



SOME MATHEMATICAL MODELS OF EVOLUTION

I: Spatial population models

Alison Etheridge
University of Oxford

Thanks

Nick Barton



Jerome Kelleher



Amandine Véber



The (neutral) Wright-Fisher model

Population of fixed size N evolves in discrete generations.

- ▶ Each individual produces (effectively infinite) number of gametes (think of them as 'potential offspring');
- ▶ Sample N offspring uniformly at random from pool of gametes.

The (neutral) Wright-Fisher model

Population of fixed size N evolves in discrete generations.

- ▶ Each individual produces (effectively infinite) number of gametes (think of them as 'potential offspring');
- ▶ Sample N offspring uniformly at random from pool of gametes.

Equivalently, new generation formed by multinomial sampling with equal weights on each parent.

The (neutral) Wright-Fisher model

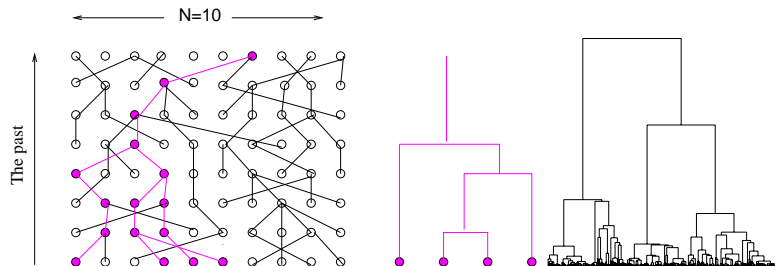
Population of fixed size N evolves in discrete generations.

- ▶ Each individual produces (effectively infinite) number of gametes (think of them as 'potential offspring');
- ▶ Sample N offspring uniformly at random from pool of gametes.

Equivalently, new generation formed by multinomial sampling with equal weights on each parent.

... or, each offspring chooses its parent uniformly at random from the previous generation

The simplest imaginable model of inheritance



Kingman 1982

$$\mathbb{P}[2 \text{ lineages coalesce in previous generation}] \approx \frac{1}{N}$$

Sample size $k \ll N^{1/3}$, pair of lineages coalesces rate $\approx \frac{1}{N} \binom{k}{2}$

Melfi & Viswanath (2018)

The (neutral) Wright-Fisher model

Population of fixed size N evolves in discrete generations.

- ▶ Each individual chooses parent uniformly at random from the previous generation;
- ▶ Offspring inherit the type of their parent.

The (neutral) Wright-Fisher model

Population of fixed size N evolves in discrete generations.

- ▶ Each individual chooses parent uniformly at random from the previous generation;
- ▶ Offspring inherit the type of their parent.

'Alleles' a, A .

Proportion p of a alleles among parents.

Number of a -offspring $\text{Bin}(N, p)$.

$\mathbb{E}[\Delta p] = 0$ (neutral); $\mathbb{E}[(\Delta p)^2] = \frac{1}{N}p(1-p)$.

The (neutral) Wright-Fisher model

Population of fixed size N evolves in discrete generations.

- ▶ Each individual chooses parent uniformly at random from the previous generation;
- ▶ Offspring inherit the type of their parent.

'Alleles' a, A .

Proportion p of a alleles among parents.

Number of a -offspring $\text{Bin}(N, p)$.

$\mathbb{E}[\Delta p] = 0$ (neutral); $\mathbb{E}[(\Delta p)^2] = \frac{1}{N}p(1-p)$.

\rightsquigarrow changes in p over timescales $\mathcal{O}(N)$ generations.

Drift (large population limit)

Time in units of N generations, $\delta t = \frac{1}{N}$, $N \rightarrow \infty$

Drift (large population limit)

Time in units of N generations, $\delta t = \frac{1}{N}$, $N \rightarrow \infty$

Forwards in time, $\Delta p = p_{t+\delta t} - p_t$,

- ▶ $\mathbb{E}[\Delta p] = 0$ (neutrality)
- ▶ $\mathbb{E}[(\Delta p)^2] = \delta t p(1-p)$
- ▶ $\mathbb{E}[(\Delta p)^4] = O(\delta t)^2$

$$dp_t = \sqrt{p_t(1-p_t)}dW_t$$

Drift (large population limit)

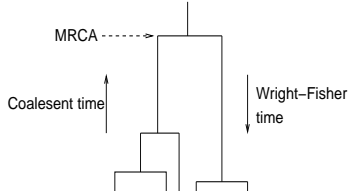
Time in units of N generations, $\delta t = \frac{1}{N}$, $N \rightarrow \infty$

Forwards in time, $\Delta p = p_{t+\delta t} - p_t$,

- ▶ $\mathbb{E}[\Delta p] = 0$ (neutrality)
- ▶ $\mathbb{E}[(\Delta p)^2] = \delta t p(1-p)$
- ▶ $\mathbb{E}[(\Delta p)^4] = O(\delta t)^2$

$$dp_t = \sqrt{p_t(1-p_t)} dW_t$$

Backwards in time



Coalescence rate $\binom{k}{2}$.

Drift (large population limit)

Time in units of N generations, $\delta t = \frac{1}{N}$, $N \rightarrow \infty$

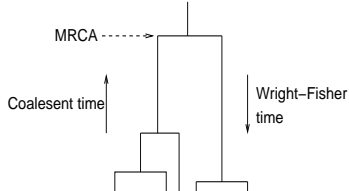
Forwards in time, $\Delta p = p_{t+\delta t} - p_t$,

- ▶ $\mathbb{E}[\Delta p] = 0$ (neutrality)
- ▶ $\mathbb{E}[(\Delta p)^2] = \delta t p(1-p)$
- ▶ $\mathbb{E}[(\Delta p)^4] = O(\delta t)^2$

$$dp_t = \sqrt{p_t(1-p_t)} dW_t$$

$$dp_\tau = \sqrt{\frac{1}{N_e} p_\tau(1-p_\tau)} dW_\tau,$$

Backwards in time



Coalescence rate $\binom{k}{2}$.

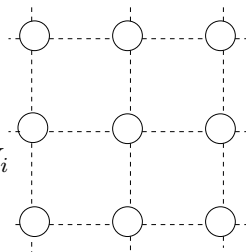
Coalescence rate $\frac{1}{N_e} \binom{k}{2}$

Spatial structure

Kimura's stepping stone model

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

System of interacting W-F diffusions

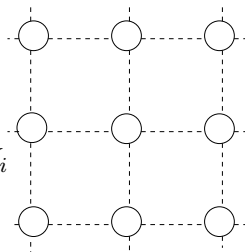


$$\sum_j m_{ij} = \sum_j m_{ji}$$

Spatial structure

Kimura's stepping stone model

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



System of interacting W-F diffusions

The coalescent dual process \underline{n} evolves as follows:

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

$$\sum_j m_{ij} = \sum_j m_{ji}$$

Evolution in a spatial continuum?

For many biological populations it is more natural to consider a spatial continuum.

Evolution in a spatial continuum?

For many biological populations it is more natural to consider a spatial continuum.

Podisma pedestris



A model for a spatial continuum?

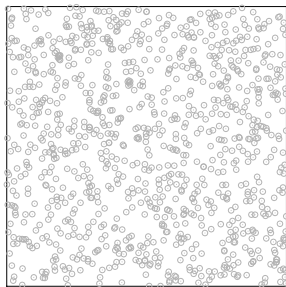
Malécot and Wright (almost) solved this problem in the 1940s:

- ▶ Initial population distributed as Poisson Point Process with constant intensity;
- ▶ Discrete generations: Each individual leaves a mean one Poisson number of offspring; ($\text{Binom}(N, 1/N) \approx \text{Poiss}(1)$)
- ▶ Offspring distributed around location of parent according to Gaussian.

~> Branching random walk

The pain in the torus

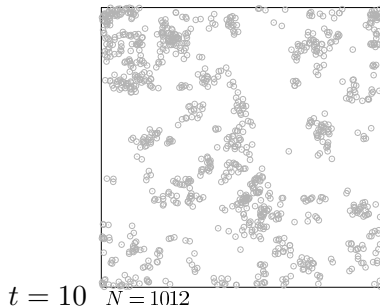
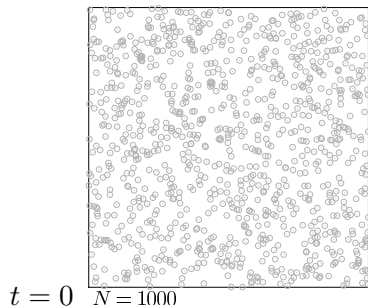
Felsenstein (1975).



$t = 0$ $N = 1000$

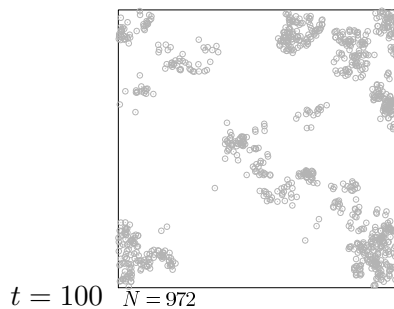
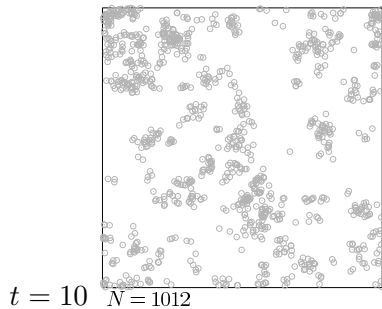
The pain in the torus

Felsenstein (1975).



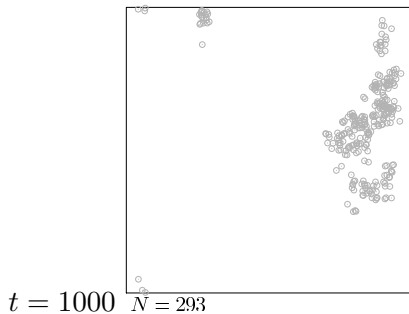
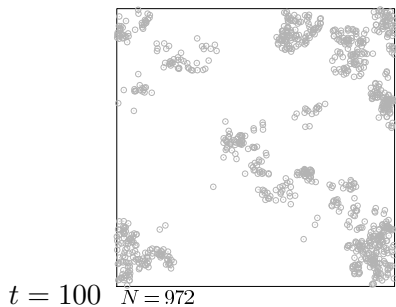
The pain in the torus

Felsenstein (1975).



The pain in the torus

Felsenstein (1975).



Mathematical problems

Felsenstein (1975). **The pain in the torus:** Independent reproduction \implies clumping;

Mathematical problems

Felsenstein (1975). **The pain in the torus:** Independent reproduction \implies clumping;

Local regulation \implies correlated reproduction.

Mathematical problems

Felsenstein (1975). **The pain in the torus:** Independent reproduction \implies clumping;

Local regulation \implies correlated reproduction.

What about modifying the stepping stone model?

$$dp_t(x) = \frac{1}{2}\Delta p_t(x) + \sqrt{\frac{1}{2N_e}p_t(x)(1 - p_t(x))}dW(t, x)$$

Mathematical problems

Felsenstein (1975). **The pain in the torus:** Independent reproduction \implies clumping;

Local regulation \implies correlated reproduction.

What about modifying the stepping stone model?

$$dp_t(x) = \frac{1}{2}\Delta p_t(x) + \sqrt{\frac{1}{2N_e}p_t(x)(1-p_t(x))}dW(t, x)$$

In 2D the diffusion limit fails over small scales

Mathematical problems

Felsenstein (1975). **The pain in the torus:** Independent reproduction \implies clumping;

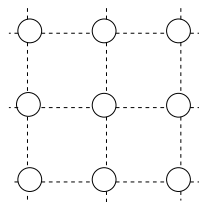
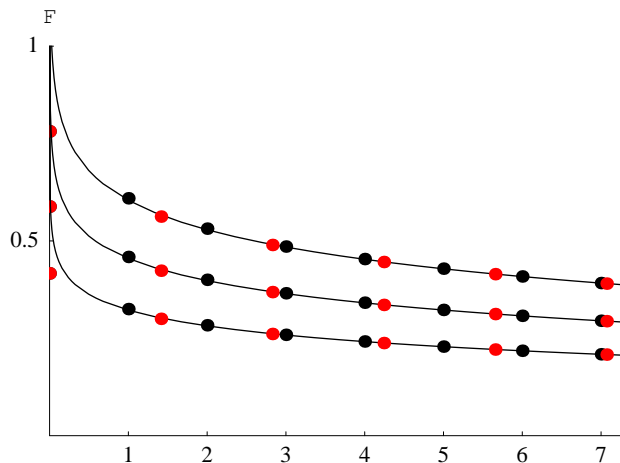
Local regulation \implies correlated reproduction.

What about modifying the stepping stone model?

$$dp_t(x) = \frac{1}{2}\Delta p_t(x) + \sqrt{\frac{1}{2N_e}p_t(x)(1-p_t(x))}dW(t, x)$$

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

Malécot-Wright versus Kimura?



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

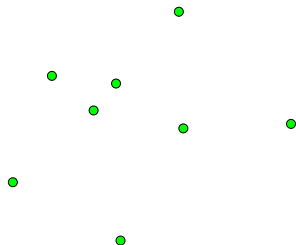
One more observation



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

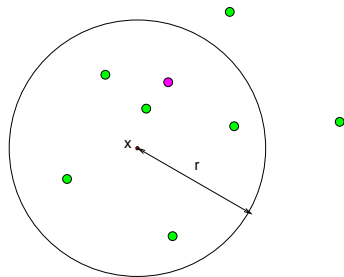
An individual based model

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



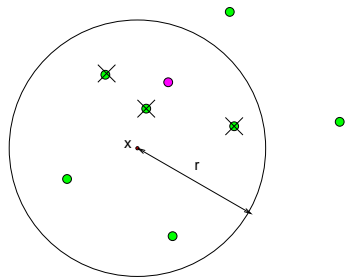
An individual based model

- ▶ Start with Poisson intensity λdx . Events rate $dt \otimes dx \otimes \xi(dr, du)$. Throw down ball $B(x, r)$.
- ▶ If region empty, do nothing, otherwise:
- ▶ Choose **parent** from $B(x, r)$,



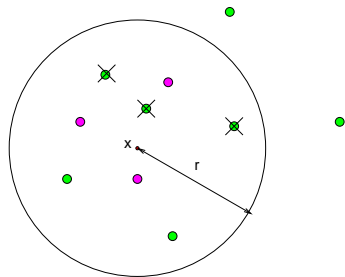
An individual based model

- ▶ Start with Poisson intensity λdx . Events rate $dt \otimes dx \otimes \xi(dr, du)$. Throw down ball $B(x, r)$.
- ▶ If region empty, do nothing, otherwise:
- ▶ Choose **parent** from $B(x, r)$,
- ▶ Each individual in region dies with probability u ,



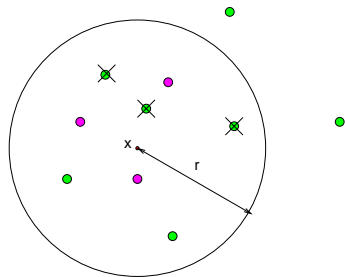
An individual based model

- ▶ Start with Poisson intensity λdx . Events rate $dt \otimes dx \otimes \xi(dr, du)$. Throw down ball $B(x, r)$.
- ▶ If region empty, do nothing, otherwise:
- ▶ Choose **parent** from $B(x, r)$,
- ▶ Each individual in region dies with probability u ,
- ▶ New individuals born according to Poisson intensity $\lambda u \mathbf{1}_{B_r(x)}$.



An individual based model

- ▶ Start with Poisson intensity λdx . Events rate $dt \otimes dx \otimes \xi(dr, du)$. Throw down ball $B(x, r)$.
- ▶ If region empty, do nothing, otherwise:
- ▶ Choose **parent** from $B(x, r)$,
- ▶ Each individual in region dies with probability u ,
- ▶ New individuals born according to Poisson intensity $\lambda u \mathbf{1}_{B_r(x)}$.



Offspring inherit type of parent

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

Start from $\text{Pois}(\lambda)$

If first reproduction event has 'impact' u

- ▶ $\text{Pois}((1 - u)\lambda)$ 'survivors';
- ▶ $\text{Pois}(u\lambda)$ offspring.

As $\lambda \rightarrow \infty$ 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 $t-$
- ▶ proportion u of population replaced by offspring of chosen individual

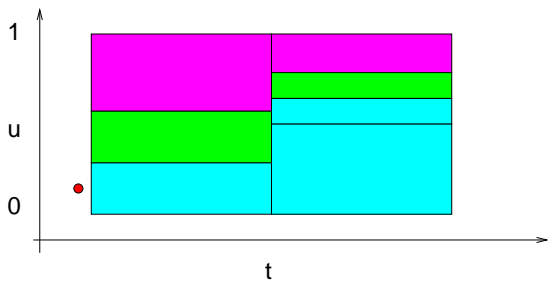
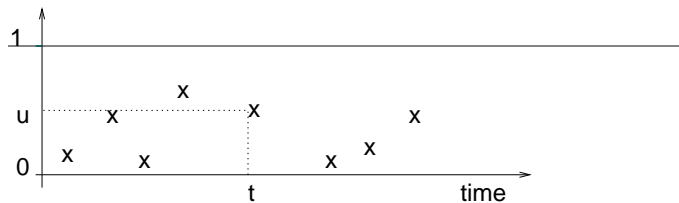
$$\rho(t, \cdot) = (1 - u)\rho(t-, \cdot) + u\delta_k.$$

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

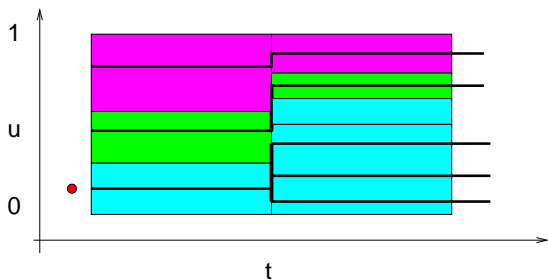
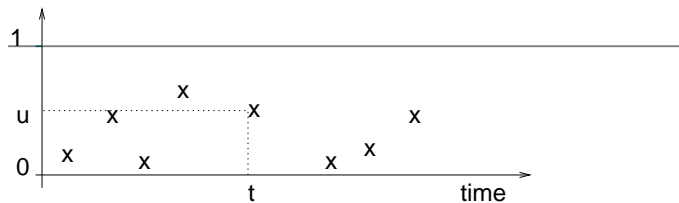
Donnelly & Kurtz (1999)

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

The Λ -Fleming-Viot process



The Λ -Fleming-Viot process



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

State $\{\rho(t, x, \cdot) \in \mathcal{M}_1(K), x \in \mathbb{R}^2, t \geq 0\}$.

The spatial Λ -Fleming-Viot process

State $\{\rho(t, x, \cdot) \in \mathcal{M}_1(K), x \in \mathbb{R}^2, t \geq 0\}$. Π Poisson point process rate $dt \otimes dx \otimes \xi(dr, du)$ on $[0, \infty) \times \mathbb{R}^2 \times [0, \infty) \times [0, 1]$.

The spatial Λ -Fleming-Viot process

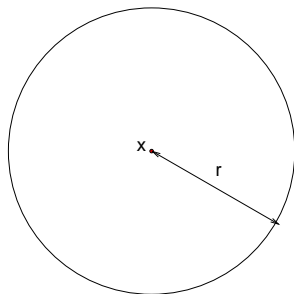
State $\{\rho(t, x, \cdot) \in \mathcal{M}_1(K), x \in \mathbb{R}^2, t \geq 0\}$. Π Poisson point process rate $dt \otimes dx \otimes \xi(dr, du)$ on $[0, \infty) \times \mathbb{R}^2 \times [0, \infty) \times [0, 1]$.

Dynamics: for each $(t, x, r, u) \in \Pi$,

The spatial Λ -Fleming-Viot process

State $\{\rho(t, x, \cdot) \in \mathcal{M}_1(K), x \in \mathbb{R}^2, t \geq 0\}$. Π Poisson point process rate $dt \otimes dx \otimes \xi(dr, du)$ on $[0, \infty) \times \mathbb{R}^2 \times [0, \infty) \times [0, 1]$.

Dynamics: for each $(t, x, r, u) \in \Pi$,

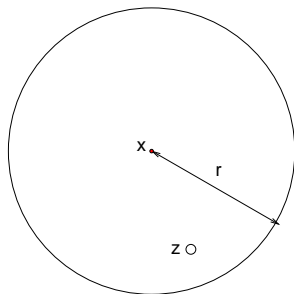


The spatial Λ -Fleming-Viot process

State $\{\rho(t, x, \cdot) \in \mathcal{M}_1(K), x \in \mathbb{R}^2, t \geq 0\}$. Π Poisson point process rate $dt \otimes dx \otimes \xi(dr, du)$ on $[0, \infty) \times \mathbb{R}^2 \times [0, \infty) \times [0, 1]$.

Dynamics: for each $(t, x, r, u) \in \Pi$,

► $z \sim U(B_r(x))$

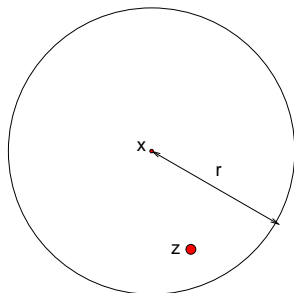


The spatial Λ -Fleming-Viot process

State $\{\rho(t, x, \cdot) \in \mathcal{M}_1(K), x \in \mathbb{R}^2, t \geq 0\}$. Π Poisson point process rate $dt \otimes dx \otimes \xi(dr, du)$ on $[0, \infty) \times \mathbb{R}^2 \times [0, \infty) \times [0, 1]$.

Dynamics: for each $(t, x, r, u) \in \Pi$,

- ▶ $z \sim U(B_r(x))$
- ▶ $k \sim \rho(t-, z, \cdot)$.



The spatial Λ -Fleming-Viot process

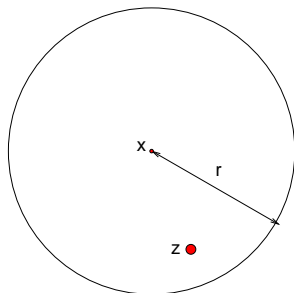
State $\{\rho(t, x, \cdot) \in \mathcal{M}_1(K), x \in \mathbb{R}^2, t \geq 0\}$. Π Poisson point process rate $dt \otimes dx \otimes \xi(dr, du)$ on $[0, \infty) \times \mathbb{R}^2 \times [0, \infty) \times [0, 1]$.

Dynamics: for each $(t, x, r, u) \in \Pi$,

- ▶ $z \sim U(B_r(x))$
- ▶ $k \sim \rho(t-, z, \cdot)$.

For all $y \in B_r(x)$,

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

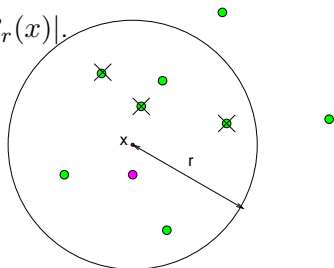


Backwards in time

- ▶ 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 $L_r(x) = |B_r(0) \cap B_r(x)|$.



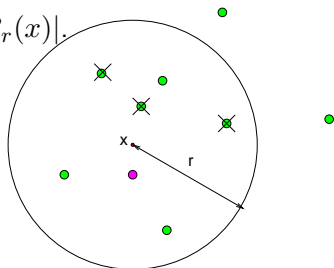
Backwards in time

- ▶ 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 $L_r(x) = |B_r(0) \cap B_r(x)|$.

- ▶ Lineages can coalesce when hit by same 'event'.



Adding selection

Warm up: the Wright-Fisher model

Two types a , A

Population of fixed size N evolves in discrete generations.

- ▶ Each individual produces (effectively infinite) number of gametes;
- ▶ A type a produces $(1 - s)$ times as many gametes as a type A ;
- ▶ Sample N offspring uniformly at random from pool of gametes.

If proportion of a -alleles in parental population is p , then the probability that an offspring is type a is

$$\frac{(1 - s)p}{(1 - s)p + (1 - p)} = \frac{(1 - s)p}{1 - sp}.$$

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 \bar{w} , then probability offspring are type a is

$$\frac{(1 - s)\bar{w}}{1 - s\bar{w}}$$

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 \bar{w} , then probability offspring are type a is

$$\frac{(1 - s)\bar{w}}{1 - s\bar{w}} = \bar{w}(1 - s) + s\bar{w}^2 + \mathcal{O}(s^2).$$

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 \bar{w} , then probability offspring are type a is

$$\frac{(1 - s)\bar{w}}{1 - s\bar{w}} = \bar{w}(1 - s) + s\bar{w}^2 + \mathcal{O}(s^2).$$

- ▶ (ii) Neutral events rate $\propto (1 - s)$, selective events rate $\propto s$. At **selective** reproduction events, sample **two** potential parents. If types aa , then an a reproduces, otherwise an A does.

(Spatial) Ancestral selection graph

Evolution of ancestry due to neutral events as before:

- ▶ lineages evolve in a series of jumps;
- ▶ they can coalesce when covered by same event.

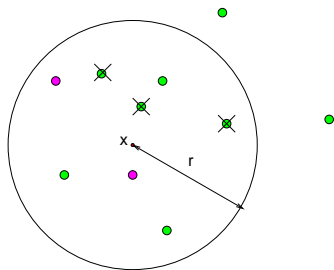
(Spatial) Ancestral selection graph

Evolution of ancestry due to neutral events as before:

- ▶ lineages evolve in a series of jumps;
- ▶ they can coalesce when covered by same event.

At *selective events*

- ▶ *Two 'potential' parents must be traced;*
- ▶ Lineages can coalesce when hit by same 'event'.



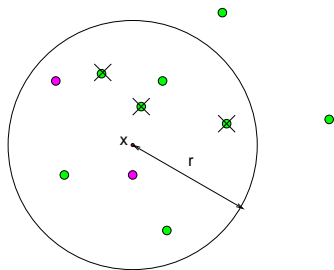
(Spatial) Ancestral selection graph

Evolution of ancestry due to neutral events as before:

- ▶ lineages evolve in a series of jumps;
- ▶ they can coalesce when covered by same event.

At *selective* events

- ▶ *Two 'potential' parents must be traced;*
- ▶ Lineages can coalesce when hit by same 'event'.



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

When can we detect selection?

Neutral mutation rate, μ , sets timescale

- ▶ Mutation rates are low;
- ▶ Scaling limits are 'robust'.

Natural question:

When, and over what spatial scales can we expect to observe a signature of natural selection?

Scaling limits: Small 'neighbourhood size':

Fix $u \in (0, 1)$.

Scaling limits: Small 'neighbourhood size':

Fix $u \in (0, 1)$.

Set $n = 1/\mu$ and rescale: $w(nt, \sqrt{n}x)$.

Scaling limits: Small 'neighbourhood size':

Fix $u \in (0, 1)$.

Set $n = 1/\mu$ and rescale: $w(nt, \sqrt{n}x)$.

Heuristics:

- ▶ At a 'branching' event in ASG, two lineages born at separation $\mathcal{O}(1/\sqrt{n})$.
- ▶ Probability they separate to $\mathcal{O}(1)$ before coalescing is
 - ▶ $d = 1$: $\mathcal{O}(1/\sqrt{n})$,
 - ▶ $d = 2$: $\mathcal{O}(1/\log n)$,
 - ▶ $d \geq 3$: $\mathcal{O}(1)$.
- ▶ Selection will only be visible if expect to see at least one pair 'separate' by time 1.

Scaling limits: Small 'neighbourhood size':

Fix $u \in (0, 1)$.

Set $n = 1/\mu$ and rescale: $w(nt, \sqrt{n}x)$.

Ability to detect selection depends on dimension:

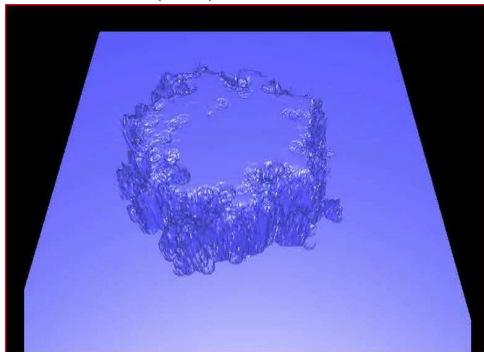
- ▶ $d = 1$, selection only visible if $s = \mathcal{O}(1/\sqrt{n}) = \mathcal{O}(\sqrt{\mu})$,
limiting ASG embedded in Brownian net;
- ▶ $d = 2$, selection only visible if
 $s = \mathcal{O}(\log n/n) = \mathcal{O}(\mu|\log(\mu)|)$,
limiting ASG 'Branching BM';
- ▶ $d \geq 3$, selection only visible if $s = \mathcal{O}(1/n) = \mathcal{O}(\mu)$,
limiting ASG Branching BM.

Technical challenges because $ns_n \rightarrow \infty$.

Straulino (2015), E., Freeman, Straulino (2015)

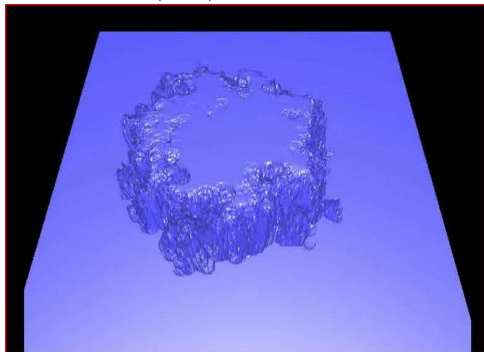
Spread of a favoured allele

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



Spread of a favoured allele

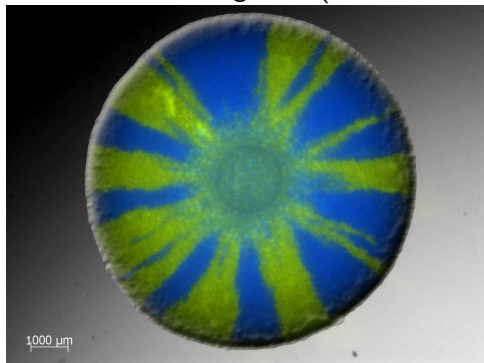
Two types, a , A . If a reproduction event affects a region $B(x, r)$ in which current proportion of a -alleles is w , then probability offspring are type a is $\frac{w}{1+s(1-w)}$.



Alternative interpretation: strong selection \sim range expansion

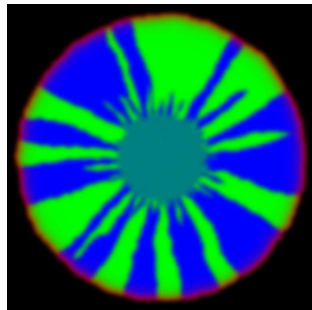
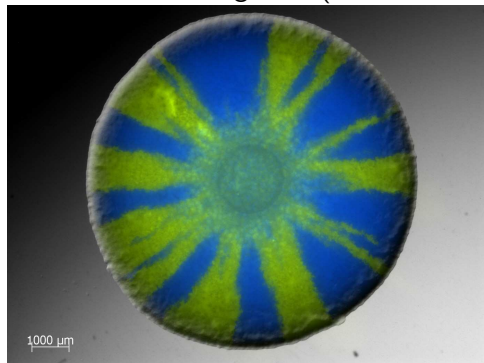
Range expansion

Pseudomonas aeruginosa (Kevin Foster)



Range expansion

Pseudomonas aeruginosa (Kevin Foster)



What's really happening?

