Some mathematical models from population genetics

III. Adding selection

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

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The neutral (haploid) 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.

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In neutral model, all individuals make equal contribution to the pool of gametes.

Adding selection (Wright-Fisher setting)

Relative fitnesses:

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$1 - s_N$	1

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During reproduction each individual produces an effectively infinite number of gametes (same genotype as parent), which combine to form a pool. An individual carrying the type a-allele, produces $(1 - s_N)$ times the number of gametes produced by an individual carrying the type A-allele. Each offspring is obtained by sampling a gamete uniformly at random from the pool.

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- Each individual independently chooses parent; prob type a:

$$\frac{(1-s_N)p}{(1-s_N)p + (1-p)} = \frac{(1-s_N)p}{1-s_N p} = (1-s_N)p + s_N p^2 + \mathcal{O}(s_N^2)$$

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Ignoring $\mathcal{O}(s_N^2)$ terms

- Number of a-offspring $\texttt{Bin}\big(N, p - s_Np(1-p)\big)$.
- $\mathbb{E}[\Delta p] = -s_Np(1-p)$; $\mathbb{E}[(\Delta p)^2] = \frac{1}{N}p(1-p) + \mathcal{O}(\frac{s_N}{N})$.

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Time in units of N generations, $N \to \infty$,

$Ns_N \to s$, $\qquad dp_t = -sp_t(1-p_t)dt + \sqrt{p_t(1-p_t)}dW_t$

Adding selection (Moran model)

Relative fitnesses:

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- Events determined by Poisson Process intensity $\binom{N}{2}dt$;
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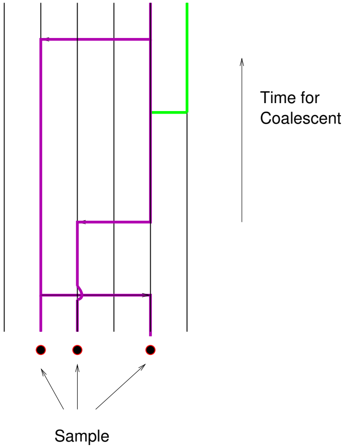
c.f. in Wright-Fisher, probability parent of type a:

$$\frac{(1 - s_N)p}{1 - s_N p} = (1 - s_N)p + s_N p^2 + \mathcal{O}(s_N^2)$$

Adding selection (alternative view)



Neutral events at rate $(1 - s_N)\binom{N}{2}$;

Selective events at rate $s_N\binom{N}{2}$:
if $\{a, A\}$ chosen, A reproduces.

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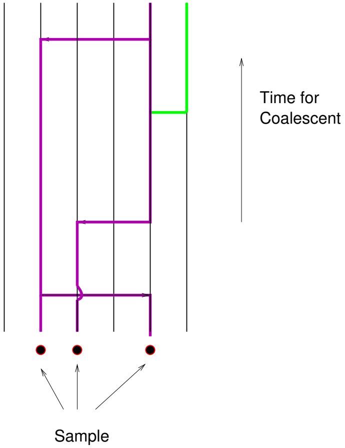

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$\mathbb{E}[p(t)^{n(0)}] = \mathbb{E}[p(0)^{n(t)}]$ where $n(t)$ a branching and coalescing dual.

The ancestral selection graph

- $n_t \mapsto n_t - 1$ rate $\binom{n_t}{2}$
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All individuals in sample are type a *iff* all their ancestors in the ASG are type a.

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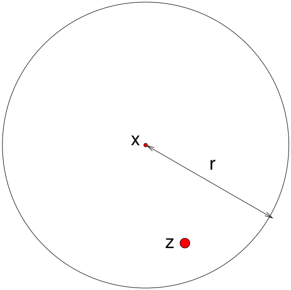
Aim to investigate the interaction of natural selection and spatial structure in the framework of the spatial Lambda-Fleming-Viot process.

Recap: 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 $y \in B_r(x)$,

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

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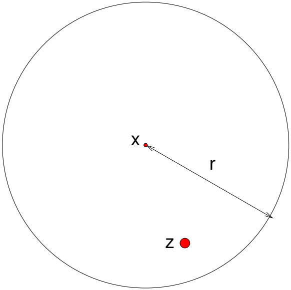


Special case: $K = \{a, A\}$, $w(t,x) := \rho(t,x,\{a\})$. If proportion of type a in ball before event is $\overline{w}$,

$$w(t,y) = \begin{cases} (1-u)w(t-,y) + u & \text{with probability } \overline{w} \\ (1-u)w(t-,y) & \text{with probability } 1-\overline{w} \end{cases}$$

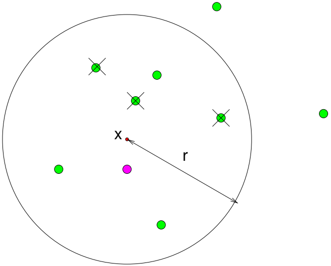
Backwards in time

- 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'.



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

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.

Introducing selection to the SLFV

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

- (i) 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

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

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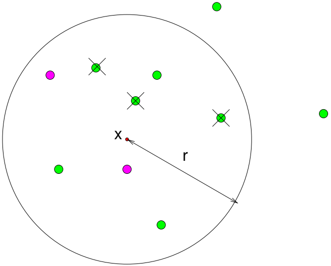
- (ii) Neutral events rate $\propto (1 - s)$, selective events rate $\propto s$. At selective reproduction events, sample two potential parents. If types aa, then an a reproduces, otherwise an A does.

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;
- 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.

Zooming out: recovering classical models

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

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

Over sufficiently large spatial and temporal scales, does the proportion of favoured alleles in the SLFV with selection look like a solution to the (stochastic) Fisher-KPP equation?

Key tool: ancestral selection graph.

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

Branching Brownian motion and the Fisher-KPP equation

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

- Individuals follow independent Brownian motions
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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 $\mathbb{E}[X_\tau] = X_0$.

Thus $\mathbb{P}[X_\tau = N] = 1/N$.

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

Reminder: parameters in SLFV with selection

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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 $nu_n s_n$ $\mathcal{O}(1)$: $1 - \gamma - \delta = 0$.

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

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Fixed impact u and event radius r, selection coefficient s

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$$dw = \frac{1}{2}\Delta w dt + sw(1-w)dt + \mathbf{1}_{d=1}\epsilon\sqrt{w(1-w)}W(dt,dx)$$

E. Véber, Yu.

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

Establishment probability: high neighbourhood size

$$dw = \frac{1}{2}\Delta w dt + sw(1-w)dt + \epsilon\sqrt{w(1-w)}W(dt,dx).$$

While rare,

$$dw \approx \frac{1}{2}\Delta w dt + swdt + \epsilon\sqrt{w}W(dt,dx).$$

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$$dX \approx sXdt + \epsilon\sqrt{X}dB_t,$$

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When neighbourhood size is high, spatial structure hardly perturbs establishment probability. . . . but in a spatial continuum, neighbourhood size can be small.

Small neighbourhood size: Why rescale?

Neutral mutation rate, μ, sets timescale

- Mutation rates are low;

Natural question:
When will we see a signature of a favourable allele in data?

Scaling limits II: Small neighbourhood size:

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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.
- Order one coalescence probability when meet, so in low dimensions need lots of branches.

Scaling limits II: Small neighbourhood size:

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

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

Ability to detect selection depends on dimension:

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

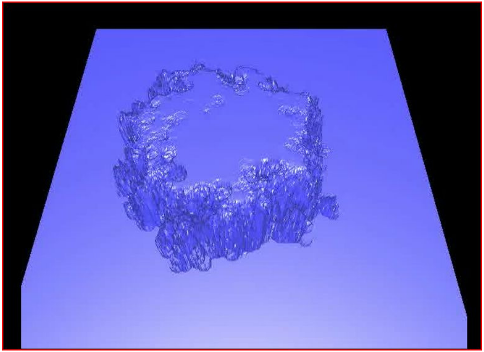
Technical challenges because $ns_n \to \infty$.

Straulino (2015); E., Freeman, Straulino (2017); E., Freeman, Penington, Straulino (2017).

SPACE MATTERS!

Spread of a favoured allele

Two types, a, A, relative fitnesses $1 : 1 + s$. 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 $\frac{w}{1+s(1-w)}$.



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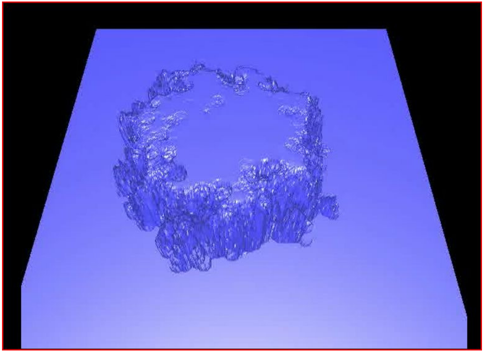
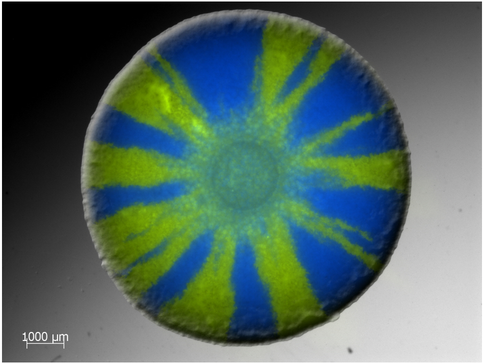


Alternative interpretation: strong selection $\sim$ range expansion

Range expansion

Pseudomanas aeruginosa (Kevin Foster)



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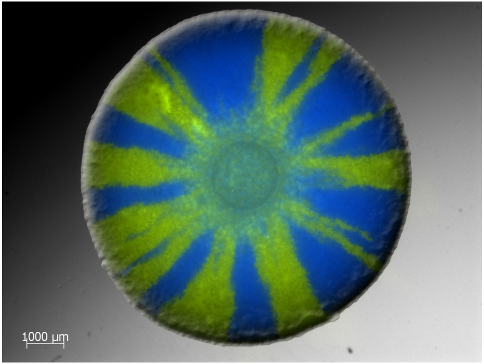

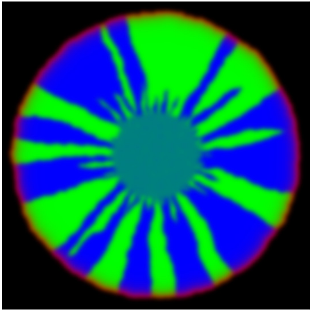

What's really happening?