

Exact Transition Probabilities of the Number of Ancestral Sample Lineages in the Discrete Ancestral Recombination Graph

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Introduction with Disclaimer

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 - for large n – current human genome samples in 10^3 's

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- We set out to compute them.

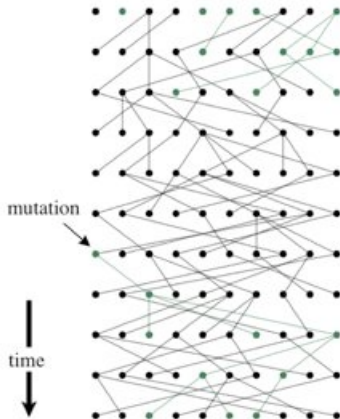
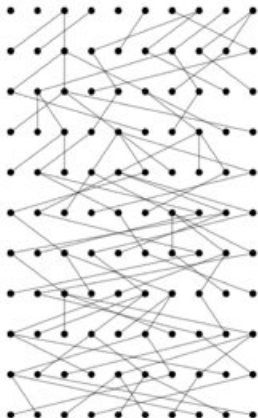
- Wright-Fisher Model – vanilla version
- The n -Coalescent Approximation
- Wright-Fisher Model with Recombination
- Ancestral Recombination Graph
- Exact Transition Probabilities
- Black Robins — a living example
- Detailed Derivation
- Blabber on Further Work

The Wright-Fisher Model – 1

Random Mating, Constant Size, No Recombination/Selection

A Population of $N = 10$ homologous DNA seqns. of length m and the Population History of site i

```
      : 1 2 3 4 5 6 7 8 9 10
1 : A A A A A A A A A C
2 : G G G G G G G G G G
...
i : T T A A A A A A A A
...
k : ...
```

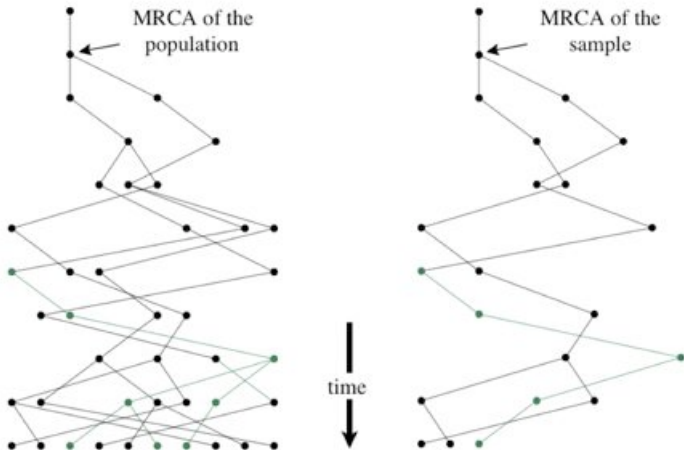


The Wright-Fisher Model – 2

Random Mating, Constant Size, No Recombination/Selection

Ex: **Data** of 3 homologous DNA sequences at site i , its **Population History** and the **Sample History** of sampled individuals 1,2, and 3.

 : 1 2 3
i : T T A



The Wright-Fisher Model & the n -Coalescent – 1

Random Mating, Constant Size, No Recombination/Selection

A **Sample Coalescent Sequence or c -sequence** ($\{\{1\}, \{2\}, \{3\}\}, \{\{1,2\}, \{3\}\}, \{\{1,2,3\}\}$) and **coalescent times or epoch times** $t_i, i \in \{3, 2\}$.

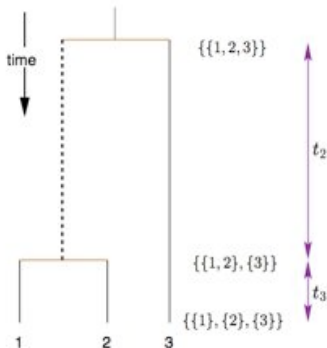
- Offspring “choose” parents uniformly and independently in W-F model
- $\Pr(2 \text{ lineages coalesce in } 1 \text{ generation}) = 1/N$
- $\Pr(2 \text{ lins. are distinct } > g \text{ gens.}) = (1 - 1/N)^g$
- Rescaled time t is g in units of N gens. Then, $\Pr(2 \text{ lins. remain distinct } > t)$ is

$$(1 - 1/N)^{\lfloor Nt \rfloor} \xrightarrow{N \rightarrow \infty} e^{-t}$$

- **Lineage Death Process:** In general, the R.V. T_i that any pair of i lineages coalesce is approximately exponentially distributed for large N .

$$T_i \sim \text{Exponential} \left(\binom{i}{2} \right)$$

- **Uniform Binary Fusion** of two extant lineages.



The Wright-Fisher Model & the n -Coalescent – 2

Random Mating, Constant Size, No Recombination/Selection

The Coalescent Approximation of the Wright-Fisher (W-F) Model (Kingman, 1982)

- The n -Coalescent is a continuous time Markov Chain on $\mathbb{C}_n \equiv \bigcup_{i=1}^n \mathbb{C}_n^i$, the set partitions of $\{1, \dots, n\}$, with rates $q(c_h | c_g)$, $c_g, c_h \in \mathbb{C}_n$:

$$q(c_h | c_g) = \begin{cases} -i(i-1)/2 & : \text{if } c_g = c_h \in \mathbb{C}_n^i \\ 1 & : \text{if } c_h \succ_c c_g \\ 0 & : \text{o.w.} \end{cases}$$

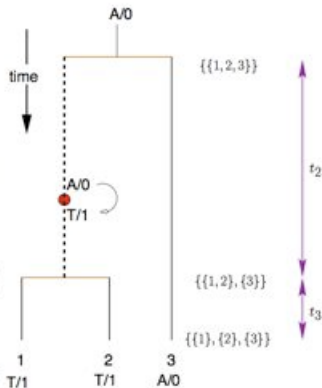
$$c_h \prec_c c_g \Leftrightarrow c_h = c_g \setminus c_{g,j} \setminus c_{g,k} \cup (c_{g,j} \cup c_{g,k})$$

a realization $c = (c_n, c_{n-1}, \dots, c_1) \in \mathbb{C}_n$

- Superimpose indep. mutations

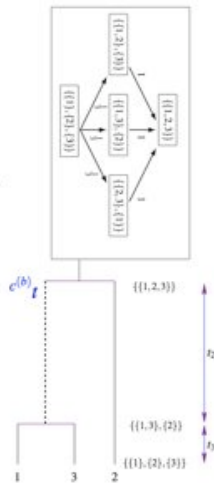
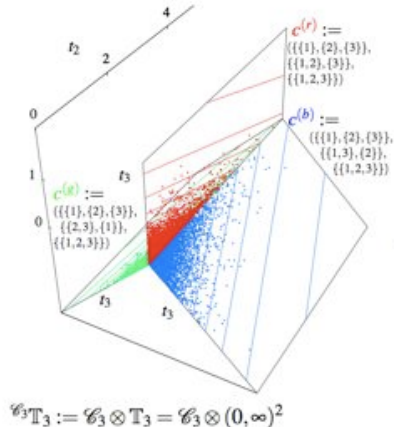
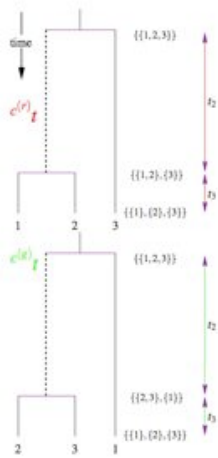
$$\sim \text{Poisson}(\theta/2 \equiv 2N\mu)$$

∞ -many-sites mutation model



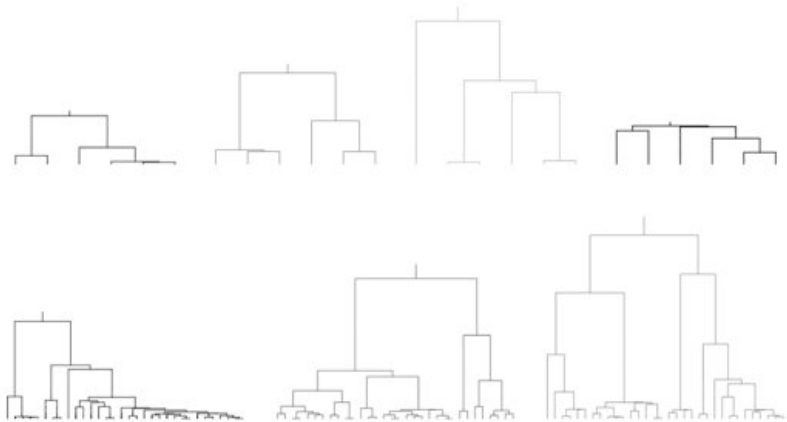
The n -Coalescent for $n = 3$

Random Mating, Constant Size, No Recombination/Selection – The Coalescent Tree Space



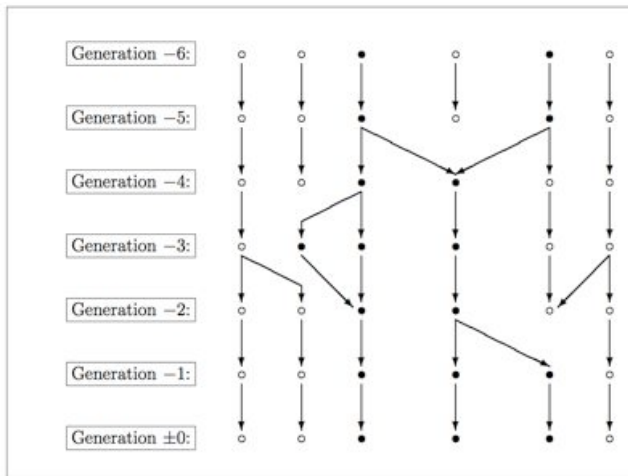
Realisations from the n -Coalescent for $n = 6$ and $n = 32$

Random Mating, Constant Size, No Recombination/Selection – The Coalescent Tree Space



The Wright-Fisher Model with Recombination – 1

Random Mating, Constant Size, Recombination, No Selection



The Wright-Fisher Model with Recombination – 2

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- Then the lines of descent of the $2N$ homologous haploid loci into the next generation, follow from the multinomial random vector $(V, U) := (V_1, V_2, \dots, V_{2N}, U_{1,2}, U_{1,3}, \dots, U_{2N-1,2N})$ of length $2N + \binom{2N}{2}$, such that, $\Sigma V_\bullet + \Sigma U_\bullet = 2N$

The Wright-Fisher Model with Recombination – 3

Random Mating, Constant Size, Recombination, No Selection

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This reproduction scheme is independently and identically enforced in each generation to obtain the Wright-Fisher **population genealogy** with recombination as we go **forward in time**.

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Now we want to track the **sample genealogy** of size n from current generation 0, within this population genealogy of size $2N$ as we go **backward in time** at the coarsest resolution of ancestral sample size **exactly**.

The Wright-Fisher Sample with Recombination – 1

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- where, $P(J|I)$ denotes the probability that the set of lineages ancestral to I in the previous generation is J .

The Wright-Fisher Sample with Recombination – 2

Let $P(J|I, K)$ be the probability that the set of lineages ancestral to I in the previous generation is J given that lineages in a fixed subset K of I are recombinants and the lineages in $I \setminus K$ are non-recombinants. Therefore,

$$P(J|I) = \sum_{K \subseteq I} r^{|K|} (1-r)^{|I|-|K|} P(J|I, K) \quad (3)$$

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Next we describe how to calculate $P(J|I, K)$ for fixed sets of lineages I, J, K .

The Wright-Fisher Sample with Recombination – 3

Let $B(J|I, K)$ be the set of bipartite graphs with vertex set $I \cup J$, with bipartition $J|I$, such that the vertices in K are of degree 2, the vertices in $I \setminus K$ are of degree 1, and no vertices in J isolated.

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$$P(J|I, K) = \frac{|B(J|I, K)|}{(2N)^{|I|-|K|} \binom{2N}{2}^{|K|}} , \quad (4)$$

since there are exactly $(2N)^{|I|-|K|} \binom{2N}{2}^{|K|}$ ways in which the lineages in I choose their ancestral lineages from the previous generation so that lineages in K are recombinants and the lineages in $I \setminus K$ are non-recombinants.

Therefore, combining Eqs. 2 through 4 (and since only the cardinalities of $|I|$, $|J|$ and $|K|$ matter) we have the expression we wanted to find:

$$P(j|i) = \binom{2N}{j} \sum_{k=0}^i \binom{i}{k} r^k (1-r)^{i-k} \frac{|B(j|i, k)|}{(2N)^{i-k} \binom{2N}{2}^k} \quad (5)$$

The Wright-Fisher Sample with Recombination – 5

From Eq. 5, the N -specific probability of i extant sample lineages in the current generation becoming j ancestral lineages in the previous generation is:

$${}^N P_{i,j} = \begin{cases} \frac{(1-r)^i}{2} \left(1 - \binom{i}{2} (2N)^{-1} \right) \\ \quad + \frac{i(i-1)(i+2)r(1-r)^{i-1}}{2N-1} + O((2N)^{-2}) & \text{if } j = i \\ \\ (1-r)^i \binom{i}{2} (2N)^{-1} + O((2N)^{-2}) & \text{if } j = i - 1 \\ \\ \binom{i}{s} \frac{r^s (1-r)^{i-s}}{2} \left(1 - \binom{i+s}{2} (2N)^{-1} \right) \\ \quad + \binom{i}{s+1} r^{s+1} (1-r)^{i-s-1} \frac{(i-s-1)(i+3s+2)+2s(s+1)}{2N-1} \\ \quad + O((2N)^{-2}) & \text{if } j = i + s, 0 \leq s \leq i \\ \\ O((2N)^{-2}) & \text{if } j = i - \ell, 1 < \ell \leq i - 1 \\ \\ 0 & \text{otherwise.} \end{cases} \tag{6}$$

If $j = i + s, 0 \leq s \leq i$, we can further simplify ${}^N P_{i, \geq i}$ to:

$$\begin{aligned}
 & O((2N)^{-2}) + \frac{1}{2} - \sum_{s=0}^i \binom{i+s}{2} \binom{i}{s} \frac{r^s (1-r)^{i-s}}{4N} \\
 & + \binom{i}{s+1} r^{s+1} (1-r)^{i-s-1} \frac{(i-s-1)(i+3s+2) + 2s(s+1)}{2N-1}.
 \end{aligned} \tag{7}$$

We now derive the Hudson/Griffiths-Marjoram scaling condition for linear recombination rate.

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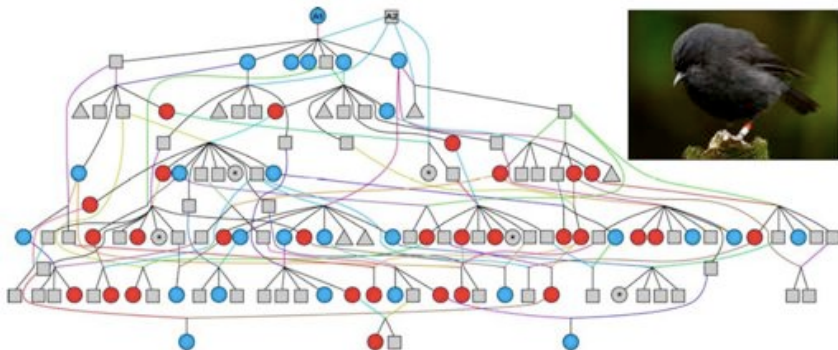
$$\begin{aligned} {}^N P_{i,>i} &= {}^N P_{i,\geq i} - {}^N P_{i,i} = \frac{1}{2} - \frac{(1-r)^i}{2} + O((2N)^{-2}) \\ &= \frac{i\rho}{4N} + O((2N)^{-2}) \end{aligned} \quad (8)$$

Therefore, in the discrete Wright-Fisher model with recombination, unlike the continuous-time ARG, the number of ancestral lineages does not necessarily reach 1 and may even oscillate about a critical ancestral size determined by r and N .

New Zealand Black Robin – a living Adam–Eve Story!

non-Random Mating, non-Constant Size, Recombination & managed-Selection in Applied Conservation Genetics

Joint work with Melanie Massaro, Antony Poole and Marie Hale,
Biologists at Univ. of Canterbury, NZ.



Approximation of (6) in detail – 1

Here we derive the approximation of (6) in detail.

To evaluate $P(j|i)$, we count the number of bipartite graphs in the class $B(J|I, K)$, where sets I, J and K are fixed, and have cardinalities i, j and k , respectively. Only the cardinalities of I, J, K are relevant to counting $|B(J|I, K)|$, therefore, we write $|B(j|i, k)|$. First, we consider the case where $j = i + s$ and $s \geq 0$. In this case $k \geq s$. Let $k = s + m$ with $m \geq 0$.

$$\begin{aligned} & \binom{2N}{j} \frac{1}{(2N)^{i-k} \binom{2N}{2}^k} \\ = & \binom{2N}{i+s} \frac{2^k}{(2N)^i (2N-1)^k} \\ = & \frac{2^{s+m}}{(i+s)!} \frac{(2N)^s}{(2N-1)^{s+m}} \left(1 - \binom{i+s}{2} (2N)^{-1} + O((2N)^{-2}) \right) \\ = & O((2N)^{-m}) \end{aligned} \tag{9}$$

Approximation of (6) in detail – 2

Therefore, we compute $|B(j|i, k)|$ only when $j = i + s$ and $k = s$ or $s + 1$, since the remaining contribution to $P(j|i)$ is $O((2N)^{-2})$.
By a direct counting we obtain

$$B(i + s|i, s) = \frac{(i + s)!}{2^s} \quad \text{and}$$

$$B(i + s|i, s + 1) = \frac{(i + s)!((i - s - 1)(i + 3s + 2) + 2s(s + 1))}{2^{s+1}}$$

Now the first and the third expressions in (6) are obtained by substituting $B(i + s|i, s)$ and $B(i + s|i, s + 1)$ in (5), and approximating with (10):

$$\frac{N_{[j]}}{N^j} := \frac{N(N-1)\cdots(N-(j-i))}{N^j} = \prod_{k=1}^{j-1} (1 - kN^{-1}) \approx 1 - \binom{j}{2} N^{-1} + O(N^{-2}) \quad . \quad (10)$$

Approximation of (6) in detail – 3

Next, we consider the case when $j = i - s$, where $s > 0$. In this case,

$$\begin{aligned} & \binom{2N}{j} \frac{1}{(2N)^{i-k} \binom{2N}{2}^k} \\ = & \binom{2N}{i-s} \frac{2^k}{(2N)^i (2N-1)^k} \\ = & \frac{2^k}{(i-s)!} \frac{1}{(2N)^s (2N-1)^k} \left(1 - \binom{i-s}{2} (2N)^{-1} + O((2N)^{-2}) \right) \\ = & O((2N)^{-s-k}) \end{aligned} \tag{11}$$

Approximation of (6) in detail – 4

Therefore, we need to compute $|B(j|i, k)|$ only in the case when $j = i - 1$ and $k = 0$ since the contribution from other terms will be $O((2N)^{-2})$. By direct counting, we have

$$B(i - 1|i, 0) = (i - 1)! \binom{i}{2},$$

which, along with (5) and (10), implies the second and the forth expressions in (6).

Finally, the last expression in (6) follows from $0 < j \leq 2i$.

For arbitrary values of i, j, k , we can count $|B(j|i, k)|$ by the following inclusion-exclusion formula, which is useful for exact calculations.

$$|B(j|i, k)| = \sum_{m=0}^j (-1)^m \binom{j}{m} \frac{(j - m)^i (j - m - 1)^k}{2^k}.$$

- Many thanks to:
 - Robert C. Griffiths for looking at the Eqs.
 - Mike Steel for a discussion of problem statement.
 - Alison Ethridge for pointing out a “thought-o” in the slides!
 - Critically endangered birds of New Zealand for inspiration.

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