Some mathematical models from population genetics

3: Selection

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Selective sweeps

The Moran model with selection.

A population of N genes occurring in two alleles, b and B, evolves in overlapping generations. At exponential rate $\binom{N}{2}$ a pair of genes is sampled (with replacement) from the population, one dies and the other splits in two. If the two genes are of different allelic types, then with probability $\frac{1+\sigma}{2}$ it is the B allele that reproduces.

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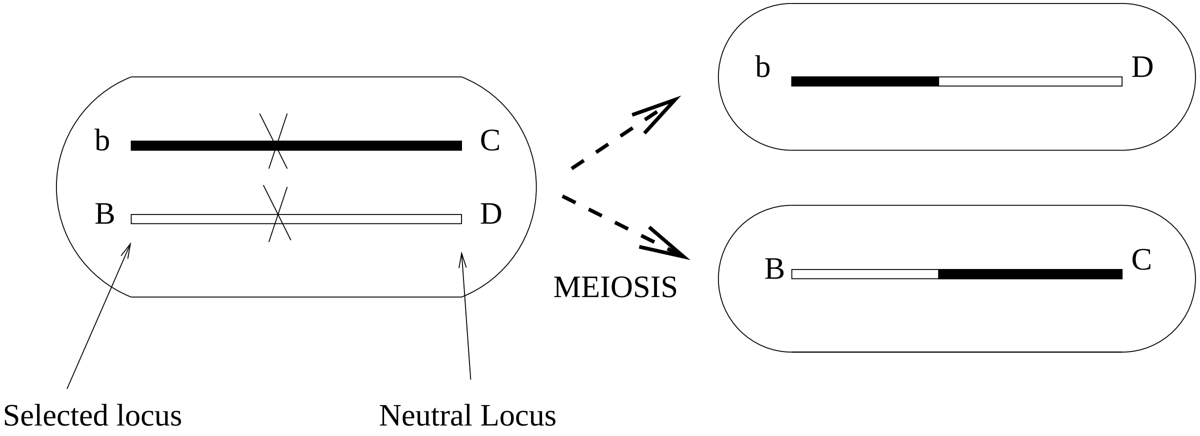
How can we detect selective sweeps?

Genetic Hitchhiking

The problem

Selection acts on a single locus. Alleles B and b.

Linked to a second neutral locus with *recombination* rate r.



What can we say about the family sizes in a sample from the neutral locus at the moment of fixation?

Durrett & Schweinsberg's model

In a population of size $2N$, individuals are labelled b and B. At exponential rate $2N$, two individuals are chosen at random (with replacement) from the population.

- If both are the same type, or if the 2nd is type B, then the first dies and the second reproduces,
- If the 1st is type B and the 2nd is type b, with probability $1 - s$ the 1st dies and the 2nd reproduces, otherwise nothing happens.

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Each individual has a second label, from a type space of $2N$ elements. When a new particle is born, it inherits its second label from its parent with probability $1 - r$, otherwise it inherits this label from an individual chosen at random from the population.

The frequency of B-alleles in the population is governed by

$$\begin{aligned}\mathcal{L}^{(N)}f(p) = (2N)^2\Big\{p(1-p)\left(f(p+\frac{1}{2N}) - f(p)\right)\\ + p(1-p)(1-s)\left(f(p-\frac{1}{2N}) - f(p)\right)\Big\},\end{aligned}$$

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Durrett and Schweinsberg approximate ancestral sample distribution at neutral locus up to error $\mathcal{O}(1/(\log N)^2)$ in probability.

A large population limit

Measure time in units of size $2N$ and set $\alpha = 2Ns$, then

$$\begin{aligned}
\mathcal{L}^{(N)} f(p) &= (2N)^2 \Big\{ p(1-p) \left(\frac{1}{2N} f'(p) + \frac{1}{2} \frac{1}{(2N)^2} f''(p) \right) \\
&\qquad + p(1-p)(1-s) \left(\frac{-1}{2N} f'(p) + \frac{1}{2} \frac{1}{(2N)^2} f''(p) \right) \Big\} + \mathcal{O}(\\
&= 2Nsp(1-p)f'(p) + \frac{2-s}{2} f''(p) + \mathcal{O}(\frac{1}{N}) \\
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\end{aligned}$$

$$dp = \alpha p(1-p)dt + \sqrt{2p(1-p)}dW.$$

Let $\rho = 2Nr$ and write T for the time of the end of the sweep.

Backwards in time

At time T when take sample all individuals type B.

Tracing backwards in time, at time of recombination event ancestors of neutral and selective loci differ so type at *selected* locus of ancestor at neutral locus *can change*. *Effective* recombination events

$$B \rightsquigarrow b \text{ rate } \rho(1-p_{T-\beta}).$$

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No mutation so two lineages can result from a common parent only if they have the same type at the selected locus.

$$\text{Two lineages in } B \text{ at time } T-\beta \text{ coalesce at rate } \frac{2}{p_{T-\beta}}.$$
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A structured coalescent

Structured coalescent in background p:

Given the path, $\{p_t\}_{0\leq t\leq T}$, of the sweep, the *structured coalescent in background* p is the system of coalescing lineages in which lineages migrate from background B to b at instantaneous rate $\rho(1-p_{T-\beta})$ and from b to B at instantaneous rate $\rho p_{T-\beta}$. Moreover, any pair of lineages in background B at time β coalesce at instantaneous rate $\frac{2}{p_{T-\beta}}$ and any pair of lineages in background b coalesce at instantaneous rate $\frac{2}{(1-p_{T-\beta})}$.

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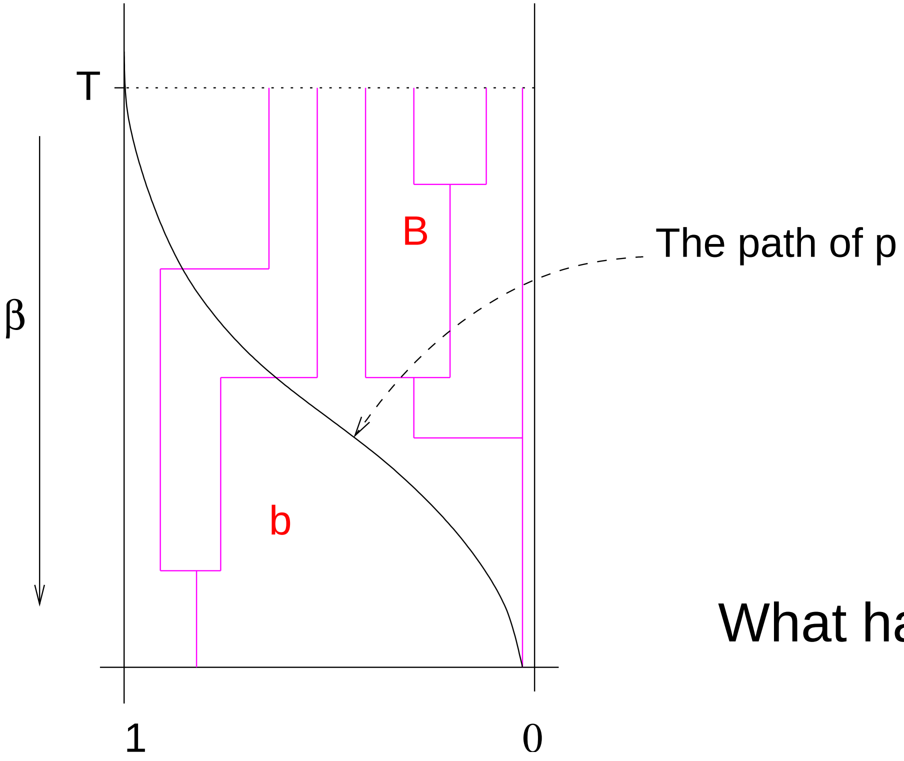
Given that a sweep takes place,

$$dp = \alpha p(1-p)\coth(\frac{\alpha}{2}p)dt + \sqrt{2p(1-p)}dW.$$

Genealogy at the *neutral* locus: structured n-coalescent in background p.

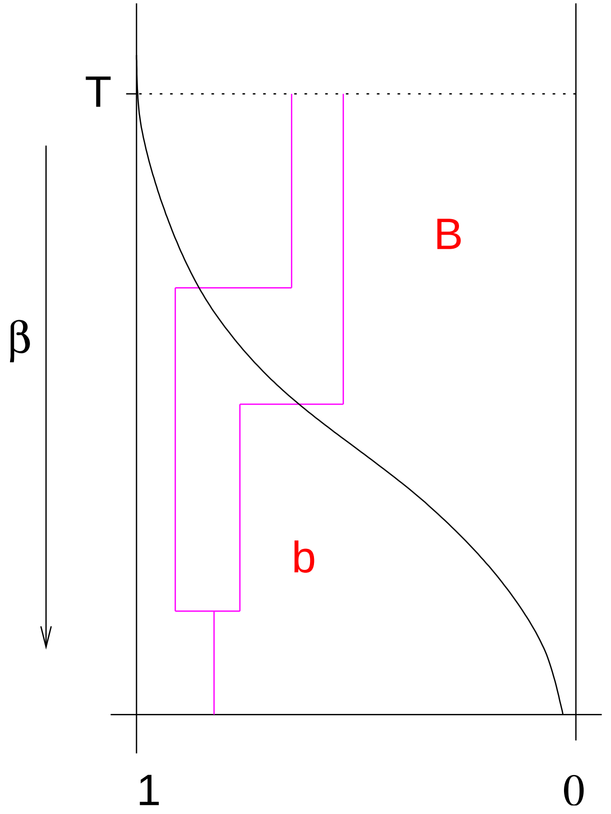


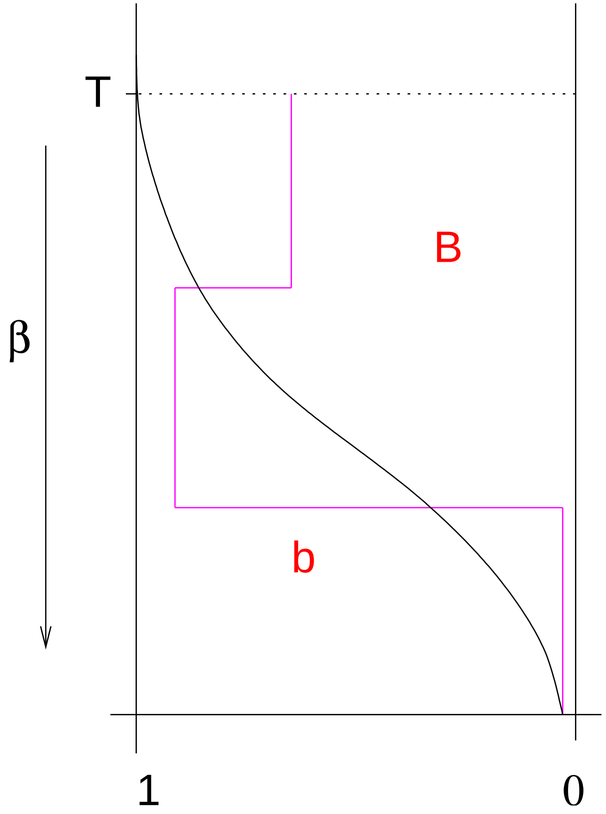
What happens as $\alpha \to \infty$?

$$\rho = 2Nr = \gamma \frac{\alpha}{\log(\alpha)}.$$

Approximation step 1

- From the structured to a marked coalescent





Each have probability of $\mathcal{O}\left(1/(\log\alpha)^2\right)$.

Approximation step 2

- From the marked coalescent to a marked Yule tree

Recall that

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Time change $t \mapsto \tau$ given by $d\tau = (1-p_t)dt$. Then $p \rightsquigarrow Z$

$$dZ = \alpha Z \coth(\frac{\alpha}{2}Z)d\tau + \sqrt{2Z}d\tilde{W}_\tau.$$

Feller diffusion conditioned on non-extinction.

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Feller diffusion conditioned on non-extinction.

Marking rate $\rightsquigarrow \rho d\tau$. Coalescence rate $\rightsquigarrow \frac{2}{Z(1-Z)} \approx \frac{2}{Z}$.

Approximation step 3

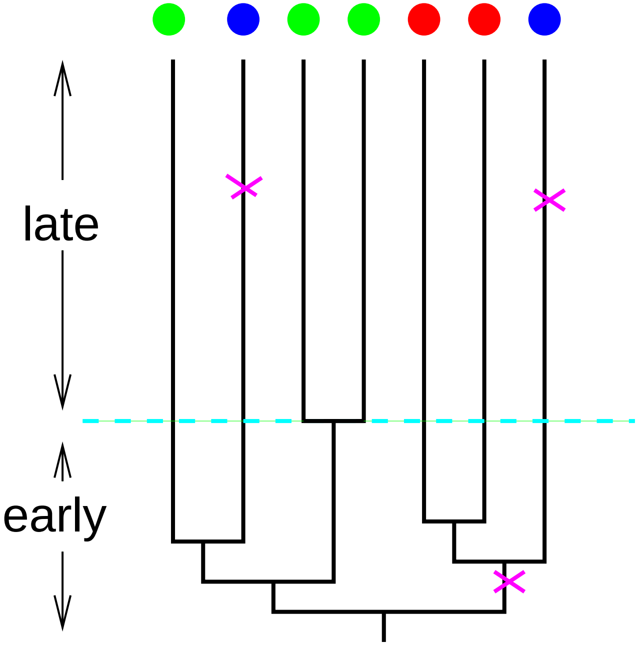
- Approximating sample partitions in marked Yule trees.

Coalescent (approximately) genealogy of a sample from a Yule tree with *constant* rate of marking.

One can construct this process *forwards* in time.

Many exact calculations are possible.

Phases of the sweep



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🔵 Late recombinant

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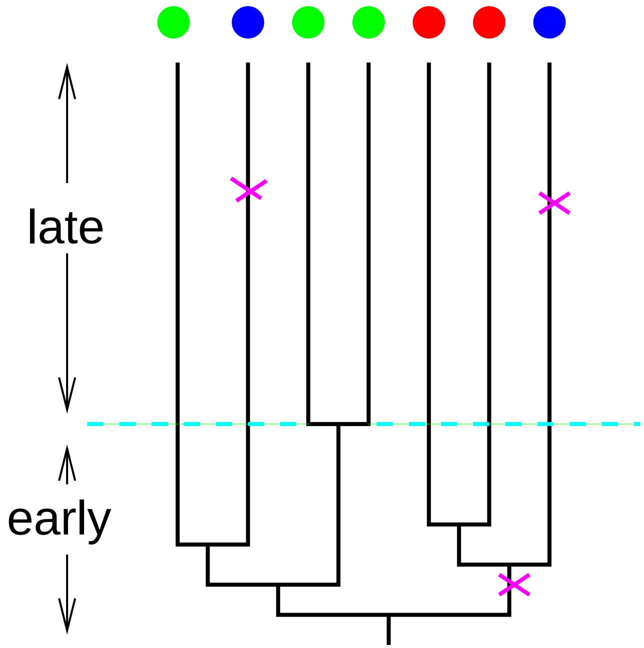

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Up to an error $\mathcal{O}(1/(\log\alpha)^2)$, we will see at most *one* early recombinant family.

Main result

Theorem

Fix n. For a selection coefficient $\alpha \gg 1$ and a recombination rate $\rho = \gamma \frac{\alpha}{\log \alpha}$, the ancestral partition of an n-sample drawn at time T consists, up to an error in probability of order $\mathcal{O}\left(\frac{1}{(\log \alpha)^2}\right)$, of

- L late recombinant singletons
- *one* family of early recombinants of size E
- one non-recombinant family of size $n - L - E$.

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$$\mathbf{P}[F \leq i] = \frac{(i-(n-1))\cdots(i-1)}{(i+(n-1))\cdots(i+1)},$$

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Given $F = f$, let L be a binomial random variable with n trials and success probability $1 - p_f$, where

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This gives us the number of late recombinants.

Independently of all this, let S be a $\{0, 1, ..., n\}$-valued random variable with

$$\mathbf{P}[S = s] = \begin{cases} \frac{\gamma n}{\log \alpha} \sum_{i=2}^{n-1} \frac{1}{i}, & s = 1, \\ \frac{\gamma n}{\log \alpha} \frac{1}{s(s-1)}, & 2 \leq s \leq n-1 \\ \frac{\gamma n}{\log \alpha} \frac{1}{n-1}, & s = n. \end{cases}$$

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This provides the ‘thinning’ of S to give the number of early recombinants at the end of the sweep.

Numerical results

We distinguish the number and types of ancestors of the sample at the beginning of the sweep.

$n = 1$

$$\text{pinb} \approx \mathbf{P}[L = 1].$$

$n = 2$

Two ancestors: ‘p2inb’, ‘p1B1b’

One ancestor: ‘p2cinb’ or a B allele.

$$\text{p2inb} \approx \mathbf{P}[L = 2 \text{ or } S = 2, L = 1],$$
$$\text{p2cinb} \approx \mathbf{P}[L = 0, S = 2],$$
$$\text{p1B1b} \approx \mathbf{P}[L = 1, S = 0].$$

	pinb	p2inb	p2cinb	p1B1b
	$N = 10^4$	$s = 0.1$	r=0.001064	
Moran	0.08203	0.00620	0.01826	0.11513
Logistic	0.09983(21%)	0.00845(36%)	0.03365(84%)	0.11544(0.3%)
SD03	0.08235(0.4%)	0.00627(1.1%)	0.01765(-3.4%)	0.11687(1.5%)
EPW05	0.0822(0.2%)	0.00659(6.3%)	0.01867(2.2%)	0.11515(0.0%)
	$N = 10^4$	$s = 0.1$	r=0.005158	
Moran	0.33656	0.10567	0.05488	0.35201
Logistic	0.39936(18%)	0.13814(31%)	0.09599(75%)	0.32646(-7.3%)
SD03	0.34065(1.2%)	0.10911(3.2%)	0.05100(-7.1%)	0.36112(2.6%)
EPW05	0.32973(-2.0%)	0.10857(2.7%)	0.05662(3.2%)	0.34157(-0.3%)

A new kind of data

Beginning to see data that documents genetic variation at genomic scales.

Can we identify the locations of selective sweeps by looking for long blocks of shared material?

Need to understand ‘false positives’.

- Rare neutral trees
- Bottlenecks
- Spatial subdivision

Examine the way in which diversity recovers as we move away from the shared block.

Balancing selection

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Diploid population of size N. Model the corresponding $2N$ genomes as haploid.

The Moran model

At exponential rate $\binom{2N}{2}$ a pair of individuals is chosen at random from the population. One dies, the other reproduces.

If the pair chosen consists of one type P and one type Q, then with probability $(1+\sigma)/2$ it is the type P individual that reproduces.

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Mutation:

		Offspring	
		P	Q
Parent	P	$1-\overline{\mu}_1$	$\overline{\mu}_1$
	Q	$\overline{\mu}_2$	$1-\overline{\mu}_2$

Transition rates

		P death P birth	P death Q birth	Q death P Birth	Q death Q birth
Parents	PP	$1-\bar{\mu}_1$	$\bar{\mu}_1$	0	0
	PQ	$\frac{(1-\sigma)}{2}\bar{\mu}_2$	$\frac{(1-\sigma)}{2}(1-\bar{\mu}_2)$	$\frac{(1+\sigma)}{2}(1-\bar{\mu}_1)$	$\frac{(1+\sigma)}{2}\bar{\mu}_1$
	QQ	0	0	$\bar{\mu}_2$	$1-\bar{\mu}_2$

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Write $p(t)$ for the proportion of P alleles in population at time t and $\mathcal{L}^{(N)}$ for the generator of the rescaled Moran model.

Weak selection limit

Lemma

For any smooth function $f : [0,1] \to \mathbb{R}$,

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Proof.

$$\mathcal{L}^{(N)} f(p)$$

$$= N(2N-1)\Big\{2p(1-p)\frac{(1+\sigma)}{2}(1-\bar{\mu}_1)+(1-p)^2\bar{\mu}_2\Big\}\left(f(p+\frac{1}{2N}) - f(p)\right)$$

$$+N(2N-1)\Big\{2p(1-p)\frac{(1-\sigma)}{2}(1-\bar{\mu}_2)+p^2\bar{\mu}_1\Big\}\left(f(p-\frac{1}{2N}) - f(p)\right).$$

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Substitute for σ and $\bar{\mu}_i$ and expand f in a Taylor series about p. □

In the weak selection limit, the frequency of P-alleles follows

$$dp_t = \Big\{ s_0 p_t (1-p_t)(1-2p_t) \\ - \mu_1 p_t + \mu_2 (1-p_t) \Big\} dt + \sqrt{p_t(1-p_t)}\, dW_t,$$

where $\{W_t\}_{t \geq 0}$ is standard Brownian motion and s_0 is a constant.

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Linked to a second neutral locus with *recombination* rate r.
The neutral locus is embedded in a fluctuating genetic background.
Migration due to mutation and recombination.

What can we say about the genealogy of a sample from the neutral locus?

Some assumptions

At the neutral locus, assume mutation to a novel type at rate ν.

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Assume that frequency of P-alleles has reached stationarity.

Some assumptions

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Assume that frequency of P-alleles has reached stationarity.

Let $n_t = (n_1(t), n_2(t))$ where $n_1(t)$ is the number of ancestors of our sample in background P at time t *before* the present, $n_2(t)$ is the number in background Q.

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Writing p_t for the frequency of P-alleles at time t *before* the present, can write down the generator of (p_t, n_t).

A weak selection limit

The model is too special.

Pass to a diffusion approximation:

$$\overline{\mu}_i = \frac{\mu_i}{N}, \quad \overline{r} = \frac{r}{N}, \quad \overline{s} = \frac{s}{N}, \quad \overline{\nu} = \frac{\nu}{N}.$$

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Let $E = [0,1] \times \{1, \ldots, n_1(0) + n_2(0)\}^2$ and suppose that $f(p, n_1, n_2) : E \to \mathbb{R}$ is C^2 as a function of p.

$$
\begin{aligned}
Af &= \frac{1}{p}\binom{n_1}{2}\big(f(p,n_1-1,n_2)-f(p,n_1,n_2)\big)\\
&+ \frac{1}{q}\binom{n_2}{2}\big(f(p,n_1,n_2-1)-f(p,n_1,n_2)\big)\\
&+ \frac{p}{q}\mu_1 n_2\big(f(p,n_1+1,n_2-1)-f(p,n_1,n_2)\big)\\
&+ \frac{q}{p}\mu_2 n_1\big(f(p,n_1-1,n_2+1)-f(p,n_1,n_2)\big)\\
&+ r n_2 p\big(f(p,n_1+1,n_2-1)-f(p,n_1,n_2)\big)\\
&+ r n_1 q\big(f(p,n_1-1,n_2+1)-f(p,n_1,n_2)\big)\\
&+ (-\mu_1 p+\mu_2 q+spq)\, f' + \frac{1}{2}pqf''
\end{aligned}
$$

where $q = 1 - p$ and $'$ denotes differentiation with respect to p.

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Crucially, if τ is first hitting time of zero by the diffusion p then $\int^{\tau} \frac{1}{p(s)} ds$ diverges. (Similar statement at $p = 1$).

Coalescence times

Let $F_{PP}(t, p)$ be the probability that the two lineages ancestral to our sample have coalesced by time t if both individuals in the sample are originally taken from the P background. Similarly define $F_{PQ}(t, p)$ and $F_{QQ}(t, p)$.

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Given that $\{p(0)\}_{t \geq 0}$ is drawn from the (reversible) stationary distribution for the process $\{p(t)\}_{t \geq 0}$, $\{F_{PP}(t, p), F_{PQ}(t, p), F_{QQ}(t, p)\}$ can be characterised as the unique *minimal* solution to the following system of differential equations subject to $F'_{PP}(t, 1) = 0$, $F'_{QQ}(t, 0) = 0$ and $F_{PP}(0, p) = F_{PQ}(0, p) = F_{QQ}(0, p) = 0$.

$$
\begin{aligned}
\dot{F}_{PP} &= \frac{1-F_{PP}}{p} + 2\left(\frac{\mu_2 q}{p} + rq\right)(F_{PQ} - F_{PP}) \\
&\quad + (-\mu_1 p + \mu_2 q + spq)\, F'_{PP} + \frac{1}{2} pq F''_{PP} \\
\dot{F}_{PQ} &= \left(\frac{p\mu_1}{q} + rp\right)(F_{PP} - F_{PQ}) \\
&\quad + \left(\frac{q\mu_2}{p} + rq\right)(F_{QQ} - F_{PQ}) \\
&\quad + (-\mu_1 p + \mu_2 q + spq)\, F'_{PQ} + \frac{1}{2} pq F''_{PQ} \\
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Integration by parts $\rightsquigarrow$

$$\begin{aligned}
0 = \quad & -2\nu f_{PP} + \frac{1-f_{PP}}{p} + 2\left(\frac{\mu_2 q}{p} + rq\right)(f_{PQ} - f_{PP}) \\
& \quad + (-\mu_1 p + \mu_2 q + spq)\, f'_{PP} + \tfrac{1}{2} pq f''_{PP} \\
0 = \quad & -2\nu f_{PQ} + \left(\frac{p\mu_1}{q} + rp\right)(f_{PP} - f_{PQ}) + \left(\frac{q\mu_2}{p} + rq\right)(f_{QQ} - f_{PQ}) \\
& \quad + (-\mu_1 p + \mu_2 q + spq)\, f'_{PQ} + \tfrac{1}{2} pq f''_{PQ} \\
0 = \quad & -2\nu f_{QQ} + \frac{1-f_{QQ}}{q} + 2\left(\frac{\mu_1 p}{q} + rp\right)(f_{PQ} - f_{QQ}) \\
& \quad + (-\mu_1 p + \mu_2 q + spq)\, f'_{QQ} + \tfrac{1}{2} pq f''_{QQ}.
\end{aligned}$$

(*minimal* solution)

A numerical example

Calculate the probability of identity of a sample of size two and thus the expected time to the most recent common ancestor, E.

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$dp = s_0 p(1-p)(1-2p)dt + \mu(1-2p)dt + \sqrt{p(1-p)}dW$.

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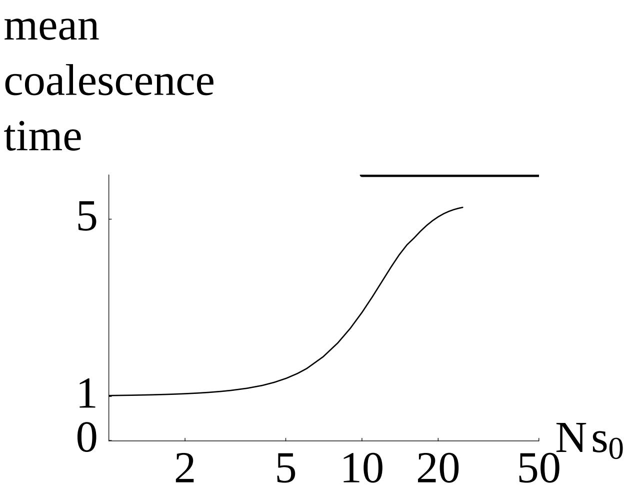

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- Biological populations are *finite*. In particular $\log N \sim 10$.
- Quoted numbers often for the *effective* population size.