

Computational Biology

Lecturers:

Tanja Stadler, Carsten Magnus & Tim Vaughan

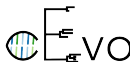
Teaching Assistants:

Jūlija Pečerska, Jérémie Sciré,
Sarah Nadeau & Marc Manceau

Computational Evolution

Department of Biosystems Science and Engineering

HS 2019



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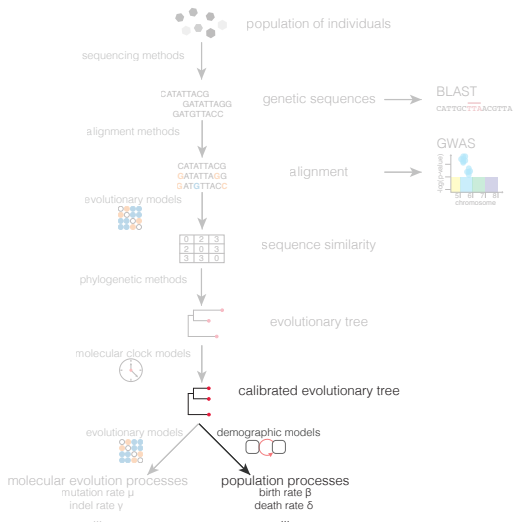
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- ❓ How does the approximate number of steps required to calculate the phylogenetic likelihood depend on the number of leaves in a phylogenetic tree? (I.e. what is the time complexity of this calculation?)
- ❓ What kind of population dynamic process could a decrease in slope in the LTT plot reflect?
- ❓ Assume a birth-death process where each individual at present is sampled with probability ρ . How is the derivation of $p(0|t, \rho)$, the probability of sampling no individual at present, different compared to the derivation of $p(0|t)$?



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- Introduced by [Kingman, 1982] (the Kingman coalescent).

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- ▶ Introduced by [Kingman, 1982] (the Kingman coalescent).
- ▶ Can be derived as a limiting distribution from several population genetic models.

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- ▶ Introduced by [Kingman, 1982] (the Kingman coalescent).
- ▶ Can be derived as a limiting distribution from several population genetic models.
- ▶ Common assumption is that the underlying population dynamics are deterministic.

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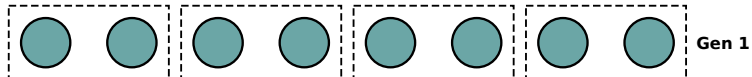
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- ▶ Introduced by [Kingman, 1982] (the Kingman coalescent).
- ▶ Can be derived as a limiting distribution from several population genetic models.
- ▶ Common assumption is that the underlying population dynamics are deterministic.
- ▶ Often used as the basis for phylodynamic inference of population size and dynamics.

The Wright-Fisher process

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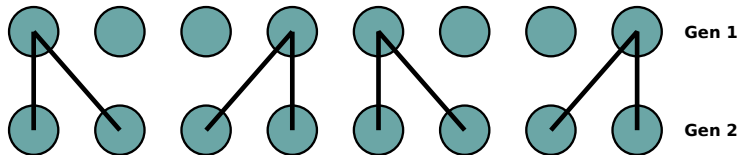
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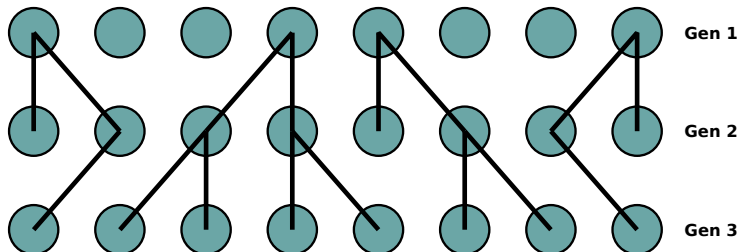
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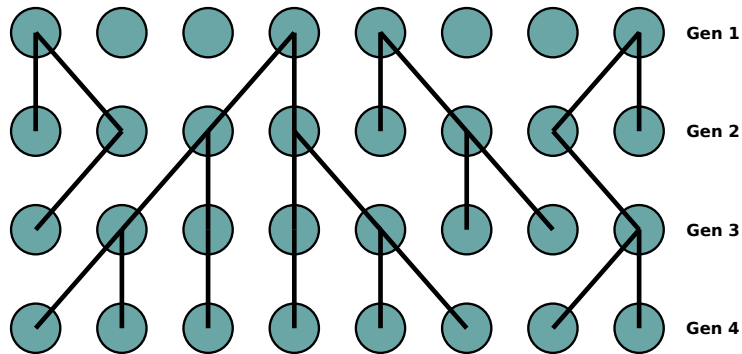
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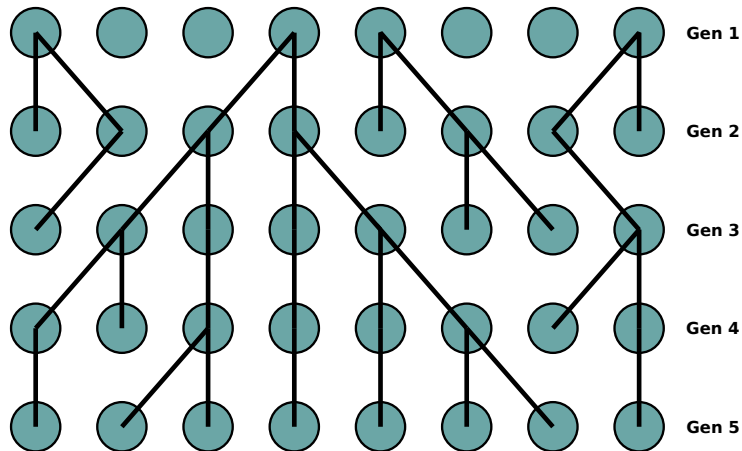
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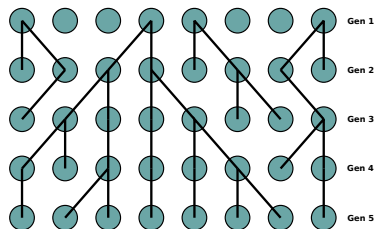
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- Discrete generations.

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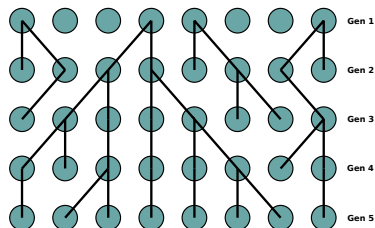
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- Discrete generations.
- Each generation consists of N individuals.

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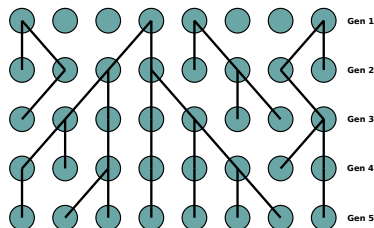
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- Discrete generations.
- Each generation consists of N individuals.
- Each individual in the offspring population chooses its parent uniformly at random from the N parents.

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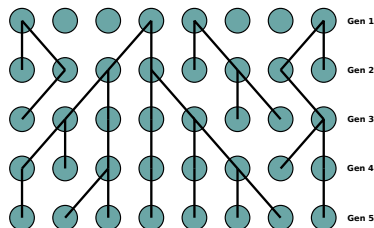
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- ▶ Discrete generations.
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- ▶ Each individual in the offspring population chooses its parent uniformly at random from the N parents.
 - ▶ A given parent has a binomially-distributed number of offspring.

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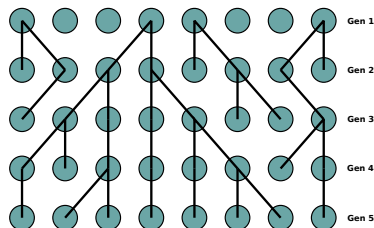
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- ▶ Discrete generations.
- ▶ Each generation consists of N individuals.
- ▶ Each individual in the offspring population chooses its parent uniformly at random from the N parents.
 - ▶ A given parent has a binomially-distributed number of offspring.
- ▶ For phylogenies of a particular gene, ploidy can be taken into account by multiplying N by a factor which accounts for the number of copies of a gene present in each individual.

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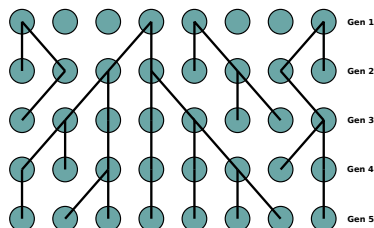
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- ▶ Discrete generations.
- ▶ Each generation consists of N individuals.
- ▶ Each individual in the offspring population chooses its parent uniformly at random from the N parents.
 - ▶ A given parent has a binomially-distributed number of offspring.
- ▶ For phylogenies of a particular gene, ploidy can be taken into account by multiplying N by a factor which accounts for the number of copies of a gene present in each individual.
 - ▶ E.g. for a diploid organism, the number of copies of a gene in the population is $2N$.

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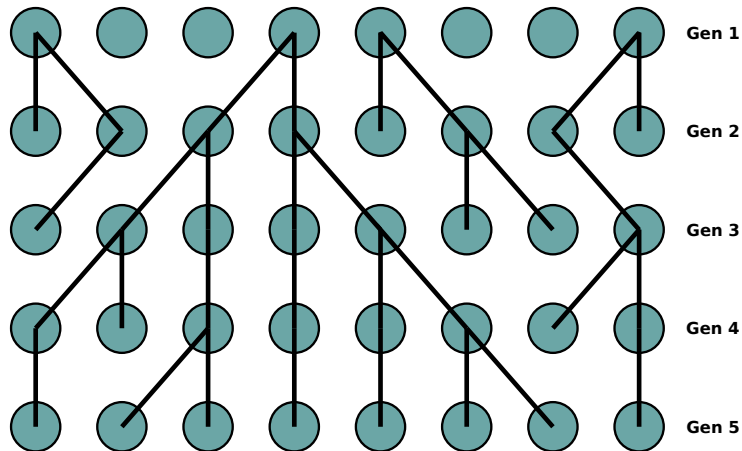
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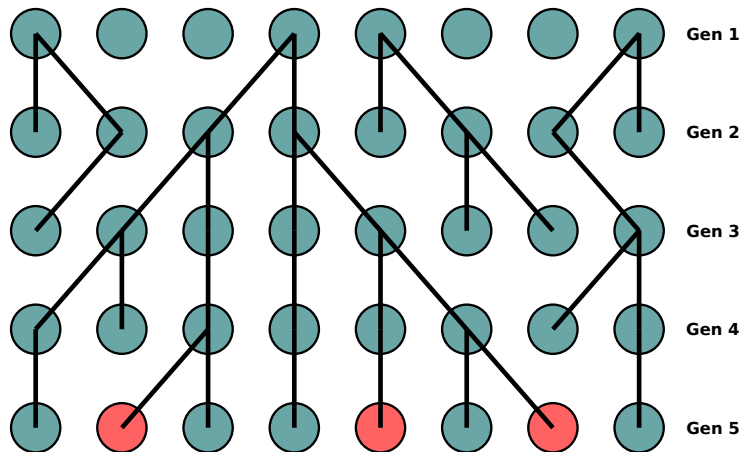
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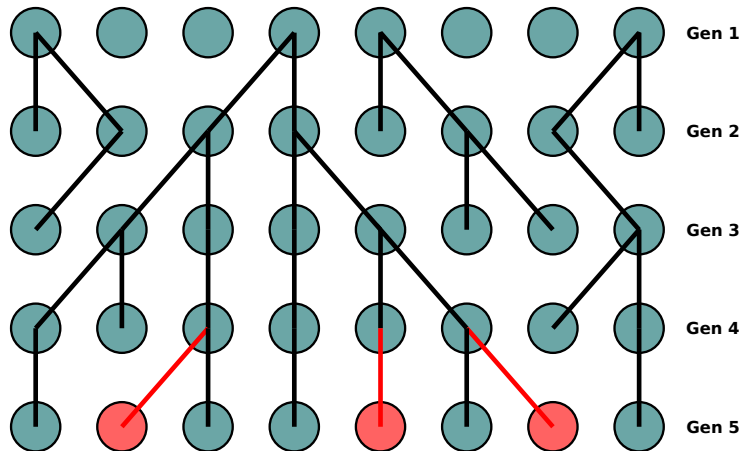
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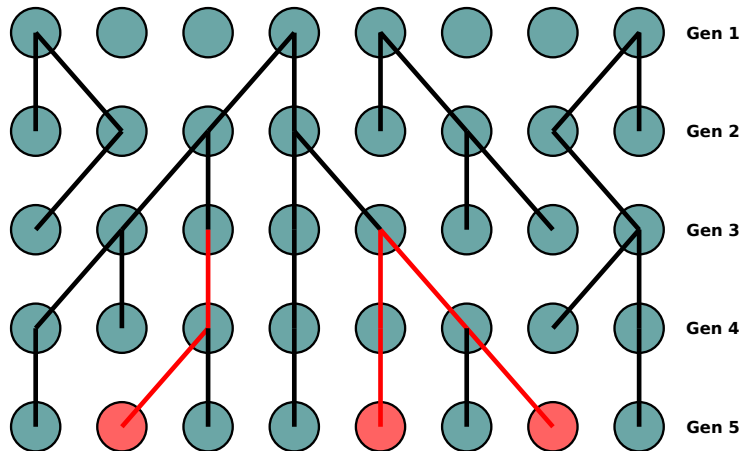
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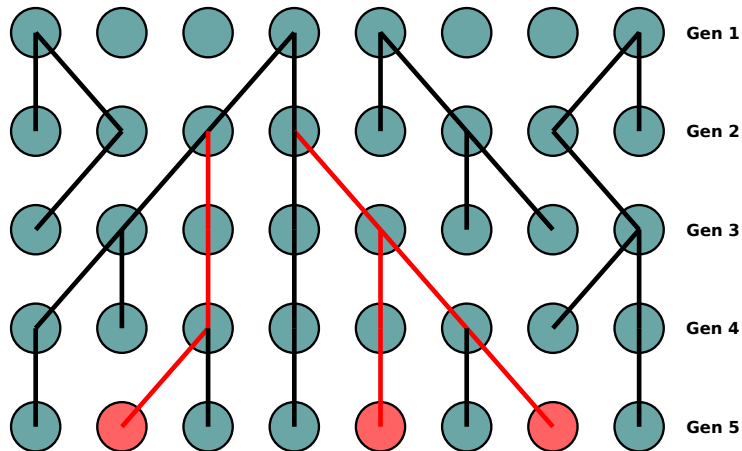
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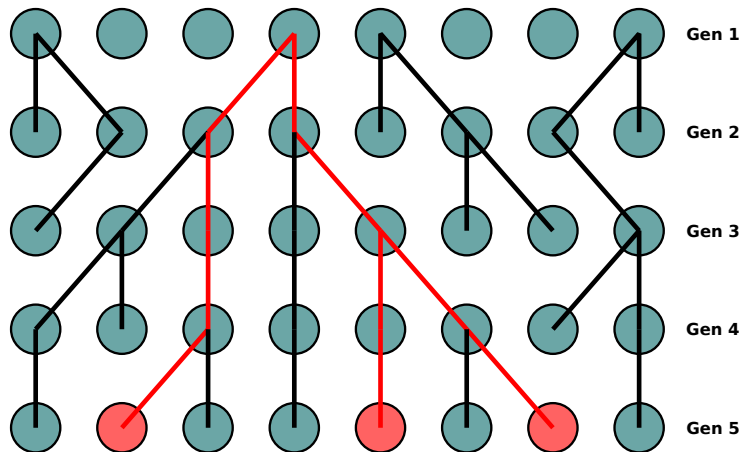
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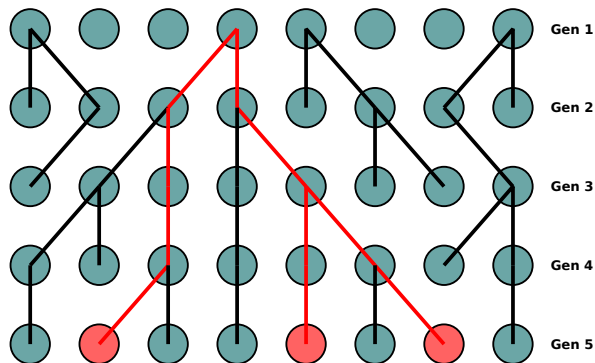
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- Generations between internal nodes related to population size.

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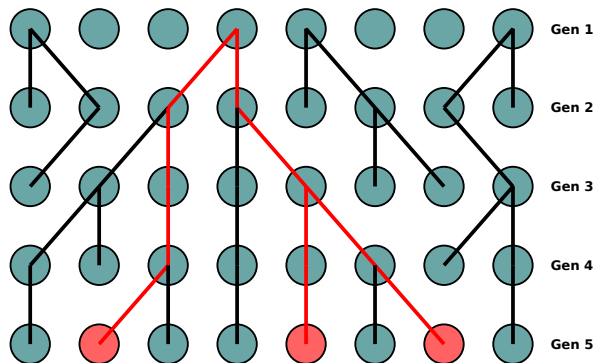
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- Generations between internal nodes related to population size.
- Can we quantify this relationship?

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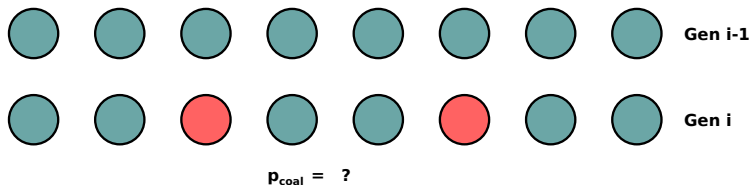
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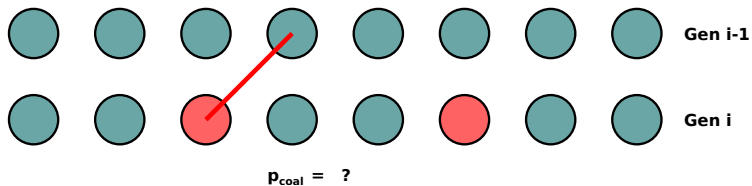
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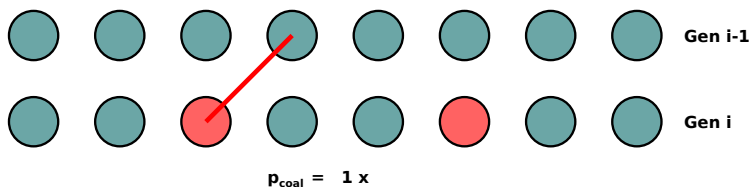
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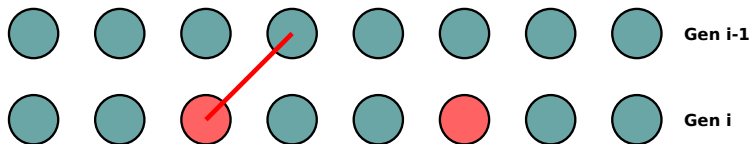
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$$p_{\text{coal}} = 1 \times 1/N$$

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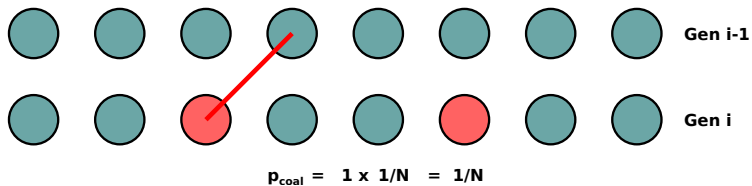
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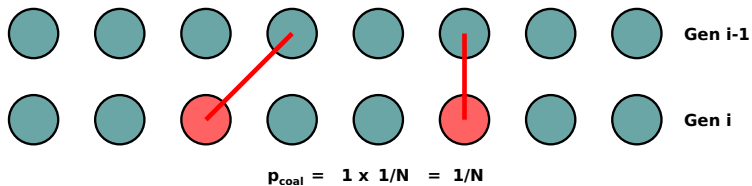
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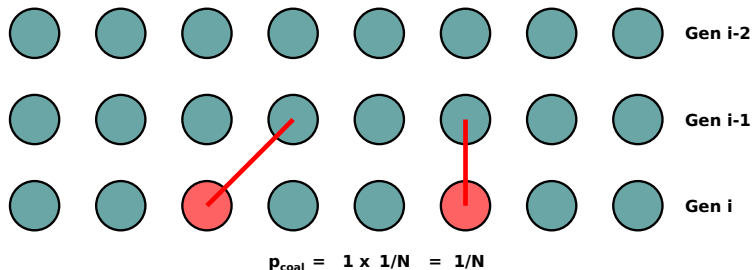
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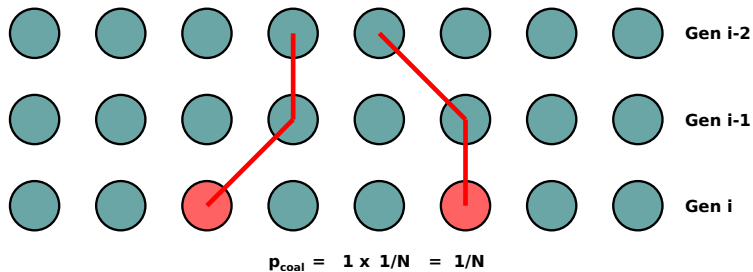
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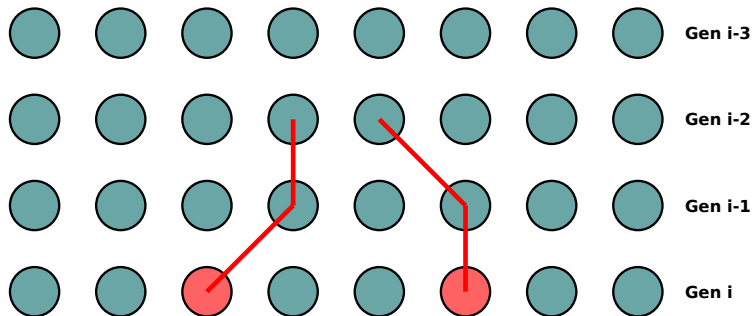
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$$p_{\text{coal}} = 1 \times 1/N = 1/N$$

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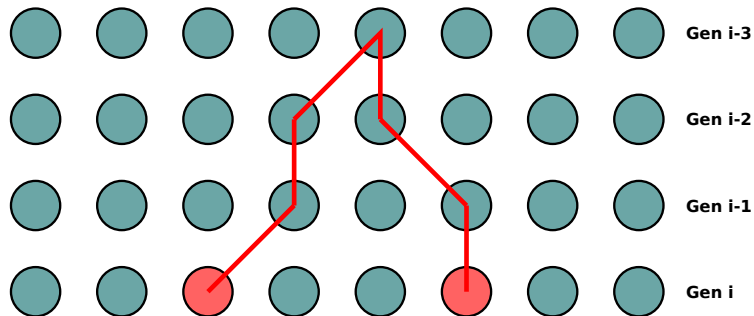
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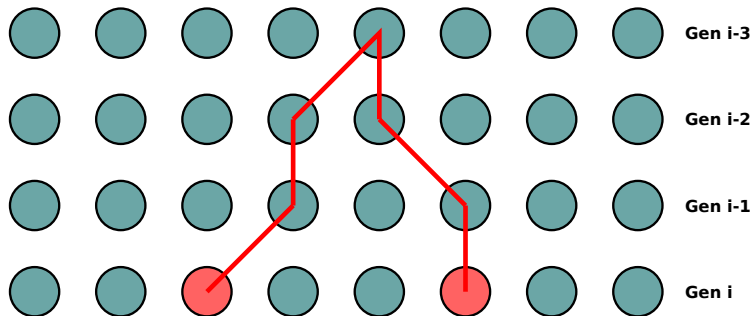
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Sampled 2-individual phylogeny



► Probability of coalescence in generation $i - m$:

$$\begin{aligned}
 P(m) &= (1 - p_{\text{coal}})^{m-1} p_{\text{coal}} \\
 &= \left(1 - \frac{1}{N}\right)^{m-1} \frac{1}{N}
 \end{aligned}$$

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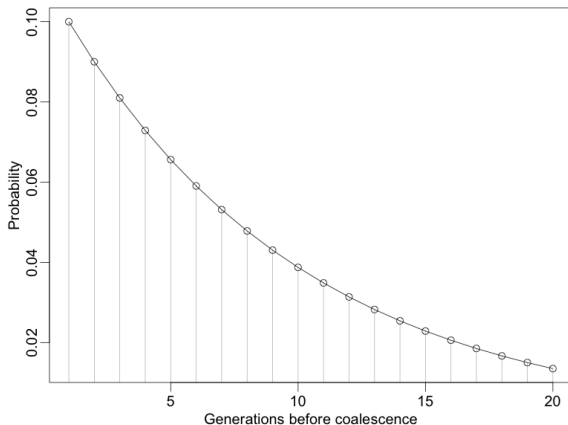
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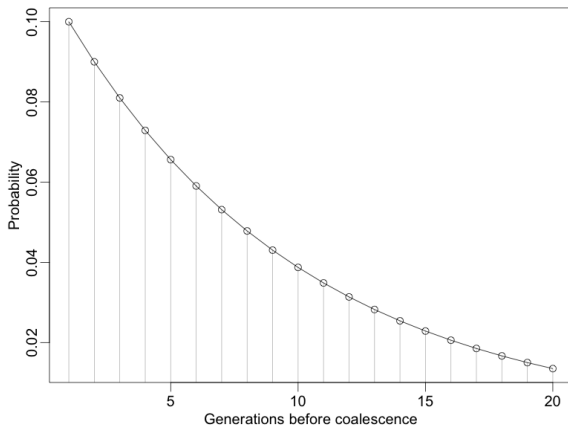
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► $P(m|N) = \left(1 - \frac{1}{N}\right)^{m-1} \frac{1}{N}$

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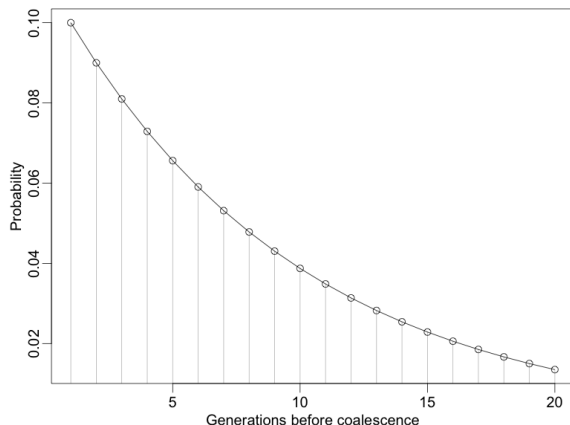
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- $P(m|N) = (1 - \frac{1}{N})^{m-1} \frac{1}{N}$
- For large N , $P(m|N) \rightarrow \exp[-\frac{m-1}{N}] \frac{1}{N}$

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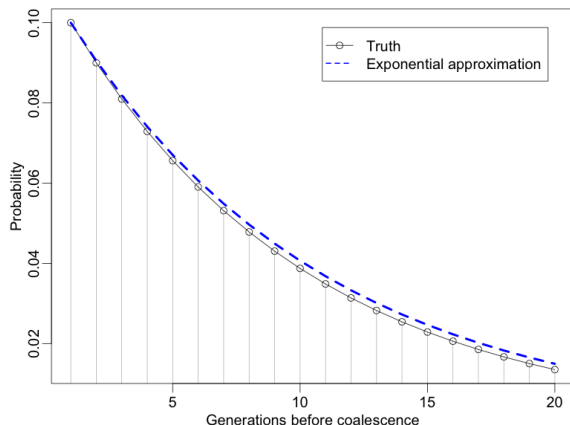
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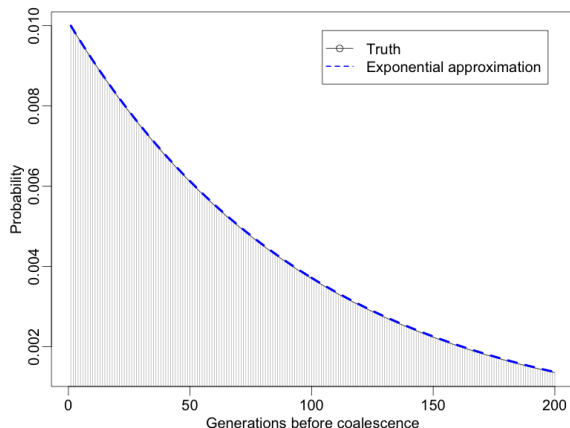
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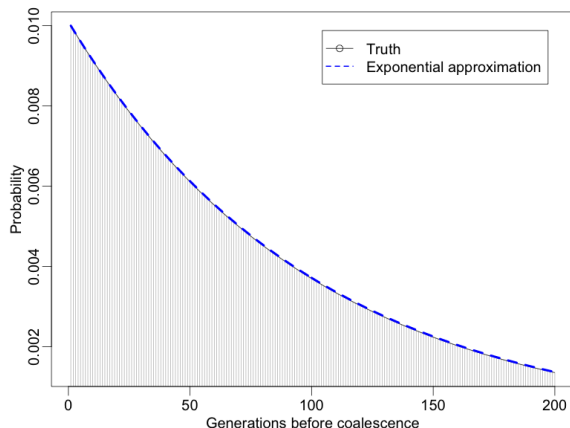
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- ▶ $P(m|N) = (1 - \frac{1}{N})^{m-1} \frac{1}{N}$
- ▶ For large N , $P(m|N) \rightarrow \exp[-\frac{m-1}{N}] \frac{1}{N}$
- ▶ To see why, note that:
 $\exp[-(m-1)/N] = (\exp[-\frac{1}{N}])^{m-1} = (1 - \frac{1}{N} + O(\frac{1}{N^2}))^{m-1}$

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- m is the number of generations. Let g be the calendar time of a generation (e.g. 5 days). Thus $\Delta t = gm$ is the calendar time span of m generations.

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- ▶ m is the number of generations. Let g be the calendar time of a generation (e.g. 5 days). Thus $\Delta t = gm$ is the calendar time span of m generations.
- ▶ In calendar time the probability *density* function for the coalescence time of two lineages is $\frac{1}{gN} e^{-\frac{\Delta t}{gN}}$.

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- ▶ m is the number of generations. Let g be the calendar time of a generation (e.g. 5 days). Thus $\Delta t = gm$ is the calendar time span of m generations.
- ▶ In calendar time the probability *density* function for the coalescence time of two lineages is $\frac{1}{gN} e^{-\frac{\Delta t}{gN}}$.
- ▶ In the large N limit, the time to coalescence is exponentially distributed with mean gN .

Sampled k-individual phylogeny

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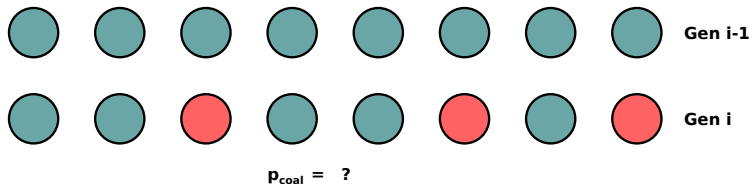
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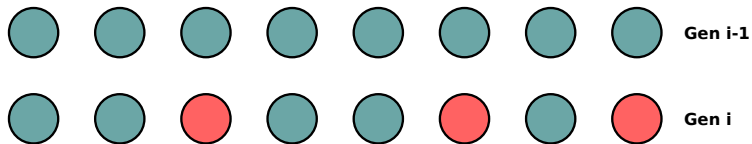
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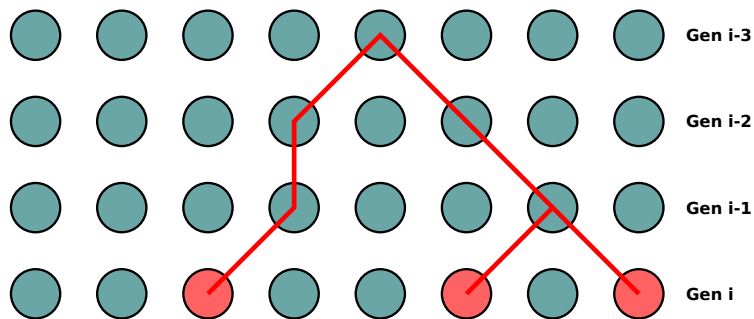
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$$p_{\text{coal}} = 3 \times 1/N \text{ (approx, assumes } N \gg 3 \text{)}$$

Sampled k-individual phylogeny

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$$p_{\text{coal}} = 3 \times 1/N \text{ (approx, assumes } N \gg 3)$$

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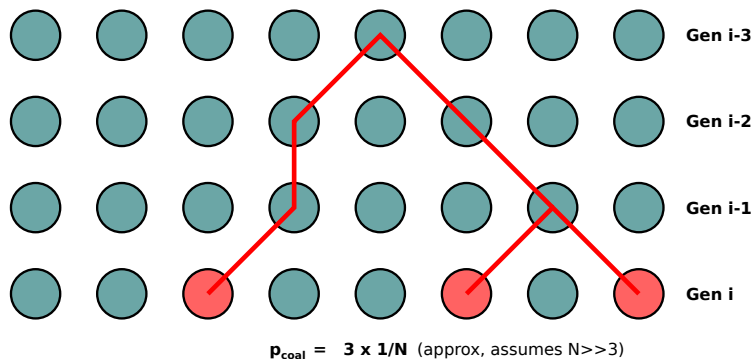
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► **Question** How can this be generalized to k samples?

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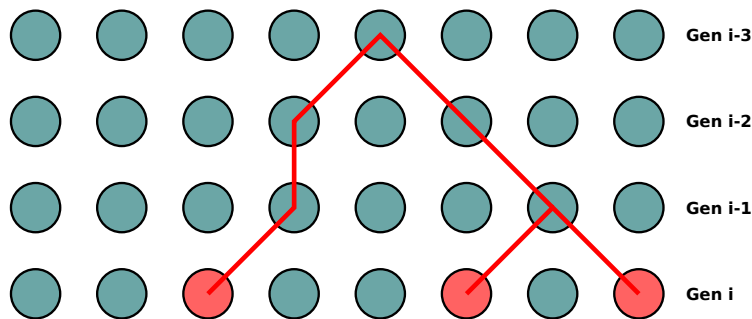
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$$p_{\text{coal}} = 3 \times 1/N \text{ (approx, assumes } N \gg 3)$$

► **Question** How can this be generalized to k samples?

► **Answer** $p_{\text{coal}} \simeq \binom{k}{2} \frac{1}{N}$

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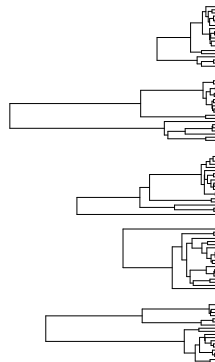
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References

- Developed by John Kingman in a series of papers in 1982.



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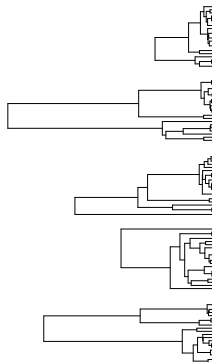
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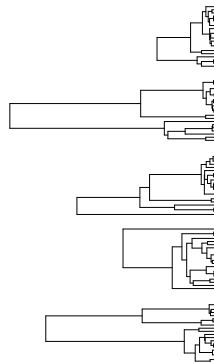
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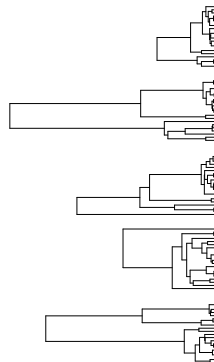
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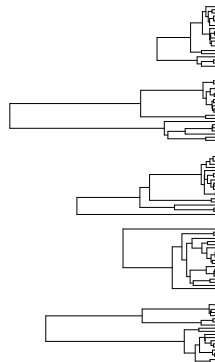
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- ▶ Equivalent to sampled trees produced by WF model when N is much larger than the number of samples.
- ▶ Times between coalescence events are drawn from exponential distributions with rate parameters $\binom{k}{2} \frac{1}{Ng}$, i.e.



$$P(\Delta t | N, g, k) = \exp \left[-\Delta t \binom{k}{2} \frac{1}{Ng} \right] \binom{k}{2} \frac{1}{Ng}.$$

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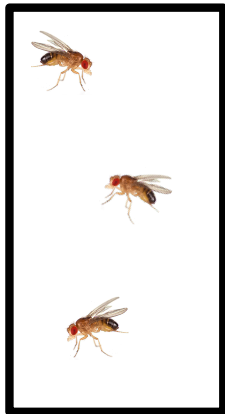
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“Bugs in a Box” analogy

Consider a box full of “hyperactive, indiscriminate, voracious, and insatiable bugs.” [Felsenstein, 2004]



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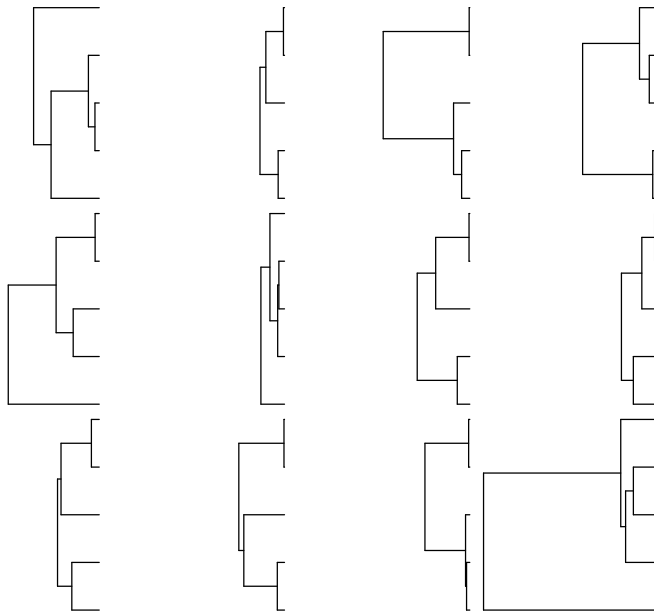
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Simulated coalescent trees (5 leaves, $g = 1$)

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The age of a coalescent tree

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Under the coalescent model, the average time required for n lineages to coalesce into one is

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The age of a coalescent tree

Under the coalescent model, the average time required for n lineages to coalesce into one is

$$E[t_{\text{root}}] = \sum_{k=2}^n \frac{Ng}{\binom{k}{2}} = Ng \sum_{k=2}^n \frac{1}{\binom{k}{2}}.$$

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► Can write $\sum_{k=2}^n \frac{1}{\binom{k}{2}} = \sum_{k=2}^n \frac{2}{k(k-1)}.$

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- ▶ Then $\sum_{k=2}^n \frac{1}{\binom{k}{2}} = \sum_{k=1}^{n-1} \frac{2}{k} - \sum_{k=2}^n \frac{2}{k} = 2(1 - \frac{1}{n}).$

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- ▶ We therefore find that $E[t_{\text{root}}] \rightarrow 2Ng$ as the number of lineages n (i.e. number of leaves in the coalescent tree) becomes large.

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- ▶ We therefore find that $E[t_{\text{root}}] \rightarrow 2Ng$ as the number of lineages n (i.e. number of leaves in the coalescent tree) becomes large.

This is an upper bound on the *expectation*: individual coalescent trees can be older than this.

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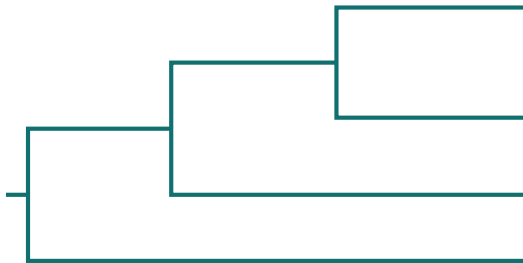
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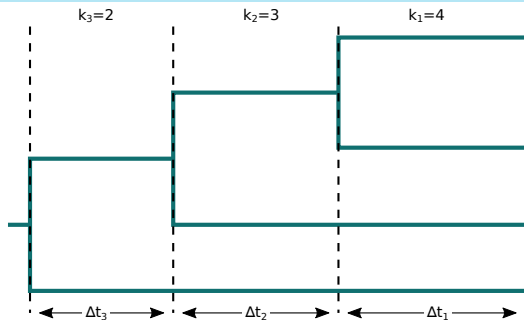
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The probability of a coalescent tree

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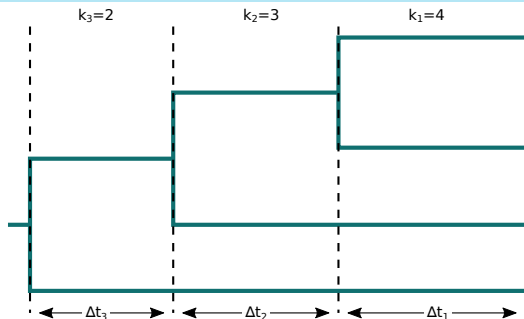
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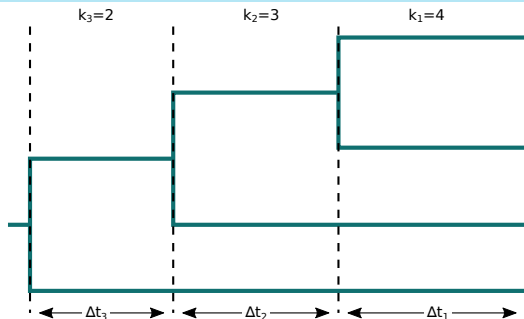
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$$P(\mathcal{T}|Ng) = e^{-\Delta t_1 \binom{4}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_2 \binom{3}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_3 \binom{2}{2} \frac{1}{Ng}} \times \frac{1}{Ng}$$
$$= \prod_{i=1}^{n-1} \left(\exp \left[-\Delta t_i \binom{k_i}{2} \frac{1}{Ng} \right] \frac{1}{Ng} \right)$$

The probability of a coalescent tree



$$P(\mathcal{T}|Ng) = e^{-\Delta t_1 \binom{4}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_2 \binom{3}{2} \frac{1}{Ng}} \times \frac{1}{Ng} \times e^{-\Delta t_3 \binom{2}{2} \frac{1}{Ng}} \times \frac{1}{Ng}$$

$$= \prod_{i=1}^{n-1} \left(\exp \left[-\Delta t_i \binom{k_i}{2} \frac{1}{Ng} \right] \frac{1}{Ng} \right)$$

The exponentials give the probability of nothing happening in interval Δt_i , and the $1/gN$ factors are the probability densities of the particular coalescent events. (Note the units!)

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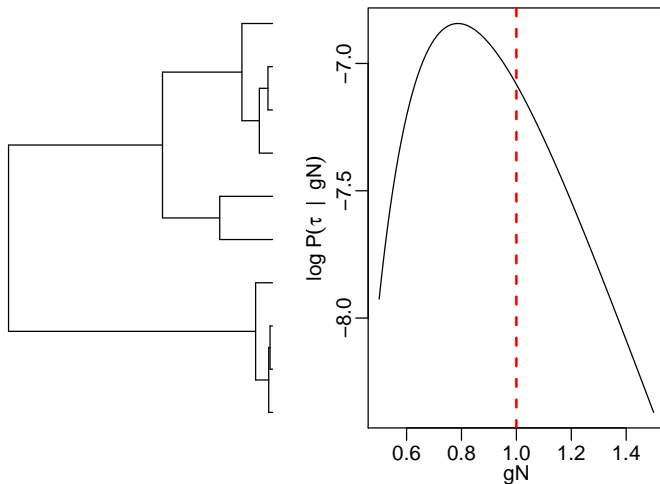
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- For a given coalescent tree \mathcal{T} , $L(gN; \mathcal{T}) = P(\mathcal{T}|gN)$.



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- If we take a real tree (e.g. one inferred from genetic data sampled from a real biological population) and infer the population size using the coalescent distribution, we can expect our result to be biased since the real dynamics differ from the WF dynamics.

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- ▶ If we take a real tree (e.g. one inferred from genetic data sampled from a real biological population) and infer the population size using the coalescent distribution, we can expect our result to be biased since the real dynamics differ from the WF dynamics.
- ▶ One of the important ways that reality differs is that real populations are *structured*, where the WF population is assumed to be completely homogeneous.

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- ▶ In any case, the inferred population size is referred to as the *effective* population size (sometimes written N_e).
- ▶ This is the size of a WF population which shares some statistical similarity with the real population.
- ▶ Care must be taken when drawing conclusions from effective population sizes.

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- The coalescent distribution/process is often derived as a limit of the Wright-Fisher process, as we have done here.

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- ▶ The coalescent distribution/process is often derived as a limit of the Wright-Fisher process, as we have done here.
- ▶ It also appears as the limit of many other population processes, for example

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 - ▶ ...
- ▶ The fact that the coalescent distribution persists in the face of many departures from the WF model is sometimes termed the “robustness of the coalescent”.

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1. Samples are members of a population that is at demographic equilibrium.
 - ▶ Justifies use of fixed or slowly varying population size.

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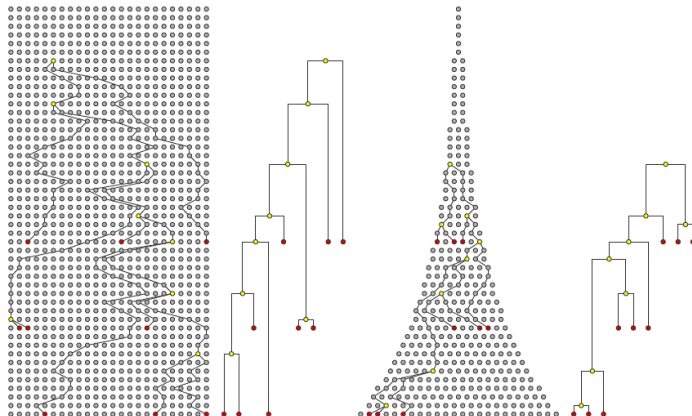
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 - ▶ Justifies use of fixed or slowly varying population size.
2. Number of samples is small compared to the total population size.
 - ▶ Justifies neglect of > 2 lineages coalescing in the same generation.
3. Population is “well mixed”, samples are drawn uniformly at random.
 - ▶ Justifies the coalescent rate between any pair of sampled lineages being equal.
 - ▶ Population structure violates this assumption.

Extension: population size changes

CB



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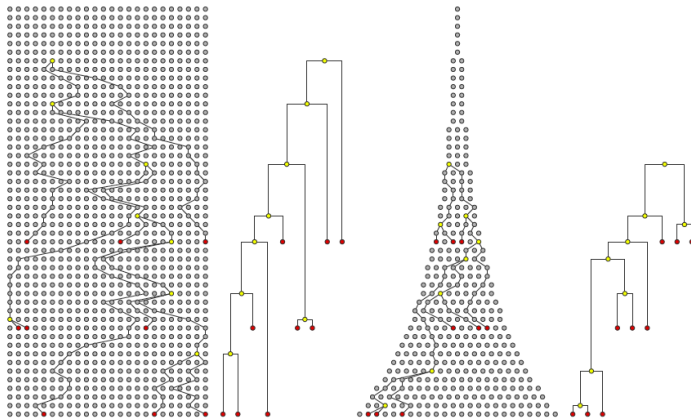
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- $P(\mathcal{T}|N(t))$ is calculated via the rate of coalescence $\frac{1}{N(t)}$ (where $N(t)$ is the population size as a function of time). Where $N(t)$ is large we have a slower coalescence rate and thus longer branches.

- Under a Wright-Fisher model with a deterministically varying population size $N(t)$, the probability of a sampled tree becomes:

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$$P(\mathcal{T}|N(t)) = \prod_{i=1}^{n-1} \left(\exp \left[- \int_{t_i}^{t_{i+1}} \binom{k_i}{2} \frac{dt}{N(t)g} \right] \frac{1}{Ng} \right)$$

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- For a given parametric form, for example $N(t) = N_0 e^{-\gamma t}$, yields $P(\mathcal{T}|N_0, \gamma) = L(N_0, \gamma; \mathcal{T})$ i.e. the likelihood for the demographic model parameters.

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- For a given parametric form, for example $N(t) = N_0 e^{-\gamma t}$, yields $P(\mathcal{T}|N_0, \gamma) = L(N_0, \gamma; \mathcal{T})$ i.e. the likelihood for the demographic model parameters.
- Thus we can directly compare and test different demographic scenarios for a given tree.

The Epidemic Behavior of the Hepatitis C Virus

Oliver G. Pybus,* Michael A. Charleston, Sunetra Gupta,
Andrew Rambaut, Edward C. Holmes, Paul H. Harvey

Hepatitis C virus (HCV) is a leading worldwide cause of liver disease. Here, we use a new model of HCV spread to investigate the epidemic behavior of the virus and to estimate its basic reproductive number from gene sequence data. We find significant differences in epidemic behavior among HCV subtypes and suggest that these differences are largely the result of subtype-specific transmission patterns. Our model builds a bridge between the disciplines of population genetics and mathematical epidemiology by using pathogen gene sequences to infer the population dynamic history of an infectious disease.

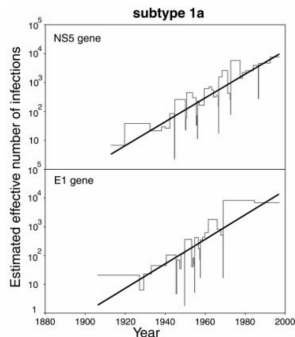


Table 1. Maximum likelihood parameter estimates for each HCV type or subtype. Seq., number of sequences.

| HCV | Gene | Seq. | ML parameter estimates (approximate 95% CIs) | | |
|-----|------|------|--|----------------------|--|
| | | | $N(0)$ | r | c |
| 1a | E1 | 34 | 13726 (6143, 32615) | 0.098 (0.081, 0.114) | ∞ (0.28, ∞) |
| | NS5 | 59 | 9858 (5488, 18430) | 0.095 (0.079, 0.109) | ∞ (0.24, ∞) |
| 1b | E1 | 76 | 46484 (11408, 114430) | 0.079 (0.068, 0.092) | 3.3 (0.12, ∞) |
| | NS5 | 53 | 11800 (3254, 62084) | 0.088 (0.068, 0.117) | 0.44 (0.015, ∞) |
| 4 | E1 | 22 | 1817 (1012, 8797) | 0.026 (0.008, 0.045) | 0.015 (3×10^{-5} , ∞) |
| | NS5 | 18 | 2498 (1328, 5820) | 0.043 (0.022, 0.071) | 6×10^{-5} (4×10^{-9} , 0.037) |
| 6 | E1 | 23 | 1579 (948, 3433) | 0.012 (0.003, 0.029) | 0.028 (2×10^{-6} , ∞) |
| | NS5 | 40 | 2500 (1680, 4532) | 0.008 (0.002, 0.018) | 0.066 (8×10^{-5} , ∞) |

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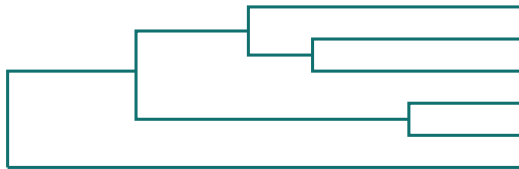
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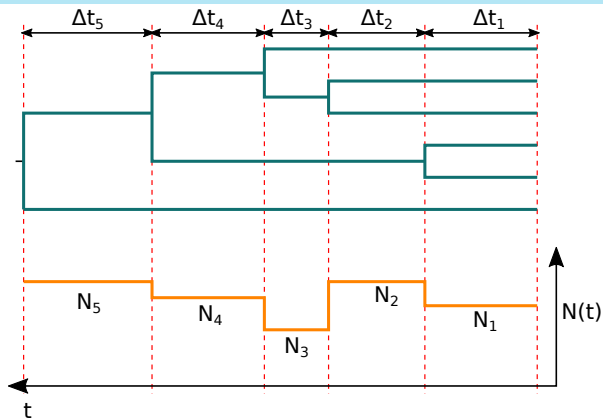
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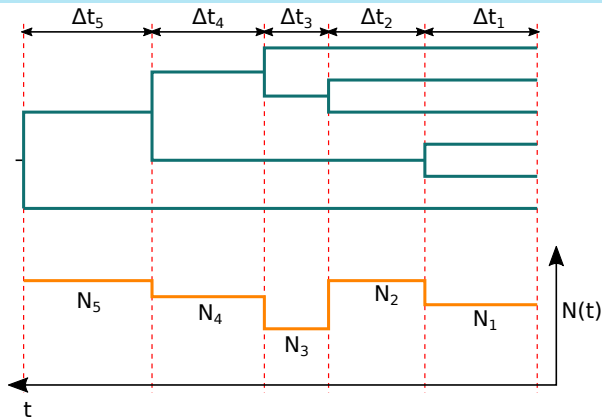
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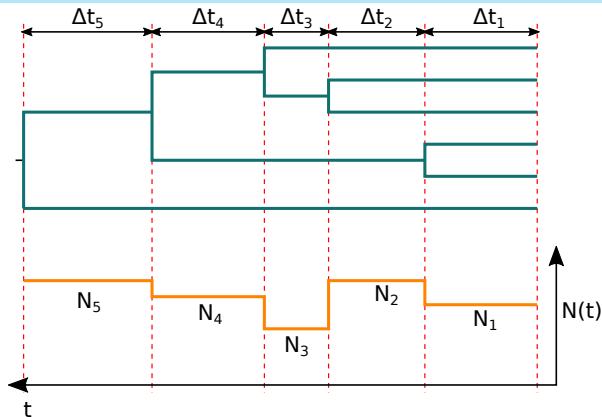
Birth-death vs Coalescent

References

- Assume population has distinct constant values in each interval between coalescent events.

Non-parametric population dynamics inference

CB



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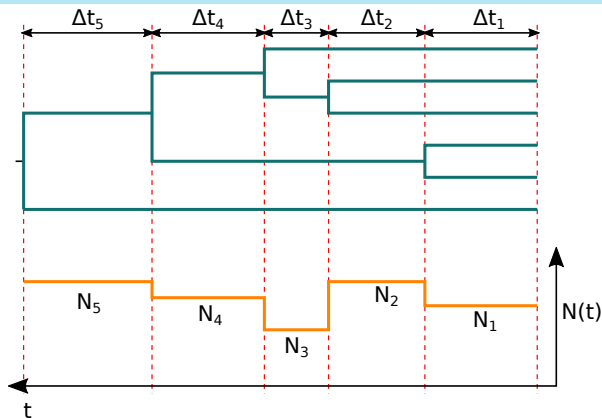
Birth-death vs Coalescent

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- Assume population has distinct constant values in each interval between coalescent events.
- Can obtain a separate ML estimate for each population size.

Non-parametric population dynamics inference

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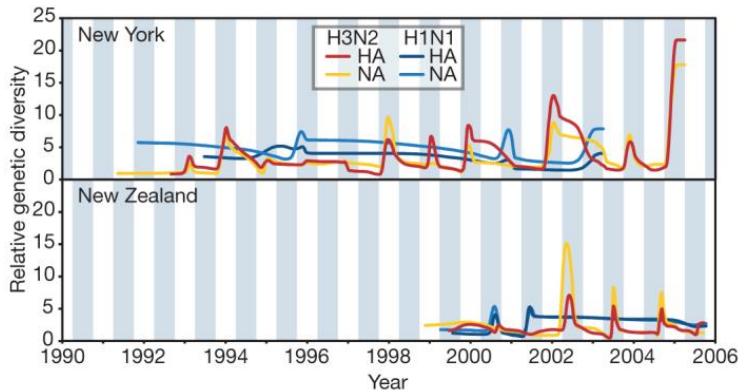
Birth-death vs Coalescent

References

- Assume population has distinct constant values in each interval between coalescent events.
- Can obtain a separate ML estimate for each population size.
- Resulting population function estimate is the “skyline plot” [Pybus et al., 2000].

Example: N_e dynamics for influenza (H3N2)

CB



[Rambaut et al., 2008]

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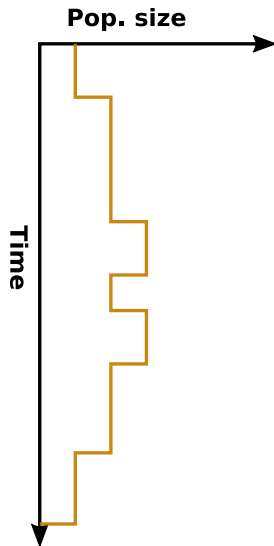
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A connection to birth-death models

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Sampled Tree

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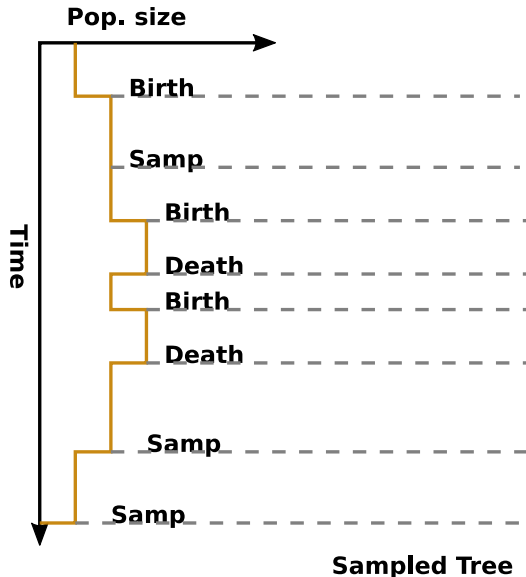
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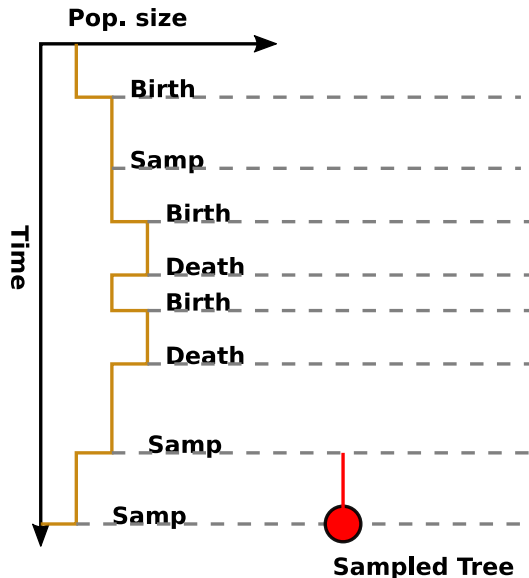
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A connection to birth-death models

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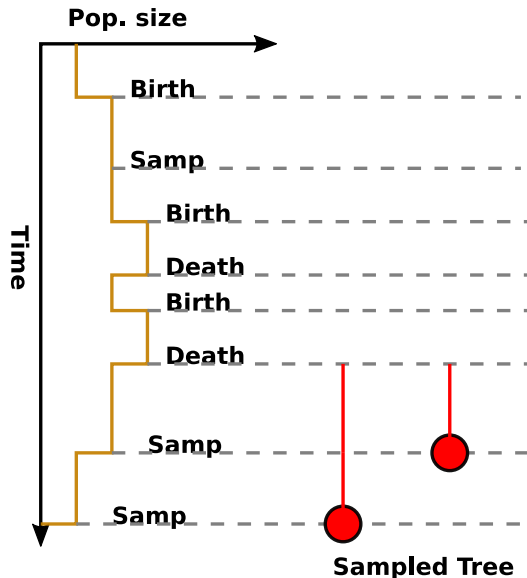
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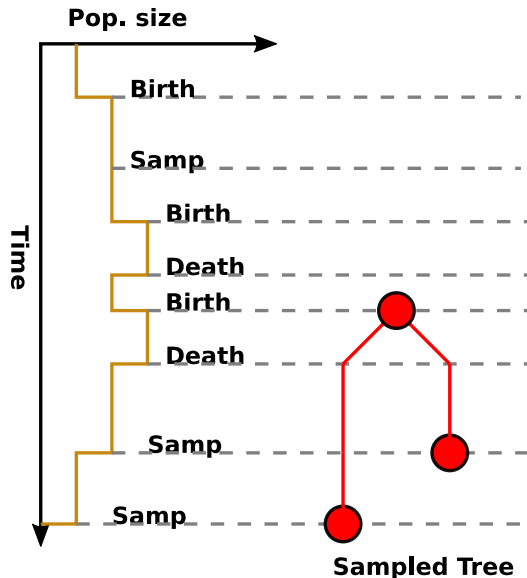
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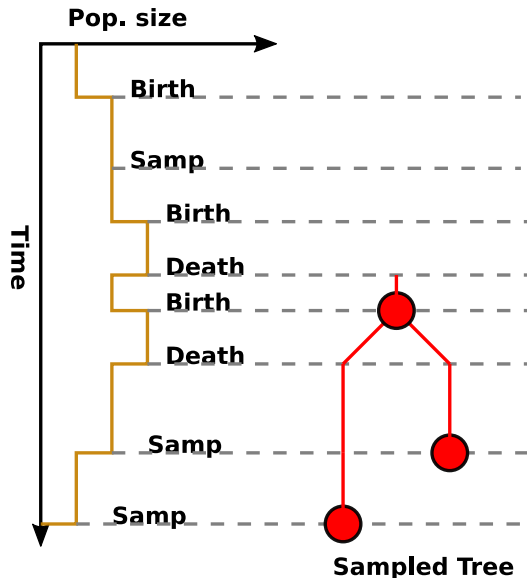
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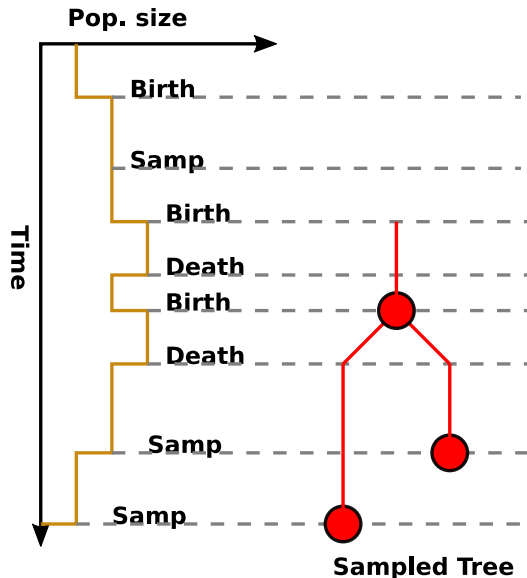
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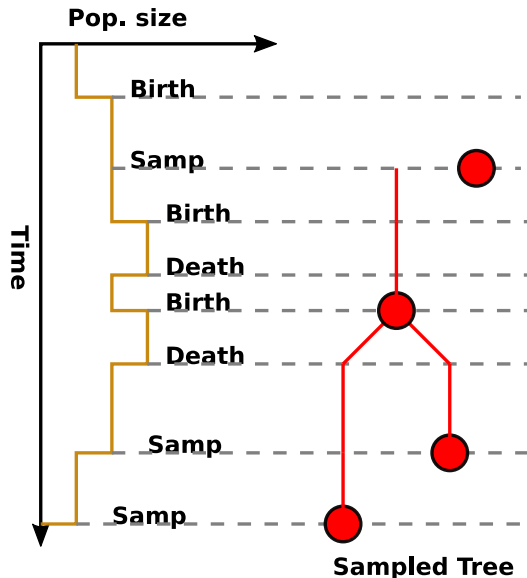
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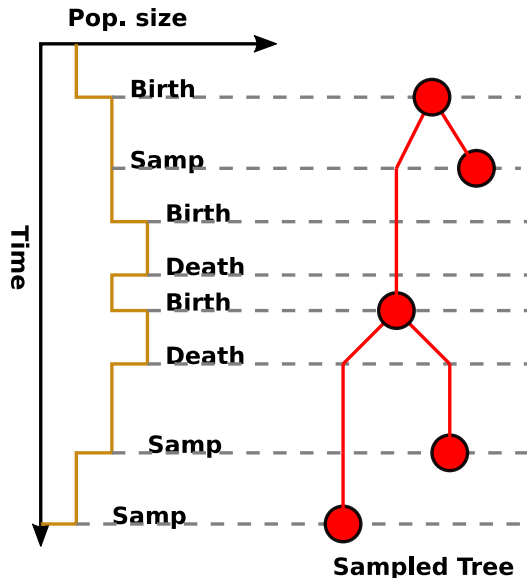
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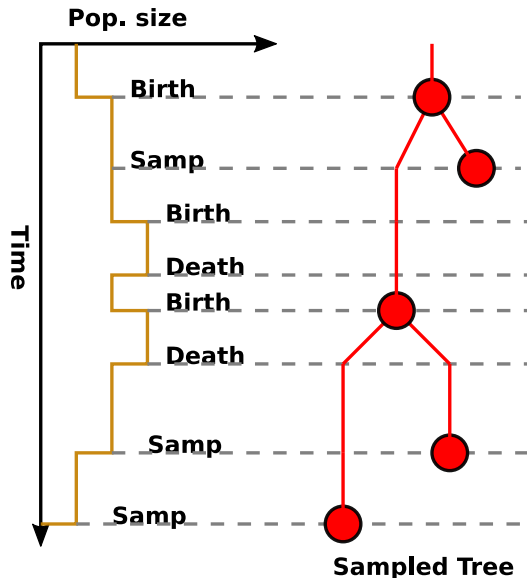
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A connection to birth-death models



Coalescent approximation of birth-death models

- It is possible to develop coalescent distributions that approximate the probability density of sampled phylogenies generated by birth-death processes. [Volz et al., 2009]

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Coalescent approximation of birth-death models

- ▶ It is possible to develop coalescent distributions that approximate the probability density of sampled phylogenies generated by birth-death processes. [Volz et al., 2009]
- ▶ Assume the approximate ODE solution $I(t) = I(T)e^{(\beta-\delta)(T-t)}$ for the linear birth-death process (last lecture) is correct.

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- ▶ Birth events occur at time t with the overall rate of $\beta I(t)$.

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- ▶ Every birth is a potential coalescence between sampled lineages.
- ▶ Probability of choosing a sampled lineage pair is $\binom{k}{2} / \binom{I(t)}{2}$.

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- Every birth is a potential coalescence between sampled lineages.
- Probability of choosing a sampled lineage pair is $\binom{k}{2} / \binom{I(t)}{2}$.
- Approximate coalescence rate is

$$\beta I(t) \frac{k(k-1)}{I(t)(I(t)-1)} \simeq \binom{k}{2} \frac{2\beta}{I(t)}$$

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- ▶ Approximate coalescence rate is

$$\beta I(t) \frac{k(k-1)}{I(t)(I(t)-1)} \simeq \binom{k}{2} \frac{2\beta}{I(t)}$$

- ▶ One can use this coalescence rate to compute an approximation to $P(\mathcal{T}|\beta, \delta, T)$.

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Coalescent approximation of birth-death models

- Quality of approximation depends heavily on how well birth-death population dynamics are approximated by deterministic ODE solution.

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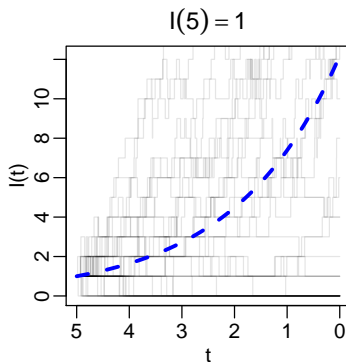
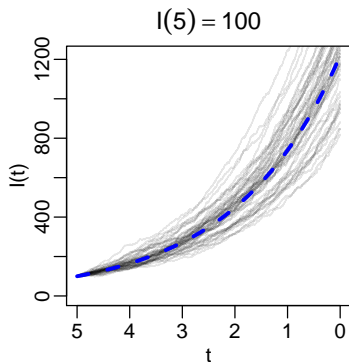
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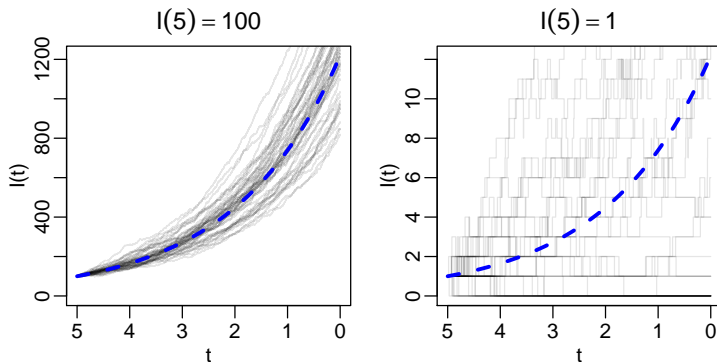
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Coalescent approximation of birth-death models

- Quality of approximation depends heavily on how well birth-death population dynamics are approximated by deterministic ODE solution.



- This approximation can perform very poorly when population size is small, *as it always is at the start of an epidemic.*

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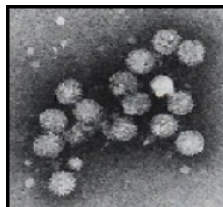
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Hepatitis C (HCV)

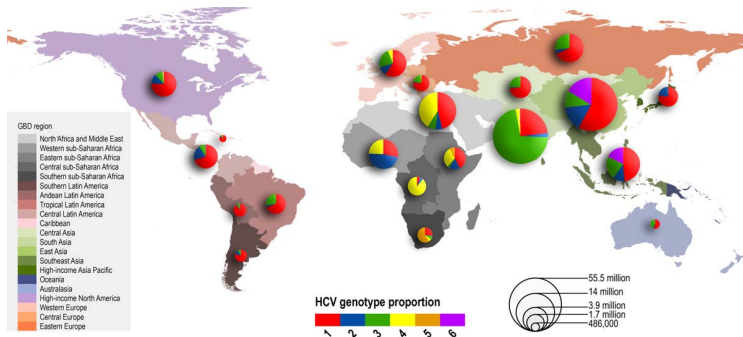
- ▶ Identified in 1989
- ▶ 9.6kb single-stranded RNA genome
- ▶ Tissue culture system only recently developed



Prevalence of HCV world wide

CB

> 185 million people infected worldwide



- ▶ ~80% infections are chronic
- ▶ Liver cirrhosis and cancer risk
- ▶ No protective immunity?

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By percutaneous exposure to infected blood

- ▶ Blood transfusion / blood products
- ▶ Sexual transmission
- ▶ Vertical transmission (mother - child)
- ▶ Injections with contaminated needles



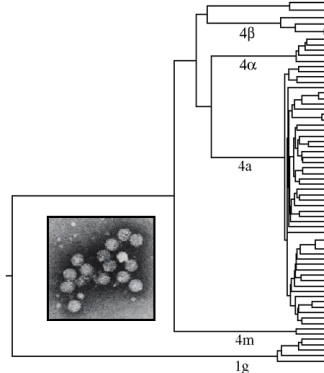
Inference of HCV spread in Egypt

CB

Egyptian HCV gene sequences

n=61

E1 gene, 411bp



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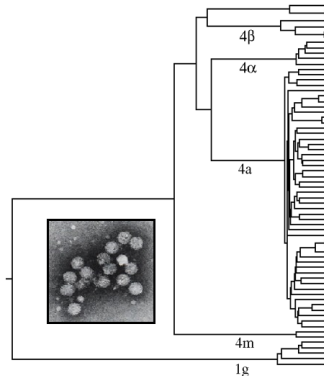
CB

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- All sequences are contemporaneous, i.e. sampled at the same time



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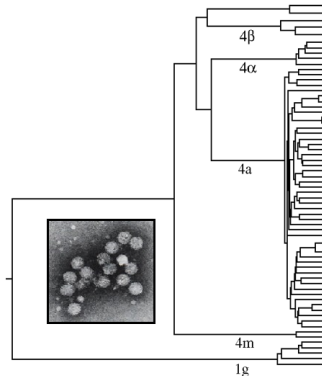
CB

Egyptian HCV gene sequences

n=61

E1 gene, 411bp

- ▶ All sequences are contemporaneous, i.e. sampled at the same time
- ▶ Egypt has the highest prevalence of HCV worldwide (10-20%)



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Inference of HCV spread in Egypt

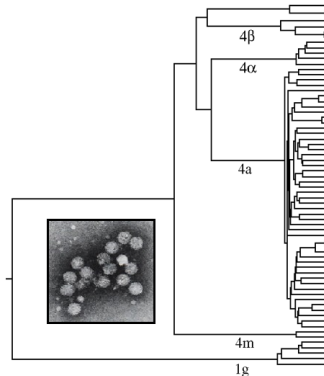
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Egyptian HCV gene sequences

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- ▶ All sequences are contemporaneous, i.e. sampled at the same time
- ▶ Egypt has the highest prevalence of HCV worldwide (10-20%)
- ▶ But low prevalence in neighbouring states



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Inference of HCV spread in Egypt

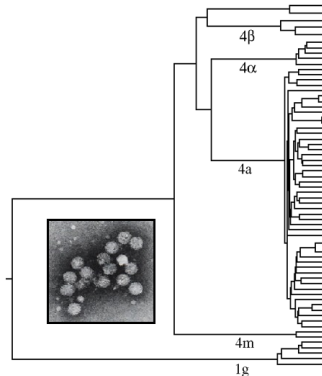
CB

Egyptian HCV gene sequences

n=61

E1 gene, 411bp

- ▶ All sequences are contemporaneous, i.e. sampled at the same time
- ▶ Egypt has the highest prevalence of HCV worldwide (10-20%)
- ▶ But low prevalence in neighbouring states
- ▶ Why is Egypt so seriously affected?



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Infected population size $N(t)$ of HCV in Egypt

CB

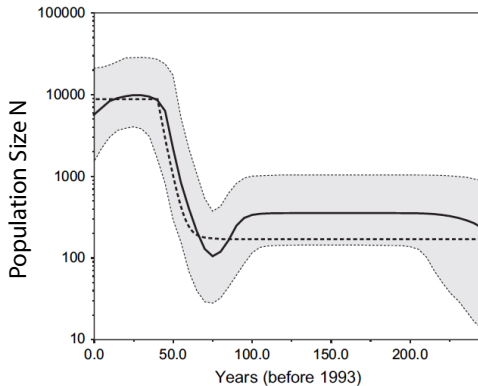


Figure adapted from [Drummond et al., 2005]

Peak in epidemic spread in first half of 20th century based on the coalescent.

[The estimates are Bayesian estimates (rather than Maximum Likelihood), which I will explain next week!]

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$R(t) = \beta(t)/\delta(t)$ of HCV in Egypt

CB

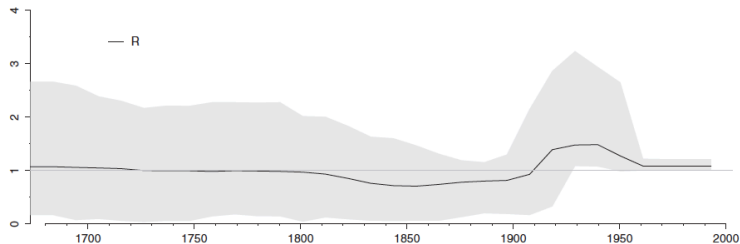


Figure adapted from [Stadler et al., 2013]

Peak in epidemic spread in first half of 20th century based on the birth-death model.

[The estimates are Bayesian estimates (rather than Maximum Likelihood), which I will explain next week!]

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What caused this peak in infections around 70 years ago?

- ▶ In first half of the 20th century schistosomal (worm) infections were treated with injection therapy.
- ▶ Needles were frequently reused and thus possibly contaminated.
- ▶ In the 1970s, antischistosomal injection therapy was gradually replaced by oral therapy.
- ▶ The use of antischistosomal injections with potentially contaminated needles coincides with the time period of HCV spread, and is thought to explain the high prevalence of HCV in Egypt.

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How do I choose?

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How do I choose?

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- Parameters: transmission rates, removal rates, sampling rates/proportions.

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How do I choose?

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- Parameters: transmission rates, removal rates, sampling rates/proportions.

Coalescent

- Parameters: effective population size (NOT actual population size).

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How do I choose?

Birth-death

- Parameters: transmission rates, removal rates, sampling rates/proportions.
- Models sampling process (sample times/locations are data).

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- Parameters: effective population size (NOT actual population size).

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Birth-death

- Parameters: transmission rates, removal rates, sampling rates/proportions.
- Models sampling process (sample times/locations are data).

Coalescent

- Parameters: effective population size (NOT actual population size).
- Assumes number of sampled lineages are small ($k \ll N$).

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Advantages

Disadvantages

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Advantages

- Accounts for stochastic variability in population dynamics.

Disadvantages

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Advantages

- ▶ Accounts for stochastic variability in population dynamics.
- ▶ Generally easier interpretation of parameters.

Disadvantages

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- ▶ Accounts for stochastic variability in population dynamics.
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- ▶ Sensitive to unmodeled changes in sampling fractions.

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Advantages

- ▶ Accounts for stochastic variability in population dynamics.
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Disadvantages

- ▶ Sensitive to unmodeled changes in sampling fractions.
- ▶ Difficult (currently!) to extend to complex population models.

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Advantages

- Generally fast likelihood calculations.

Disadvantages

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Advantages

- ▶ Generally fast likelihood calculations.
- ▶ Easy to extend to complex population dynamics (see [Volz, 2012]).

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- ▶ Generally fast likelihood calculations.
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- ▶ Generally fast likelihood calculations.
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Disadvantages

- ▶ Sensitive to uncertainty in population dynamics at high sampling ([Boskova et al., 2014], Masters thesis in our group).

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- ▶ Sensitive to uncertainty in population dynamics at high sampling ([Boskova et al., 2014], Masters thesis in our group).
- ▶ Sensitive to hidden population structure and nonrandom sampling.

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- Both birth-death and coalescent models probabilistically relate a population's demography to its phylogenetic history.

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- ▶ Both birth-death and coalescent models probabilistically relate a population's demography to its phylogenetic history.
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- ▶ Both birth-death and coalescent models probabilistically relate a population's demography to its phylogenetic history.
- ▶ Both allow for model-based inference of demographic and epidemiological parameters, but may differ in their parameterization.
- ▶ Which model to use depends on which assumptions you are willing to make and what you want to infer.

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- ❓ Under the Wright-Fisher model, how many generations do we have to go back before we find the common ancestor of a pair of genes sampled from a haploid population of size N ?
- ❓ Suppose you had a tree inferred using present-day samples from a population that experienced a severe bottleneck in its recent past. How and why would this bottleneck likely affect our ability to infer ancestral population dynamics?
- ❓ Imagine spreading a Wright-Fisher population across islands in an archipelago, so that movement between the islands is restricted but within each island the population is “well-mixed”. Qualitatively, how would you expect this population structure to influence estimates of the effective population size?

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References