# Some mathematical models from population genetics

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

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# What we have so far: Wright-Fisher/Moran models

In time units of $N_e$ generations, $p =$ proportion $a$-alleles

- (Forwards time) The Wright-Fisher diffusion (with and without selection)

$$dp_t = -sp_t(1-p_t)dt + \sqrt{p_t(1-p_t)}dW_t;$$

- (Backwards time) The Kingman coalescent/ ASG

$$n_t \mapsto n_t - 1 \text{ at rate } \binom{n_t}{2}, \quad n_t \mapsto n_t + 1 \text{ at rate } sn_t;$$

- Sampling probabilities

$$\mathbb{E}[p(t)^{n(0)}] = \mathbb{E}[p(0)^{n(t)}]$$

Stronger result holds. Kingman coalescent really describes genealogy of random sample from (neutral) population.

# Adding spatial structure: subdivided populations

Population subdivided into demes = islands = colonies

- Vertices of graph, $i \in I$;
- $i \sim j$ if $i$, $j$ neighbours
- $N_i =$ population size in deme $i$

**Structured Wright-Fisher model**

Reproduction in discrete generations

- neutral Wright-Fisher within each deme
- proportion $m_{ij}$ of individuals in deme $i$ migrate to deme $j$

$$N_i \sum_{j \sim i} m_{ij} = \sum_{j \sim i} N_j m_{ji}$$

# Genealogy of structured Wright-Fisher model

1. Two lineages sampled from deme $i$

$$\mathbb{P}\big[\text{coalesce in } j \neq i \text{ in previous generation}\big] = \frac{\binom{m_{ji}N_j}{2}}{\binom{N_i}{2}} \frac{1}{N_j}$$

$$\mathbb{P}\big[\text{coalesce in } i \text{ in previous generation}\big] = \frac{\binom{N_i - \sum_{j\sim i} m_{ji}N_j}{2}}{\binom{N_i}{2}} \frac{1}{N_i}$$

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2. Two lineages sampled from demes $i \neq j$

$$\mathbb{P}\big[\text{coalesce in } k \notin \{i,j\} \text{ in previous generation}\big] = \frac{m_{ki}N_k}{N_i} \frac{m_{kj}N_k}{N_j} \frac{1}{N_k}$$

$$\mathbb{P}\big[\text{coalesce in } j \text{ in previous generation}\big] = \frac{m_{ji}N_j}{N_i} \frac{\left(N_j - \sum_{l\sim j} m_{lj}N_l\right)}{N_j} \frac{1}{N_j}$$

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**The structured coalescent** $\underline{n} = (n_i)_{i\in I}$:

- $\begin{cases} n_i \mapsto n_i - 1 \\ n_j \mapsto n_j + 1 \end{cases}$ at rate $n_i \frac{N_e(j)}{N_e(i)} m_{ji}$
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Ancestral lineages drawn into more populous demes

# Forwards in time?

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Alleles $a$, $A$. $p_i(t) =$ proportion of type $a$ in deme $i$ at time $t$

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\mathbb{E}\big[\Delta p_i\big] &= \frac{1}{N_i}\Big(\big(1-\sum_{j\sim i} m_{ij}\big)N_i p_i + \sum_{j\sim i} m_{ji} N_j p_j\Big) - p_i \\
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$\mathbb{E}\big[(\Delta p_i)^2\big] = \frac{1}{N_i}\big(p_i(1-p_i)+O(1/N)\big)$ $\qquad$ $\mathtt{Cov}\big(\Delta p_i, \Delta p_j\big) = O(1/N^2)$

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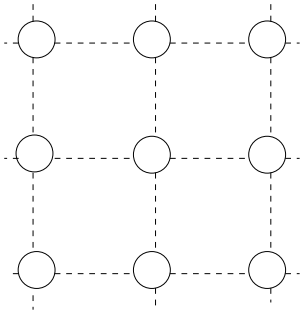
As $N \to \infty$ recover a system of diffusions coupled through migration

# Kimura's stepping stone model

$\sum_j N_e(i)m_{ij} = \sum_j N_e(j)m_{ji}$

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



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

System of W-F diffusions coupled through migration

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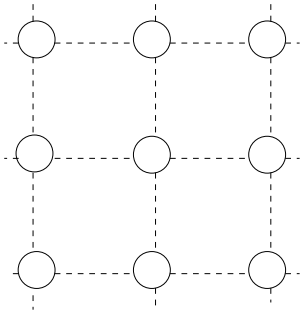

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# Duality

*for simplicity* $N_i \equiv N_e$

$$dp_i = \sum_j m_{ji}(p_j - p_i)dt + \sqrt{\tfrac{1}{N_e} p_i(1-p_i)}\, dW_i \qquad \underline{p^n} := \prod_{i \in I} p_i^{n_i}.$$

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&= \sum n_i \sum_j m_{ji} \left( \underline{p}^{\underline{n}+\underline{e}_j-\underline{e}_i} - \underline{p}^{\underline{n}} \right) dt \\
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$\underline{n} \mapsto \underline{n} + \underline{e}_j - \underline{e}_i$ at rate $n_i m_{ji}$

$\underline{n} \mapsto \underline{n} - \underline{e}_i$ at rate $\frac{1}{N_e}\binom{n_i}{2}$

$$\frac{d}{du}\mathbb{E}\left[\underline{p}_{\underline{u}}^{\underline{n}_{t-u}}\right] = 0$$

$$\mathbb{E}\left[\underline{p}_{\underline{t}}^{\underline{n}_0}\right] = \mathbb{E}\left[\underline{p}_{\underline{0}}^{\underline{n}_t}\right].$$

# Interpretation

$$\mathbb{E}\left[\underline{p}_t^{n_0}\right] = \mathbb{E}\left[\underline{p}_0^{n_t}\right].$$

- Sample $n_i(0)$ individuals from deme $i$, $\sum_i n_i(0) < \infty$,
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Need to account for mutation in our model

# Adding mutation

Simplest example:

- Infinitely many alleles model of mutation: each individual in each generation, independently, with small probability $\mu$ mutates to a type never before seen in the population
- *Probability of identity by descent* of two individuals, $F$, $=$ probability no mutation since most recent common ancestor (MRCA)
- Equivalently $F = (1-2\mu)^T \approx \exp(-2\mu T)$ is the Laplace transform of the distribution of the time to the MRCA.

The neutral mutation rate dictates the timescales over which we can reconstruct information about genealogies.

# Isolation by distance

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Isolation by distance (Wright 1943)

In $\mathbb{Z}$ with nearest neighbour migration there is an explicit expression for the probability of identity. It declines exponentially with distance. But the exact formula is very special.

# Probability of identity in subdivided population

Population on $\mathbb{Z}^2$, $N$ individuals per deme, discrete generations

- Reproduction according to Wright-Fisher model in each deme;
- Proportion $g_1(x-y)$ of offspring in deme $x$ migrate to deme $y$.

$T=$ time to MRCA of sample of size two

$$F(x) = \mathbb{E}_x[(1-2\mu)^T]$$

($x$ vector in $\mathbb{Z}^2$)

$$\psi_t(x) = \mathbb{P}_x[T=t],$$

$$\psi_1(x) = \frac{G_1(x)}{N}, \quad G_1(x) = \int g_1(x,z)g_1(0,z)dz.$$

# Calculating $F(x)$

If $t > 1$, partition over location immediate ancestors

$$\psi_t(x) = \sum_y G_1(x-y)\psi_{t-1}(y) - \frac{1}{N} G_1(x)\psi_{t-1}(0).$$

Then

$$(*) \qquad \psi_t(x) = \frac{1}{N}\left( G_t(x) - \sum_{\tau=1}^{t-1} G_{t-\tau}(x)\psi_\tau(0) \right)$$

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Write $\phi(z,x) = \mathbb{E}_x[z^T]$,

$$(\dagger) \qquad \phi(z,x) = \frac{1}{N}\widetilde{G}(z,x)\Big(1 - \phi(z,0)\Big)$$

(convolution $\rightarrow$ product under LT)

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If $g_1$ approximately Gaussian

$$\frac{1}{N}\widetilde{G}(z,0) = \frac{1}{2\mathcal{N}}\log\Big(\frac{1}{\sqrt{1-z}}\Big); \quad \frac{1}{N}\widetilde{G}(z,x) = \frac{1}{\mathcal{N}}K_0\Big(\frac{|x|}{\sigma}\sqrt{1-z}\Big)$$

$\mathcal{N} = 2N\pi\sigma^2$ is Wright's neighbourhood size, $K_0$ modified Bessel function of second kind of degree zero.

# Calculating $F(x)$

Have shown

$$\phi(z,x) \approx \frac{K_0\left(\frac{|x|}{\sigma}\sqrt{1-z}\right)}{\mathcal{N} - \log(\sqrt{1-z})}$$

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DIVERGES as $x \to 0$

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Assume solution constant over small scale $\kappa$, use $K_0(y) \approx -\log y$ as $y \downarrow 0$, set $z = 1 - 2\mu \approx \exp(-2\mu)$ and substitute:

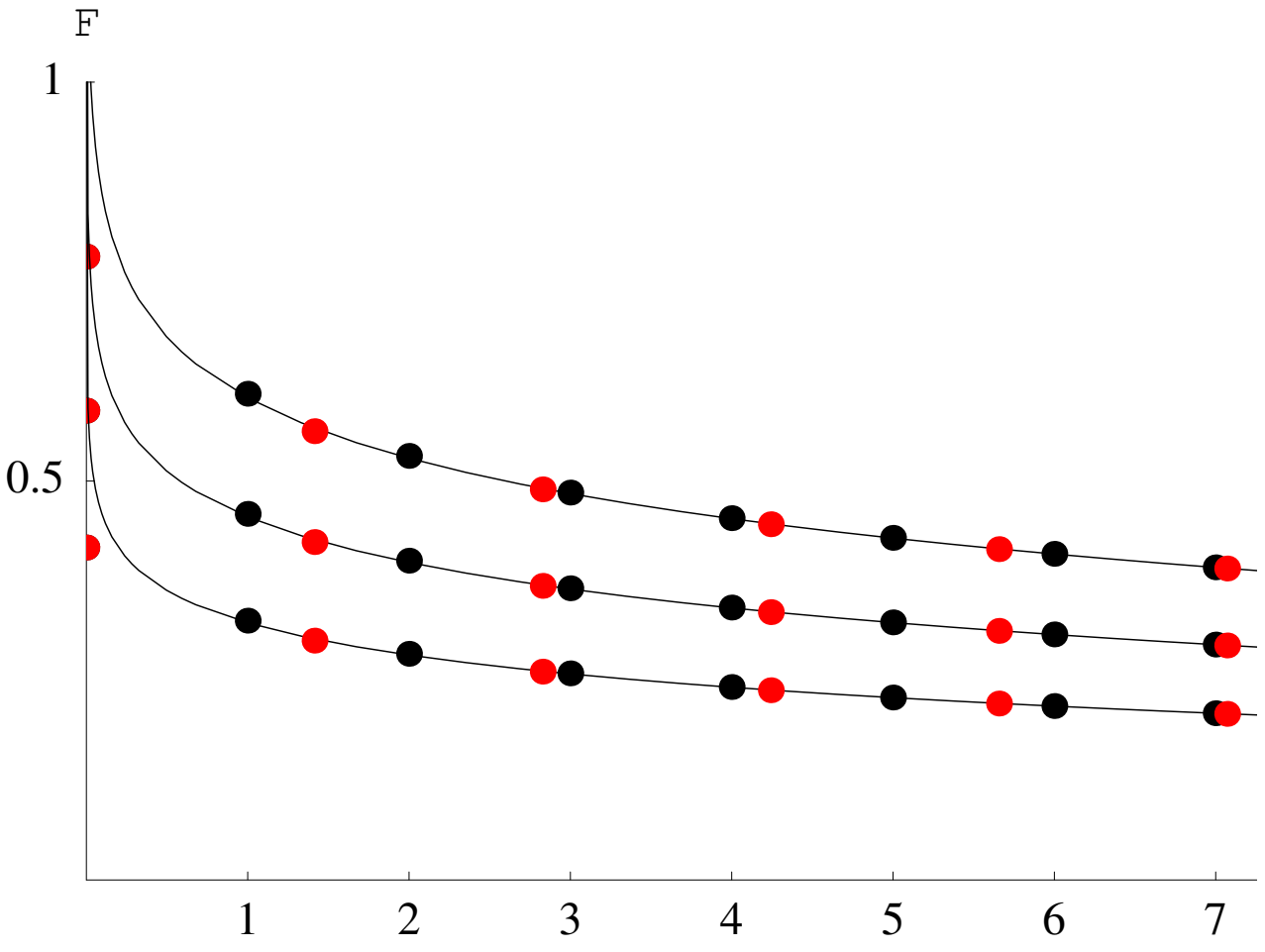
$$(*) \qquad F(x) = \mathbb{E}_x[e^{-2\mu T}] \approx \frac{K_0\big(|x|/l_\mu\big)}{\mathcal{N} + \log(l_\mu/\kappa)} \qquad |x| > \kappa$$

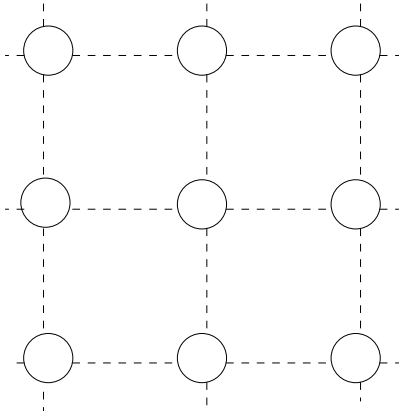
where $l_\mu = \sigma/2\mu$,

$$\mathbb{E}_0[e^{-2\mu T}] \approx \frac{\log(l_\mu/\kappa)}{\mathcal{N} + \log(l_\mu/\kappa)}.$$

$(*)$ is known as the Wright-Malécot formula.

# Malécot-Wright approximation for the stepping stone model



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

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

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Why does it work?

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If $X_0 = 0$, local CLT $\implies$ $\mathbb{P}_0[X_t = 0] \approx 1/(4\pi\sigma^2 t)$

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# The distribution of $T_0$

$$1 = \int_0^{L^2} \mathbb{P}_\pi[X_t = 0]dt = \int_0^{L^2} \mathbb{P}_\pi[T_0 = s] \int_0^{L^2-s} \mathbb{P}_0[X_t = 0]dtds$$

$$\approx \mathbb{P}_\pi[T_0 \leq L^2] \frac{\log(L^2)}{4\pi\sigma^2}$$

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$$\mathbb{P}[\tau > s + t | \tau > s] = \mathbb{P}[\tau > t] \quad \text{as } L \to \infty$$

i.e (asymptotically) $\tau$ has exponential distribution

$$\mathbb{P}_\pi\left[T_0 > \frac{L^2 \log L}{2\pi\sigma^2} t\right] \to e^{-t}$$

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- Unless $N$ grows with $L$, $T_0$ dominates

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