large events and frequent small events



Evol, Volume 64, Issue 9, 1 September 2010, Pages 2701–2715, https://doi.org/10.1111/j.1558-5646.2010.01019.x

Recap: The Wright-Fisher model with selection

Two types a, A, relative fitnesses $\begin{array}{c|c} a & A \\ \hline 1-s & 1 \end{array}$

During reproduction, each individual produces large number of juveniles from which next generation sampled.

If proportion A-alleles in parental population is q, proportion in pool of juveniles is

$$q^* = \frac{q}{1 - s(1-q)} \approx q + sq(1-q).$$

Population size N (fixed).

Establishment of a favourable allele (Fisher 1930)

While rare, No. offspring of a favoured individual $\sim \texttt{Binom}(N, (1+s)/N) \approx \texttt{Poiss}(1+s)$.

Branching process approximation: probability extinction satisfies

$$x = \exp(-(1+s)(1-x)),$$

Survival probability, $y = 1 - x$,

$$y = 1 - \exp(-(1+s)y) = (1+s)y - \frac{1}{2}(1+s)^2 y^2 + \mathcal{O}(y^3).$$

Rearranging:

$$\frac{1}{2}(1+s)^2 y^2 = sy \quad \Longrightarrow \quad y \approx 2s.$$

Does space matter?

Maryuama (1970),

- subdivided population, demes (large) constant size;
- selection acts independently in each deme;
- contribution of each deme to next generation proportional to size.

$\rightsquigarrow$ Fixation probability independent of population subdivision.

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Aim to investigate the interaction of natural selection and spatial structure in the framework of the spatial Lambda-Fleming-Viot process.

Introducing selection to the SLFV

WARNING: There are lots of ways to do this.

Here we mimic what we did for the Wright-Fisher/Moran models in the first lecture.

Introducing selection to the SLFV

$K = \{a, A\}$, $w(t,x) = \rho(t,x,a)$ proportion of type a

- (i) Two types, a, A. Weight type a by $(1-s)$. If a reproduction event affects a region $B(x,r)$ in which current proportion of a-alleles is $\overline{w}$, then probability offspring are type a is

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c.f. what we did for Moran model

(Spatial) Ancestral selection graph

Evolution of ancestry due to neutral events as before:

- lineages evolve in a series of jumps;
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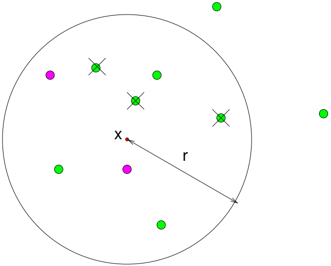

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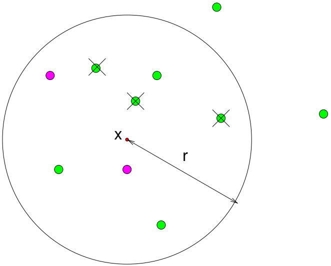

A sampled individual is type a *iff* all lineages in the corresponding ASG are type a at any previous time.

Zooming out: recovering classical models

The spread of a *favoured* allele is classically modelled through the (stochastic) Fisher-KPP equation:

$$du = \Big(\frac{1}{2}\Delta u + su(1-u)\Big)dt + \mathbf{1}_{d=1}\epsilon\sqrt{u(1-u)}W(dt,dx).$$

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Stochastic Fisher-KPP is dual to branching and coalescing Brownian motion

Branching Brownian motion and the Fisher-KPP equation

Binary branching BM $\mathbf{X}_t = \{X_t^1, \dots, X_t^{N_t}\}$

- Individuals follow independent Brownian motions
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$S \sim \mathtt{Exp}(s)$= lifetime ancestor started at x, $h \ll 1$,

$$\begin{aligned}\mathbb{E}_x\Big[\prod_{i=1}^{N_{t+h}} w(0, X_{t+h}^i)\Big] &= \mathbb{E}_x\Big[\prod_{i=1}^{N_{t+h}} w(0, X_{t+h}^i)\Big| S < h\Big]\mathbb{P}[S < h] \\ &\quad + \mathbb{E}_x\Big[\prod_{i=1}^{N_{t+h}} w(0, X_{t+h}^i)\Big| S > h\Big]\mathbb{P}[S > h]\end{aligned}$$

$$\mathbb{E}_x\Big[\prod_{i=1}^{N_{t+h}} w(0,X^i_{t+h})\Big| S<h\Big]\mathbb{P}[S<h] = sh\left(\mathbb{E}_x\big[\prod_{i=1}^{N_t} w(0,X^i_t)\big]\right)^2 + O(h^2)$$

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$u(t,x)=1-w(t,x)$ solves $\frac{\partial u}{\partial t}=\frac{1}{2}\Delta u+su(1-u)$

Convergence of SLFV with selection

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Recall Wright-Fisher diffusion (genetic drift) dual to Kingman coalescent
In spatial setting, Wright-Fisher noise reflected in coalescence in dual - lineages coalesce at rate determined by *local time* they spend together, but only makes sense in $d = 1$

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To identify convergence to (stochastic) Fisher-KPP, show convergence of the dual processes

Brief aside on random walk

Suppose X is simple random walk on $\mathbb{Z}$.

Write τ for hitting time of $\{0, N\}$

Take $X_0 = 1$. Doob's Optional Stopping Theorem says $\mathbb{E}[X_\tau] = X_0$.

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In $d = 2$, corresponding quantity has mean $\propto \log N$.

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- Events driven by Poisson Point Process Π that specifies
  - centre and *radius* event
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- *selection coefficient* determines proportion of selective events

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Dual lineages make jumps of length $O(r)$ at rate proportional to ur^d, and branch at rate proportional to sur^d

lineages can only coalesce when at separation less than $4r$

Scaling limits I: High neighbourhood size

Set $u_n = u/n^\gamma$, $s_n = s/n^\delta$, $w^{(n)}(t,x) = w(nt, n^\beta x)$,
Jump rate nu_n, jump size $1/n^\beta$. Diffusive scaling: $2\beta = 1 - \gamma$

- At 'branching' event, two lineages at separation $\mathcal{O}(1/n^\beta)$.
- Probability separate to $\mathcal{O}(1)$ before come back together is $\mathcal{O}(1/n^\beta)$, $(d = 1)$; $\mathcal{O}(1/\log n)$, $(d = 2)$; $\mathcal{O}(1)$, $(d \geq 3)$.
- If two lineages hit by same event, given one jumps, they coalesce with probability $\mathcal{O}(1/n^\gamma)$.

$d \geq 2$: Probability 'long' excursion before coalesce $\mathcal{O}(1)$;

$d = 1$: Number attempts to reach separation $\mathcal{O}(1)$
$\sim$ number of attempts to coalesce: $\beta = \gamma$;

Selection events rate nu_ns_n $\mathcal{O}(1)$: $1 - \gamma - \delta = 0$.

$$\rightsquigarrow \beta = \gamma = 1/3, \quad \delta = 2/3.$$

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E. Véber, Yu.

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$\gamma > \beta$ (even bigger neighbourhood size) $\rightsquigarrow$ deterministic equation in all dimensions