Population Genetics and Evolution – III

Statistics of Genealogies: The Coalescent

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Outline

Introduction

The Coalescent

The Coalescent with selection

Introduction

Genealogies

- How far in the past must we go to reach the last common ancestor of n individuals? of the whole population?
- How many different genotypes can we expect to find by sampling n individuals?
- How do the times to the last common ancestor depend on the particular chosen sample? on the population size?
- How do they fluctuate as the population evolves in time?
- How are they affected by selection?

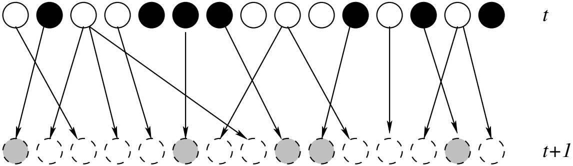
These questions can be addressed by using the concept of the *Coalescent*

The Coalescent

JFC Kingman

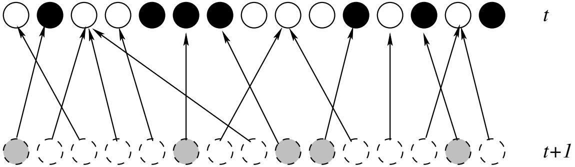
The Wright-Fisher model

Two ways of looking at the Wright-Fisher model:

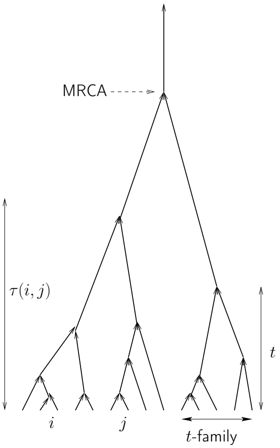


The Wright-Fisher model

Two ways of looking at the Wright-Fisher model:



Iterating the process



Iterating the process

Neutral Wright-Fisher process:

- Set $t = 0$ for the present, and count generations *backward* from the present
- Individual labels: $\{1, \dots, N\}$
- At each generation, define the application $p: \; i \mapsto p_t(i)$ from i to its parent
- $p_t(i)$ is extracted at random, independently for each i and each t
- Ancestor: $a_t(i) = \underbrace{p_t(p_{t-1}(\cdots p_2(p_1}_{t \text{ times}}(i))))$
- Lineage: $\mathrm{L}(i) = (a_0(i) = i, a_1(i), a_2(i), \dots)$
- Lineage coalescence: $a_t(i) = a_t(j)$, $i \neq j$
- Coalescence time: $\tau(i,j)$: $a_\tau(i) = a_\tau(j)$, $a_{\tau-1}(i) \neq a_{\tau-1}(j)$

Iterating the process

Disclaimer:

> *In this [lecture] gene genealogies will sometimes be referred to simply as genealogies. It should be understood that this refers to the genetic ancestry of a sample at some locus in the genome and not to the usual definition of a genealogy, being the family relationship of a set of individuals.*

J. WAKELEY, 2009

Iterating the process

Questions:

- How many generations to the MRCA?
- What is the distribution of $\tau(i, j)$?
- What are the consequences for quantities we can measure?

N.B.: When treating *diploids*, set $N = 2 \cdot$ population size
Discussion of the *effective* population size: later!

Coalescent statistics

Hypotheses:

1. Equal fitness for all types (neutral process)
2. No subdivisions in the population (geographical or otherwise)
3. Constant population size

Assumptions 1. and 2. lead to *exchangeability*: the number of offspring of any individual is statistically the same random variable as for any other individual

Coalescent statistics

- Probability that n individuals have all different parents:

$$\begin{aligned} w_n &= \left(1-\frac{1}{N}\right)\left(1-\frac{2}{N}\right)\cdots\left(1-\frac{n-1}{N}\right) \\ &\simeq 1-\frac{n(n-1)}{2N} \qquad\qquad n \ll N \end{aligned}$$

- $\Pi_n(t)$: probability of n independent lineages at time t

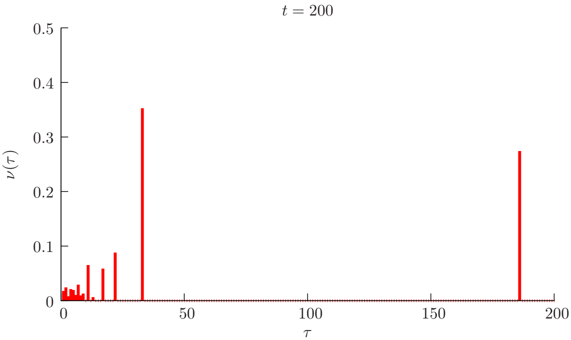
$$\Pi_n(t+1) = w_n \Pi_n(t) \simeq \left(1-\frac{n(n-1)}{2N}\right)\Pi_n(t)$$

- $\Pi_n(t) = \left(1-\frac{n(n-1)}{2N}\right)^t \simeq \mathrm{e}^{-n(n-1)t/(2N)}$
- In particular $\Pi_2(t) \simeq \mathrm{e}^{-t/N}$

Coalescent statistics

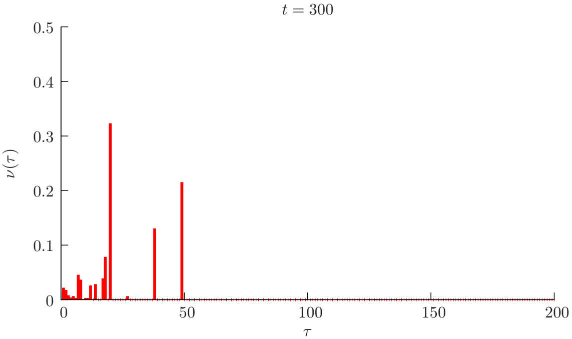
- Averages over the *process* are expressed by $\left[\ldots\right]_{\mathrm{av}}$
- Averages over the *population* are expressed by $\langle\ldots\rangle$
- Thus $[\tau(i,j)]_{\mathrm{av}} = N$
- Mutation rate u per genome and generation, infinite *site* model
- Expected # of mutations wrt the common ancestor: Nu
- Expected # of mutations between i and j: $2Nu = \theta$

Distribution of coalescent times



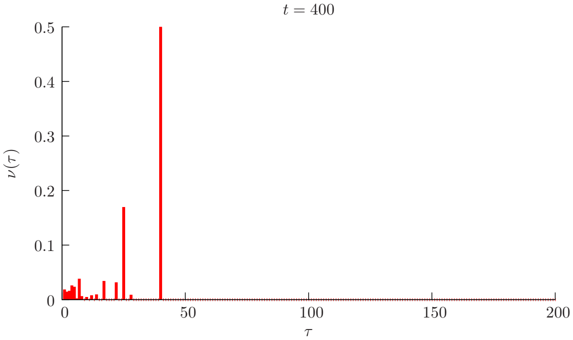
$N = 50$

Distribution of coalescent times



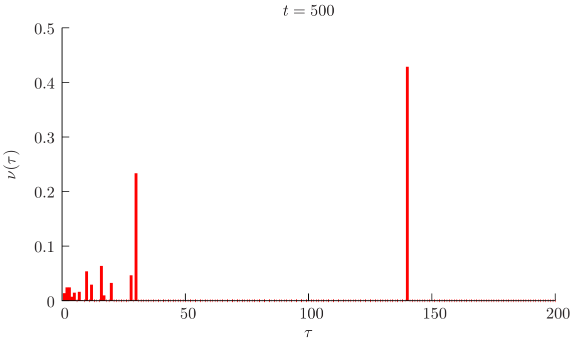
$N = 50$

Distribution of coalescent times



$N = 50$

Distribution of coalescent times



$N = 50$

Universality of the coalescent

- Reproduction model: Distribution of offspring size m: π_m

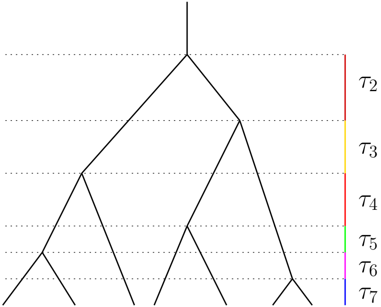
$$\begin{aligned} \text{WF model: } \pi_m &= \mathrm{e}^{-1}/m! \qquad \text{(Poisson)} \\ \text{Moran model: } \pi_0 &= \pi_2 = \frac{1}{N}\left(1-\frac{1}{N}\right),\ \pi_1 = 1-\frac{2}{N}\left(1-\frac{1}{N}\right) \end{aligned}$$

- $[m]_{\mathrm{av}} = \sum_m m\,\pi_m = 1$
- Probability of coalescence for n lineages:

$$1-w_n = \binom{n}{2}\frac{1}{N}\sum_m m(m-1)\,\pi_m = \frac{n(n-1)}{2N}\left(\left[m^2\right]_{\mathrm{av}}-1\right)$$

- Define $[m(m-1)]_{\mathrm{av}} = \left[m^2\right]_{\mathrm{av}} - 1 = \kappa$
- Thus $w_n = 1 - \frac{n(n-1)}{2}\frac{\kappa}{N}$
- If $\left[m^2\right]_{\mathrm{av}} < \infty$, all results hold, up to a time rescaling
- Choose time units so that $w_n = 1 - \frac{n(n-1)}{2}$

Probability of a genealogy



$$P(\tau_2, \ldots, \tau_7) = \exp\left\{-\frac{1}{2}\left[7 \cdot 6 \cdot \tau_7 + 6 \cdot 5 \cdot \tau_6 + \cdots + 2 \cdot 1 \cdot \tau_2\right]\right\}$$

Each τ_k is independent, with distribution $\mathcal{P}_k(\tau) = \binom{k}{2}\, \mathrm{e}^{-\binom{k}{2}\tau}$

Distribution of the total length

- Define $T_{\mathrm{total}} = \sum_{k=2}^{n} T_k$, $T_k = k \cdot \tau_k$
- Then each T_k is an exponentially distributed random variable, of average $[T_k]_{\mathrm{av}} = 2/(k-1)$

Distribution of the total length

$$\mathcal{P}_{\mathrm{total}}(T) = \mathrm{Prob}(T_{\mathrm{total}} = T) = \int_0^\infty \prod_{k=2}^{n} \left(\mathrm{d}\,T_k \, \frac{(k-1)\,\mathrm{e}^{-(k-1)T_k/2}}{2} \right)$$

$$\times\, \delta\left(\sum_{k=2}^{N} T_k - T \right)$$

$$= \int_{-\mathrm{i}\infty}^{+\mathrm{i}\infty} \frac{\mathrm{d}\lambda}{2\pi\mathrm{i}} \int_0^\infty \prod_{k=2}^{n} \left(\mathrm{d}\,T_k \, \frac{k-1}{2}\, \mathrm{e}^{-(k-1)T_k/2} \right)$$

$$\times \exp\left[-\lambda \left(\sum_{k=2}^{N} T_k - T \right) \right]$$

$$= \int_{-\mathrm{i}\infty}^{+\mathrm{i}\infty} \frac{\mathrm{d}\lambda}{2\pi\mathrm{i}}\, \mathrm{e}^{\lambda T} \prod_{k=2}^{n} \left(\frac{k-1}{2\lambda + (k-1)} \right)$$

Distribution of the total length

Summing over the residues

$$\begin{aligned}\mathcal{P}_{\text{total}}(T) &= \sum_{k=2}^{n} \frac{k-1}{2}\,\mathrm{e}^{-(k-1)T/2} \prod_{j\,(\neq k)} \frac{j-1}{j-k} \\ &= \sum_{k=2}^{n} (-1)^k \binom{n-1}{k-1} \frac{k-1}{2}\,\mathrm{e}^{-(k-1)T/2} \\ &= \frac{n-1}{2}\mathrm{e}^{-T/2}\left(1-\mathrm{e}^{-T/2}\right)^{n-2}\end{aligned}$$

TAVARÉ, 1984; WIUF AND HEIN, 1999

Distribution of the age of the MRCA

- Define T_{MRCA} as the age of the MRCA of n samples
- Then $T_{\mathrm{MRCA}} = \sum_{k=2}^{n} \tau_k$
- Each τ_k is exponentially distributed, with average $[\tau_k]_{\mathrm{av}} = \left[\binom{k}{2}\right]^{-1}$

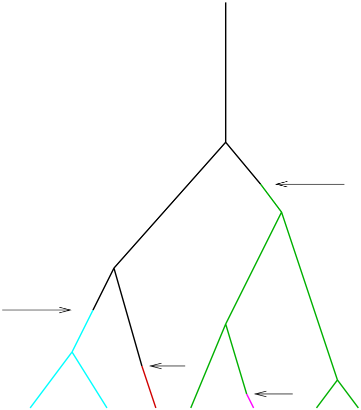
Distribution of the age of the MRCA

Using the same method one obtains

$$\begin{aligned}\mathcal{P}_{\mathrm{MRCA}}(T) &= \mathrm{Prob}(T_{\mathrm{MRCA}} = T)\\ &= \sum_{k=2}^{n} \binom{k}{2} \mathrm{e}^{-\binom{k}{2}T} \prod_{j\,(\neq k)} \frac{\binom{j}{2}}{\binom{j}{2} - \binom{k}{2}}\\ &= \sum_{k=2}^{n} \binom{k}{2} (-1)^k (2k-1) \frac{n(n-1)\cdots(n-k+1)}{n(n+1)\cdots(n+k-1)}\, \mathrm{e}^{-\binom{k}{2}T}\end{aligned}$$

TAVARÉ, 1984; TAKAHATA AND NEI, 1985

Coalescence and mutations



The probability of a mutation occurring is uniform per unit length of the genealogy

Coalescence and mutations

- Assume mutation rate u per genome and generation, infinite *allele* model
- Two individuals carry the same allele if they encounter no mutation before their last common ancestor
- The probability of *not* having a mutation in a generation in a lineage is $1 - u$
- The probability that *neither* lineage exhibits a mutation is $(1-u)^{2\tau(i,j)} \simeq \exp\left(-2u\tau(i,j)\right)$
- Thus the probability that two individuals have the same allele is

$$
\begin{aligned}
p_{\text{same}} &= \frac{1}{N}\int_0^\infty \mathrm{d}\tau\ \mathrm{e}^{-2u\tau-\tau/N} \\
&= \frac{1}{1+2uN} = \frac{1}{1+\theta}
\end{aligned}
$$

Ewens' sampling formula

- Infinite-allele model
- Take n samples from a large population with $\theta = 2Nu$
- Samples belong to the same group if they exhibit the same allele
- What is the probability that there are b_1 groups with 1 element, b_2 groups with 2 elements,... b_k with k elements,... ?

Ewens' sampling formula

$$n = \sum_{k=1}^{n} k\, b_k \qquad \text{\# of samples}$$

$$\boxed{P(b_1, \ldots, b_n) = \frac{n!}{\theta(\theta+1)\cdots(\theta+n-1)} \frac{1}{1^{b_1} \cdot 2^{b_2} \cdots n^{b_n}} \frac{\theta^{\sum_k b_k}}{b_1! b_2! \cdots b_n!}}$$

The Chinese Restaurant Process

The Chinese Restaurant Process

At each step, when there are n customers:

- The customer sits at a new empty table with probability $\theta/(\theta + n)$, or
- The customer picks up one of the customers at random and sits at the same table

The Chinese Restaurant Process

- At each step, we get a factor $1/(\theta + n)$ $(n = 0, 1, \ldots)$
- Each new table gets a factor θ
- In going from k to $k+1$, each table gets a factor k
- Thus the probability that the (labeled) customers sit at ℓ tables, $i = 1, \ldots, \ell$ of size k_i, $\sum_{i=1}^{\ell} k_i = n$ is given by

$$P^{\text{lab}}(k_1, \ldots, k_\ell) = \frac{\theta^\ell}{\theta(\theta+1)\cdots(\theta+n-1)} \prod_{i=1}^{\ell} (k_i - 1)!$$

- There are $n!/(k_1! \cdots k_\ell!)$ distributions of the customers compatible with $(k_1, \ldots, k_\ell)$, thus

$$\begin{aligned} P(k_1, \ldots, k_\ell) &= \frac{n!}{k_1! \cdots k_\ell!} \frac{\theta^\ell}{\theta(\theta+1)\cdots(\theta+n-1)} \prod_{i=1}^{\ell} (k_i - 1)! \\ &= \frac{n!\, \theta^\ell}{\theta(\theta+1)\cdots(\theta+n-1)} \prod_{i=1}^{\ell} \frac{1}{k_i} \end{aligned}$$

The Chinese Restaurant Process

- Labelling the tables has introduced an overcounting: only the sizes of the tables matter! Thus defining

$$b_j = \sum_{i=1}^{\ell} \delta_{k_i,j}$$

we obtain

$$P(b_1,\ldots,b_n) = \frac{n!\,\theta^{\ell}}{\theta(\theta+1)\cdots(\theta+n-1)}\frac{1}{1^{b_1}\cdots n^{b_n}}\underbrace{\frac{1}{b_1!\cdots b_n!}}_{\text{Table permutations}}$$

Observables

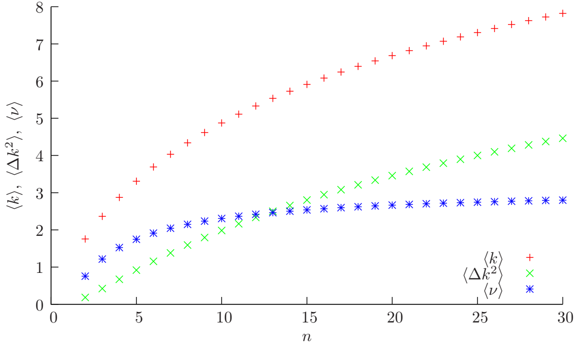
- Distribution of the number k of segregating alleles:

$$
\begin{aligned}
p_k(n+1) &= \frac{n}{\theta+n}p_k(n)+\frac{\theta}{\theta+n}p_{k-1}(n) \\
[k(n+1)]_{\mathrm{av}} &= [k(n)]_{\mathrm{av}}+\frac{\theta}{\theta+n}=\theta\sum_{j=1}^{n-1}\frac{1}{\theta+j} \\
\left[\Delta k^2(n+1)\right]_{\mathrm{av}} &= \left[k^2(n)\right]_{\mathrm{av}}-[k(n)]_{\mathrm{av}}^2=\left[\Delta k^2(n)\right]_{\mathrm{av}}+\frac{n\theta}{(\theta+n)^2}
\end{aligned}
$$

- Distribution of the number ν of singletons:

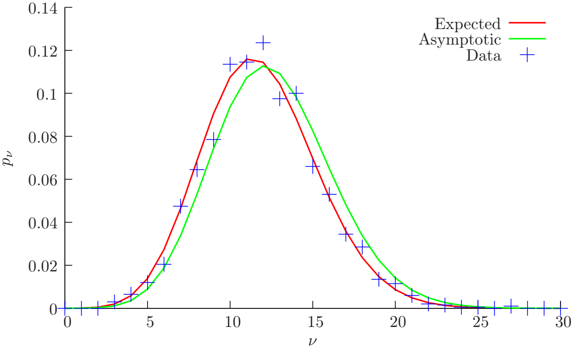
$$
\begin{aligned}
p_\nu(n+1) &= \frac{\theta}{\theta+n}p_{\nu-1}(n)+\frac{\nu}{\theta+n}p_{\nu+1}(n)+\frac{n-\nu}{\theta+n}p_\nu(n) \\
[\nu(n)]_{\mathrm{av}} &= \frac{n\theta}{\theta+n-1}
\end{aligned}
$$

Observables



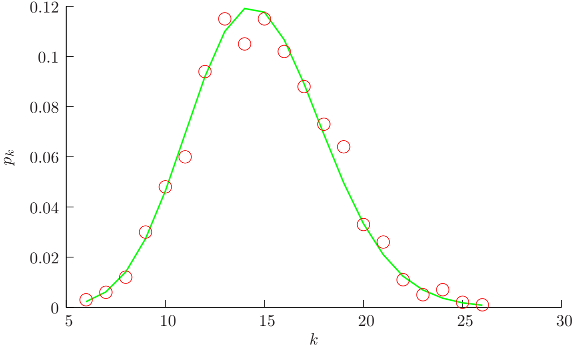
Average $[k]_{\mathrm{av}}$, variance $\left[\Delta k^2\right]_{\mathrm{av}}$ of segregating alleles and average $[\nu]_{\mathrm{av}}$ of singletons vs. n for $\theta = 3.1$

Observables



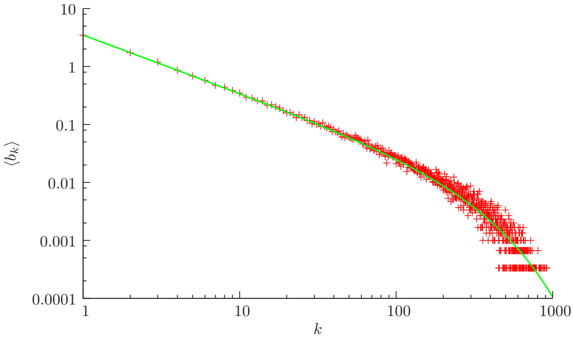
Distribution p_ν of the number of singletons for $n = 200$ and $\theta = 12.6$, together with the asymptotic distribution for $n \to \infty$ and simulation data over 1000 samples

Observables



Distribution p_k of the number of segregating alleles for $n = 300$ and $\theta = 3.1$, together with simulation data averaged over 1000 samples

Frequency spectrum



Average number $[b_k]_{\mathrm{av}}$ of groups of size k with $n = 1000$ and $\theta = 3.5$. The average is taken over 3000 realizations of the process.

The line corresponds to $[b_k]_{\mathrm{av}} = [b_1]_{\mathrm{av}}\, \mathrm{e}^{-\theta k/n}/k$, with $[b_1]_{\mathrm{av}} = n\theta/(\theta + n - 1)$

Effective population size N_e

The *effective population size* N_e can be different from the *census population* N:

- In sexual populations, because only some males actually reproduce(*leks*)
- Generally due to fluctuating population size:

$$\frac{1}{N_\mathrm{e}} \simeq \left[\frac{1}{N}\right]_\mathrm{av} > \frac{1}{[N]_\mathrm{av}}$$

- If fitness is nonuniform N_e is reduced wrt N:

$$N_\mathrm{e} = \frac{N}{1 + \mathrm{var}(\#\mathrm{offspring})}$$

Effective population size N_{e}

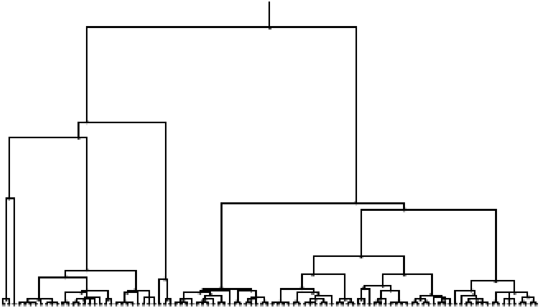
In practice, N_{e} is chosen to fit the data:

- For several human genes, $T_{\mathrm{MRCA}} \simeq 400\,000\ \mathrm{yrs}$
- One generation $\simeq 20\ \mathrm{yrs}$
- Assuming neutrality, $N_{\mathrm{e}} \simeq 10\,000$ (diploidy!)
- "Out-of-Africa" bottleneck?

The Coalescent with selection

The Coalescent in the presence of selection

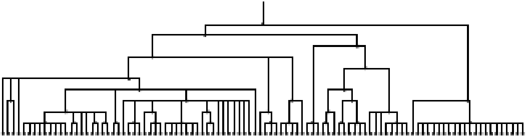
BRUNET, DERRIDA *et al.*, 2006–2012



Neutral genealogy: $N = 100$, $T_{\mathrm{MRCA}} = 125$

The Coalescent in the presence of selection

BRUNET, DERRIDA *et al.*, 2006–2012



Genealogy with selection: $N = 100$, $T_{\mathrm{MRCA}} = 10$

Coalescent times

A general coalescence model (Λ-coalescent):

- One starts with N points: in each interval of duration $\mathrm{d}t$ there is a probability $\pi_k \,\mathrm{d}t$ for every subset of k points to coalesce into one
- Then for some measure Λ one has

$$\pi_k = \int_0^1 x^k \,\Lambda(\mathrm{d}x)$$

- Rate $\lambda_{b,k}$ at which k ($2 \leq k \leq p$) points out of p coalesce into one is given by

$$\lambda_{p,k} = \int_0^1 x^{k-2}(1-x)^{p-k}\lambda(\mathrm{d}x) = \sum_{n=0}^{p-k} \frac{(p-k)!}{n!(p-k-n)!}(-1)^n \pi_{n+k}$$

- $r_p(\ell)\,\mathrm{d}t$: probability of having ℓ lineages at time $t + \mathrm{d}t$ if there are p lineages at time t:

$$r_p(\ell) = \frac{p!}{(\ell-1)!(p-\ell+1)!}\lambda_{p,p-\ell+1}$$

Coalescent times

- T_p: coalescence time for p lineages
- Assume steady state:

$$[T_p]_{\mathrm{av}} = \mathrm{d}t + [T_p]_{\mathrm{av}} \left(1 - \mathrm{d}t \sum_{k<p} r_p(k) \right) + \mathrm{d}t \sum_{k<p} r_p(k) \, [T_k]_{\mathrm{av}}$$

Thus

$$\begin{aligned} [T_2]_{\mathrm{av}} &= \frac{1}{\pi_2} \\ \frac{[T_3]_{\mathrm{av}}}{[T_2]_{\mathrm{av}}} &= \frac{4\pi_2 - 3\pi_3}{3\pi_2 - 2\pi_3} \\ \frac{[T_4]_{\mathrm{av}}}{[T_2]_{\mathrm{av}}} &= \frac{27\pi_2^2 - 56\pi_2\pi_3 + 28\pi_3^2 + 12\pi_2\pi_4 + 10\pi_3\pi_4}{(3\pi_2 - 2\pi_3)(6\pi_2 - 8\pi_3 + 3\pi_4)} \\ &\vdots \end{aligned}$$

Coalescent times

In particular:

- The Kingman coalescent:

$$\pi_2 \neq 0 \qquad \pi_k = 0, \quad \forall k > 2$$

  yields

$$[T_2]_{\mathrm{av}} = \frac{1}{\pi_2}, \quad \frac{[T_3]_{\mathrm{av}}}{[T_2]_{\mathrm{av}}} = \frac{4}{3}, \quad \frac{[T_4]_{\mathrm{av}}}{[T_2]_{\mathrm{av}}} = \frac{3}{2} \quad \ldots$$

- The *Bolthausen-Sznitman coalescent*:

$$\pi_k = \frac{\pi_2}{k-1}$$

  yields

$$[T_2]_{\mathrm{av}} = \frac{1}{\pi_2}, \quad \frac{[T_3]_{\mathrm{av}}}{[T_2]_{\mathrm{av}}} = \frac{5}{4}, \quad \frac{[T_4]_{\mathrm{av}}}{[T_2]_{\mathrm{av}}} = \frac{25}{18} \quad \ldots$$

A solvable model

Brunet, Derrida et al., 2006–2012

- N individuals, discrete generations
- Individual i at generation t has “fitness” $x_i(t)$
- *Reproduction*: Probability that one offspring of individual i has “fitness” between x and $x + \mathrm{d}x$:

  $$P(x)\,\mathrm{d}x = \mathrm{e}^{-(x - x_i(t))}\,\mathrm{d}x$$

  Infinite # of offspring: but only finite # on the right of any given point
- *Selection*: At generation $t + 1$ one keeps only the N rightmost individuals

A solvable model

BRUNET, DERRIDA ET AL., 2006–2012

- Now

$$\sum_{i=1}^{N} \mathrm{e}^{-(x-x_i(t))} = \mathrm{e}^{-(x_i-X_t)} \qquad \text{with} \qquad \mathrm{e}^{X_t} = \sum_{i=1}^{N} \mathrm{e}^{x_i(t)}$$

- Thus generation $(t+1)$ is given by the N rightmost points of a Poisson process with density $\mathrm{e}^{-(x-X_t)}$
- Thus we have

$$x_i(t+1) = X_t + Y_{t+1} + y_i(t+1)$$

with

$$\begin{aligned} P(Y)\,\mathrm{d}Y &= \frac{1}{N!}\exp\left[-(N+1)Y - \mathrm{e}^{-Y}\right]\,\mathrm{d}Y \\ P(y)\,\mathrm{d}y &= \theta_{\mathrm{H}}(y)\,\mathrm{e}^{-y}\,\mathrm{d}y \end{aligned}$$

A solvable model

BRUNET, DERRIDA ET AL., 2006–2012

Results:

- Probability that the parent of *i* has “fitness” *x*:

$$p_i(x) = \frac{\mathrm{e}^{-(x-x_i(t))}}{\sum_j \mathrm{e}^{-(x-x_k(t))}} = \frac{\mathrm{e}^{y_i(t)}}{\sum_j \mathrm{e}^{y_{j(t)}}}$$

- Rate of *k*-coalescences:

$$\pi_k = \left[\sum_i p_i^k\right]_{\mathrm{av}} \simeq \frac{1}{(k-1)\log N}$$

Bolthausen-Sznitman!

- Speed of adaptation:

$$v = \langle X_t - X_{t-1}\rangle = \langle Y_t\rangle + \left\langle \log \sum_{i=1}^{N} \mathrm{e}^{y_i(t)} \right\rangle \sim \log\log N$$

A solvable model

BRUNET, DERRIDA ET AL., 2006–2012

Conditioning on the speed:

- Introduce a weighting parameter β:

$$[T_k]_\beta = \lim_{t\to\infty} \frac{1}{t} \sum_{t'=1}^{t} \frac{\left[\mathrm{e}^{-\beta X_t} \langle T_k(t') \rangle\right]_{\mathrm{av}}}{\left[\mathrm{e}^{-\beta X_t}\right]_{\mathrm{av}}}$$

- Coalescence rates:

$$\begin{aligned}\pi_k &= \frac{\left[\sum_i \mathrm{e}^{k y_i(t)} \left(\sum_j \mathrm{e}^{y_j(t)}\right)^{-\beta-k}\right]_{\mathrm{av}}}{\left[\left(\sum_j \mathrm{e}^{y_j(t)}\right)^{-\beta}\right]_{\mathrm{av}}} \\ &\simeq \frac{1}{\log N} \frac{(k-2)!\Gamma(\beta+1)}{\Gamma(\beta+k)}\end{aligned}$$

Interpolates between Bolthausen-Sznitman ($\beta = 0$) and Kingman ($\beta \to \infty$)

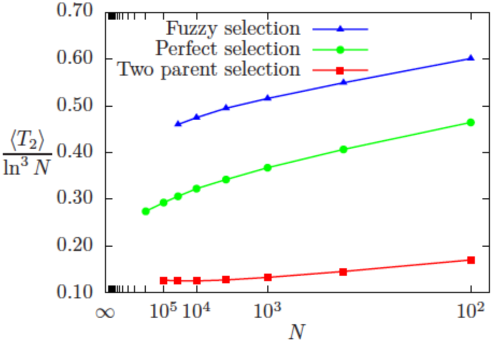
More generic models

BRUNET ET AL., 2006–2012

- Each individual has two potential offspring
- The fitness of each offspring is shifted by z wrt to the parent's one, with pdf $\rho(z)$ (flat in the simulations)
- Selection modes:
  - *Perfect selection*: The best N are retained
  - *Fuzzy selection*: Random choice among the $3N/2$ best
  - *Two-parent selection*: Each individual chooses two parents, but only the better one is kept

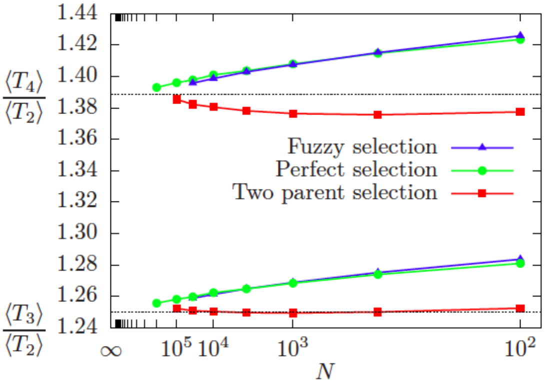
More generic models

BRUNET ET AL., 2006–2012



More generic models

BRUNET ET AL., 2006–2012



More generic models

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Coalescence time scale: $[T_2]_{\mathrm{av}} \sim \log^3 N$
Phenomenological theory

- The population looks like an advancing Kolmogorov-Fisher wave in “fitness” space
- Most of the time its motion is deterministic
- At intervals $\sim \log^3 N$ exceptionally “adapted” individuals arise
- These individual “sweep” a finite fraction of the population in a short time (multiple coalescence!)
- The distribution of the “sweep” sizes corresponds to the Bolthausen-Sznitman coalescent