Computing likelihoods under Λ-coalescents

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Joint project with Jochen Blath and Matthias Steinrücken, TU Berlin

Probabilistic Models of Evolutionary Biology
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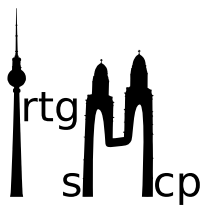

Outline

- Introduction
- Beta$(2-\alpha, \alpha)$-coalescents
- Mutation models: Infinitely-many-alleles, infinitely-many-sites
- Computing likelihoods under (Λ-)coalescents
- Importance sampling methods
- Summary & Outlook

Genetic variability at the mitochondrial cyt *b* locus in Atlantic cod

	468	481	487	488	490	496	508	523	562	601	631	643	649	685	691
66	t	a	a	c	a	a	t	g	a	t	g	a	c	c	g
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(a random subsample of the sample described in Árnason, *Genetics* 2004)

The Great Obsession of population geneticists (J. Gillespie)

What evolutionary forces could have lead to such divergence between individuals of the same species?

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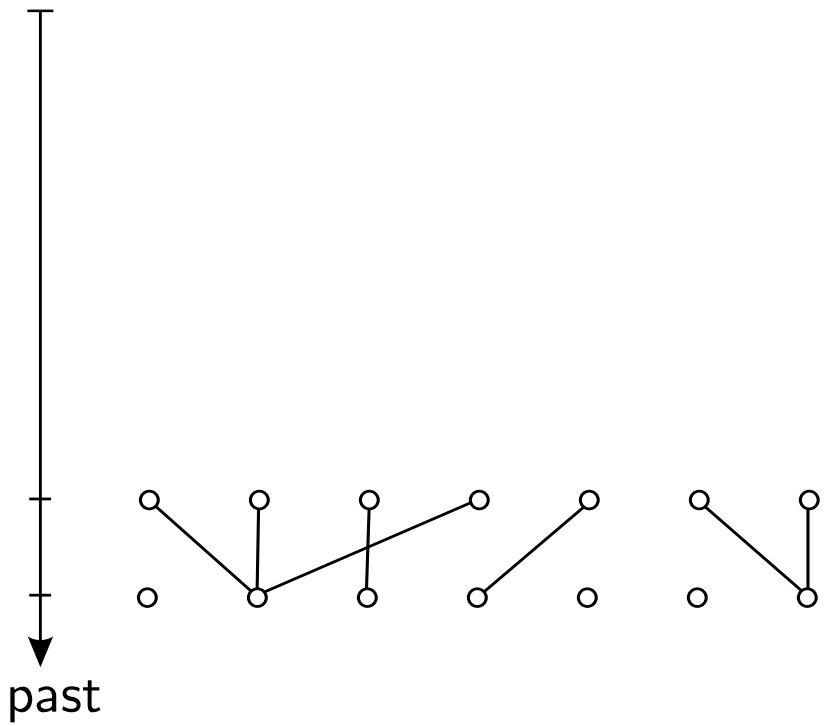
In this talk, we will focus on *neutral* genetic variation, and thus the interplay of *mutation* and *genetic drift*.

Wright-Fisher model: The fundamental model for 'genetic drift'

- A (haploid) population of N individuals per generation,
- each individual in the present generation picks a 'parent' at random from the previous generation,
- genetic types are inherited (possibly with a small probability of mutation).



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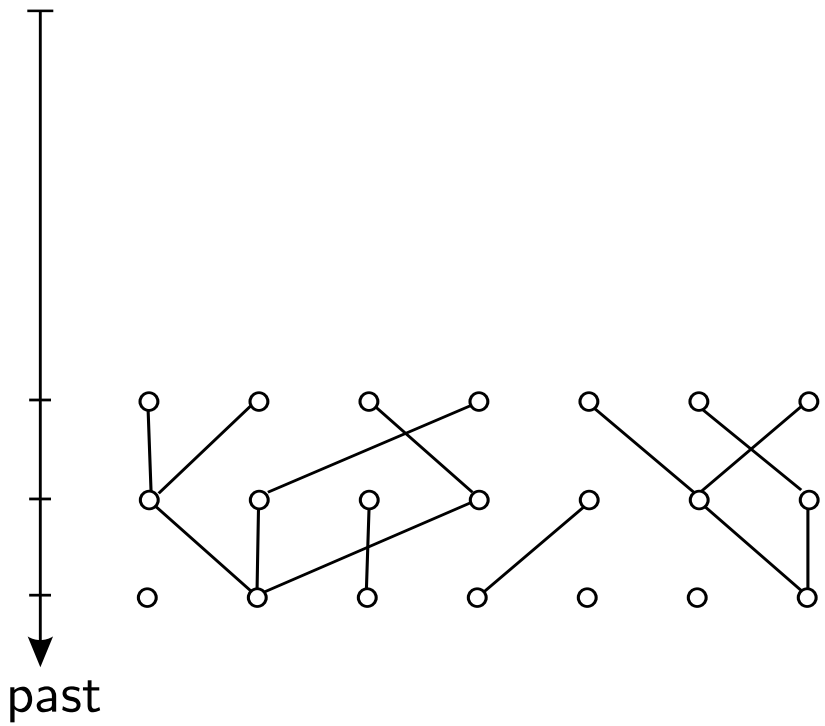

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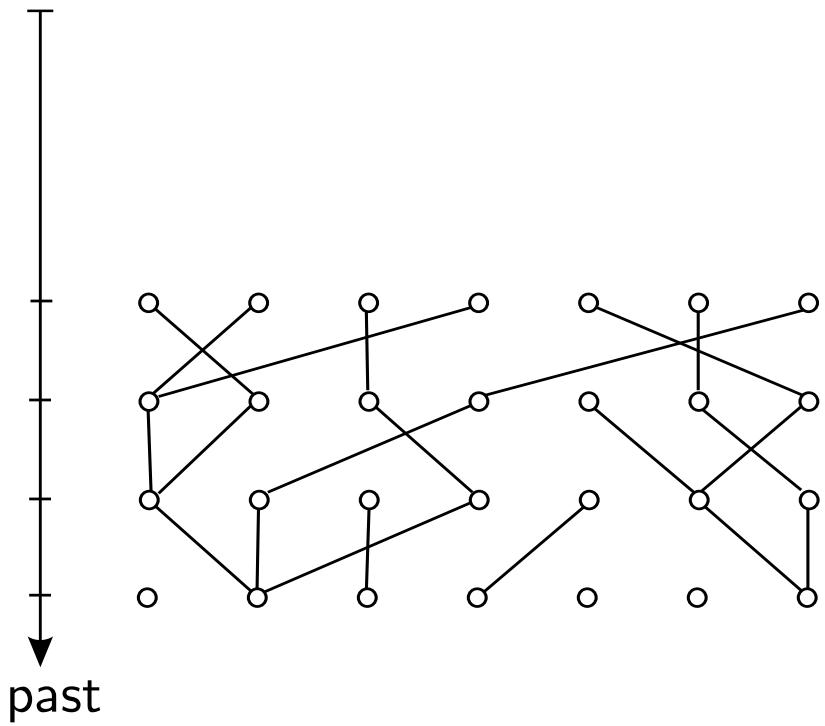

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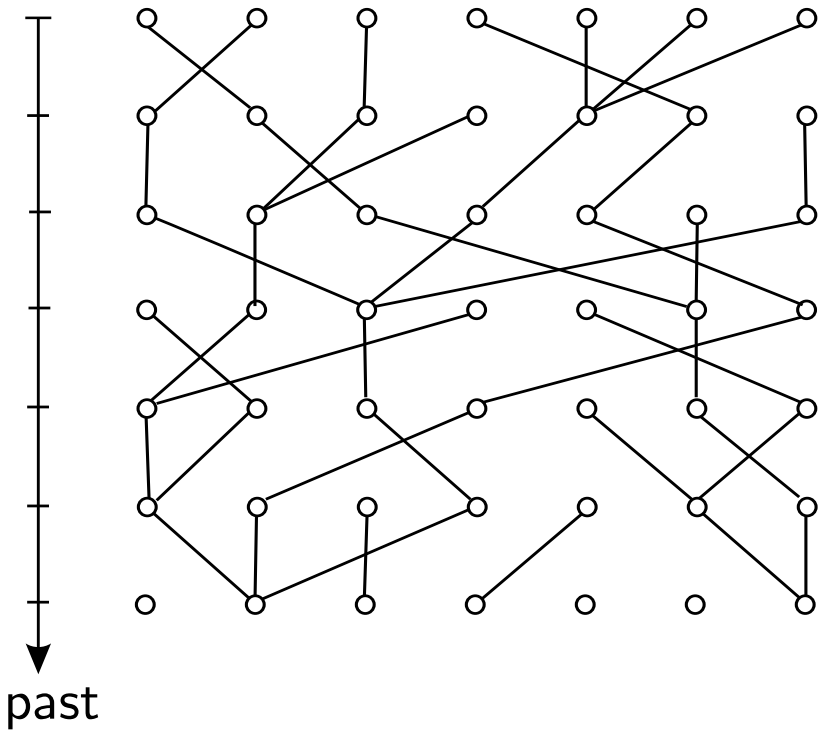
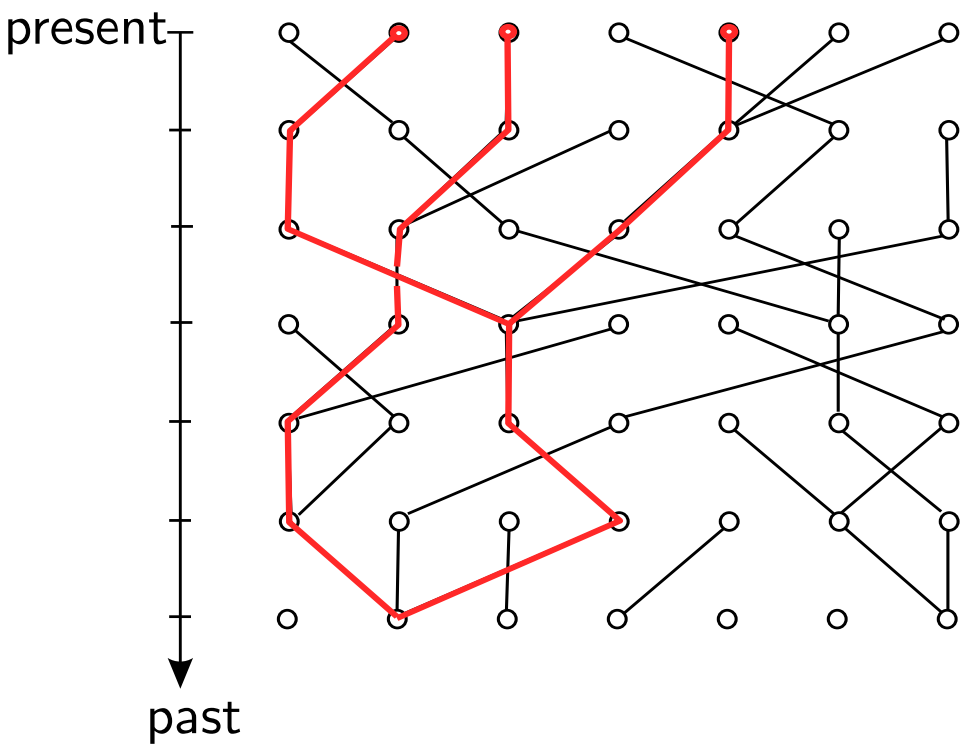


Genealogical point of view

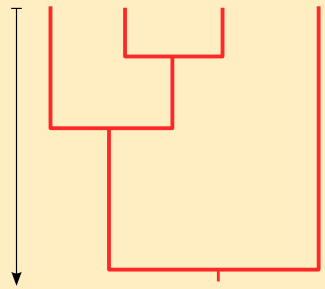
Sample $n\,(\ll N)$ individuals from the 'present generation'



Kingman's coalescent

Theorem (Kingman (& Hudson, Griffiths), 1982)

In the limit $N \to \infty$, the genealogy of an n-sample, measured in units of N generations, is described by a continuous-time Markov chain where each pair of lineages merges at rate 1.



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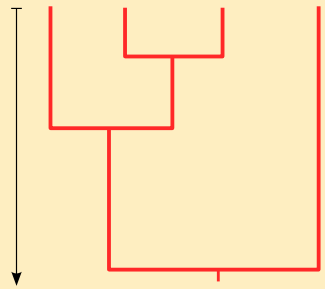
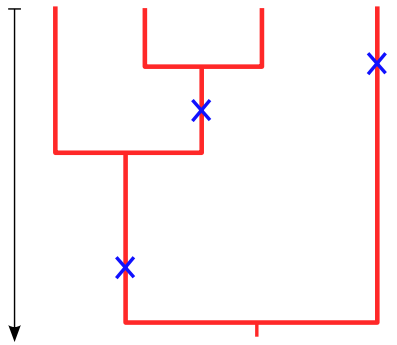


Robustness. The same limit appears for any *exchangeable* offspring vectors

$$(\nu_1, \ldots, \nu_N), \qquad \text{(independent over generations)},$$

if time is measured in units of $\dfrac{N}{\sigma^2}$ generations, where $\sigma^2 = \lim\limits_{N\to\infty} \mathrm{Var}(\nu_1)$ (under a third moment condition on ν_1).

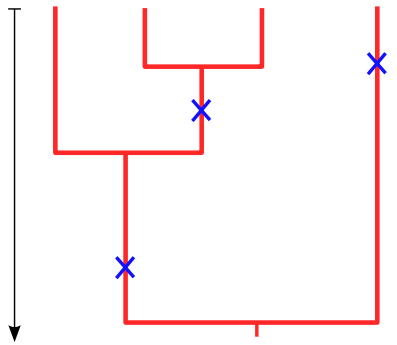
Modeling neutral variation: Superimposing types on the coalescent



Assume that the considered genetic types
do not affect their bearer's reproductive succes.

If as population size $N \to \infty$,
$\frac{N}{\sigma^2} \times$ mutation prob. per ind. per generation $\to r$,
the type configuration in the sample can be described by putting mutations with rate r along the genealogy.

Modeling neutral variation: Superimposing types on the coalescent



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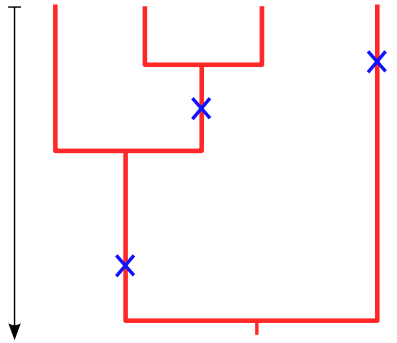
Kingman's coalescent is the *standard model* of mathematical population genetics.

Modeling neutral variation: infinitely-many-alleles model

If mutations always generate a *completely new type*, information in n-sample is equivalent to allelic partition

$$(a_1, a_2, \ldots, a_n)$$



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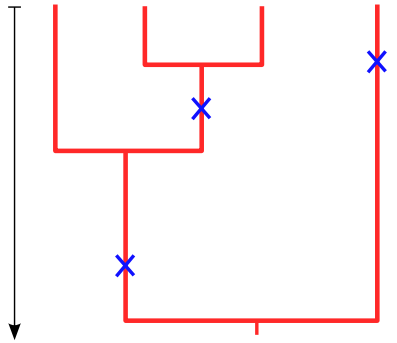

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Then (Ewens' sampling formula, 1972)

$$p_r\big((a_1, a_2, \ldots, a_n)\big) = \frac{n!}{2r(2r+1)\cdots(2r+n-1)} \prod_{j=1} \frac{(2r/j)^{a_j}}{a_j!}.$$

Question

What if the variability of surviving offspring numbers across individuals is so large that reasonably

$$\text{individual offspring variance } \sigma^2 \approx \infty \text{ ?}$$

This might happen e.g. in marine species (so-called *reproduction sweepstakes*).

Coalescents with multiple collisions, aka 'Λ-coalescents'

While n lineages, any k coalesce at rate $\lambda_{n,k} = \int_{[0,1]} x^{k-2}(1-x)^{n-k}\,\Lambda(dx)$,

where Λ is a finite measure on $[0,1]$. (Sagitov, 1999; Pitman, 1999).

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Interpretation:
re-write $\lambda_{n,k} = \int_{[0,1]} x^k(1-x)^{n-k}\,\frac{1}{x^2}\Lambda(dx)$ to see:
at rate $\frac{1}{x^2}\Lambda([x, x+dx])$, an '$x$-resampling event' occurs.

Thinking forwards in time, this corresponds to an event in which the fraction x of the total population is replaced by the offspring of a single individual.

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Note: $\Lambda = \delta_0$ corresponds to Kingman's coalescent.

Cannings' models in the 'domain of attraction of a Λ-coalescent'

Fixed population size N, *exchangeable* offspring numbers in one generation

$$\big(\nu_1, \nu_2, \ldots, \nu_N\big).$$

Sagitov (1999), Möhle & Sagitov (2001) clarify under which conditions the genealogies of a sequence of exchangeable finite population models are described by a Λ-coalescent:

- $c_N :=$ pair coalescence probability over one generation $\to 0$
  ($c_N = \frac{1}{N-1}\mathbb{E}[\nu_1(\nu_1 - 1)]$)
- two double mergers asymptotically negligible compared to one triple merger
- $Nc_N \Pr\big(\text{a given family has size} \geq Nx\big) \sim \int_x^1 y^{-2}\Lambda(dy)$

Time is measured in $1/c_N$ generations (in general $\neq 1/\text{pop. size}$)

Note: There are many Λ-coalescents.

Maybe a natural "first candidate":

$$\Lambda = w\delta_0 + (1-w)\delta_\psi \quad \text{with} \quad w, \psi \in (0,1)$$

(as considered by Eldon & Wakeley, *Genetics* 2006)

A 'heavy-tailed' Cannings model and Beta-coalescents

Haploid population of size N. Individual i has X_i *potential offspring*,
$X_1, X_2, \ldots, X_N$ are i.i.d. with mean $m := \mathbb{E}\left[X_1\right] > 1$,
$\Pr\left(X_1 \geq k\right) \sim$ Const. $\times\, k^{-\alpha}$ with $\alpha \in (1, 2)$.
Note: infinite variance.

Sample N without replacement from all potential offspring to form the next generation.

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Theorem (Schweinsberg, 2003)

Let c_N = prob. of pair coalescence one generation back in N-th model. $c_N \sim$ const. $N^{1-\alpha}$, measured in units of $1/c_N$ generations, the genealogy of a sample from the N-th model is approximately described by a Λ-coalescent with $\Lambda = \mathrm{Beta}(2-\alpha,\alpha)$.

$\left(\mathrm{Beta}(2-\alpha,\alpha)(dx) = \mathbb{1}_{[0,1]}(x)\frac{1}{\Gamma(2-\alpha)\Gamma(\alpha)} x^{1-\alpha}(1-x)^{\alpha-1}\,dx \right)$

Why $\Lambda = \mathrm{Beta}(2-\alpha, \alpha)$?

Heuristic argument:

Probability that first individual's offspring provides

more than fraction y of the next generation,

given that the family is substantial (i.e. given $X_1 \geq \varepsilon N$, for $y > \varepsilon$)

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$$\approx \quad \mathbb{P}\Big(\frac{X_1}{X_1 + (N-1)m} \geq y \Big| X_1 \geq \varepsilon N\Big)$$

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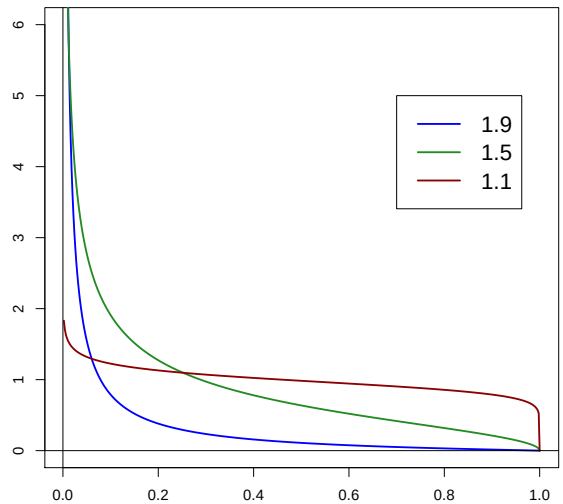
The family $\mathrm{Beta}(2-\alpha,\alpha)$, $\alpha \in (1,2]$

- Kingman's coalescent included as boundary case: $\mathrm{Beta}(2-\alpha,\alpha) \to \delta_0$ weakly as $\alpha \to 2$.
- Smaller α means tendency towards more extreme resampling events.
- For $\alpha \leq 1$, corresponding coalescents *do not* come down from infinity.

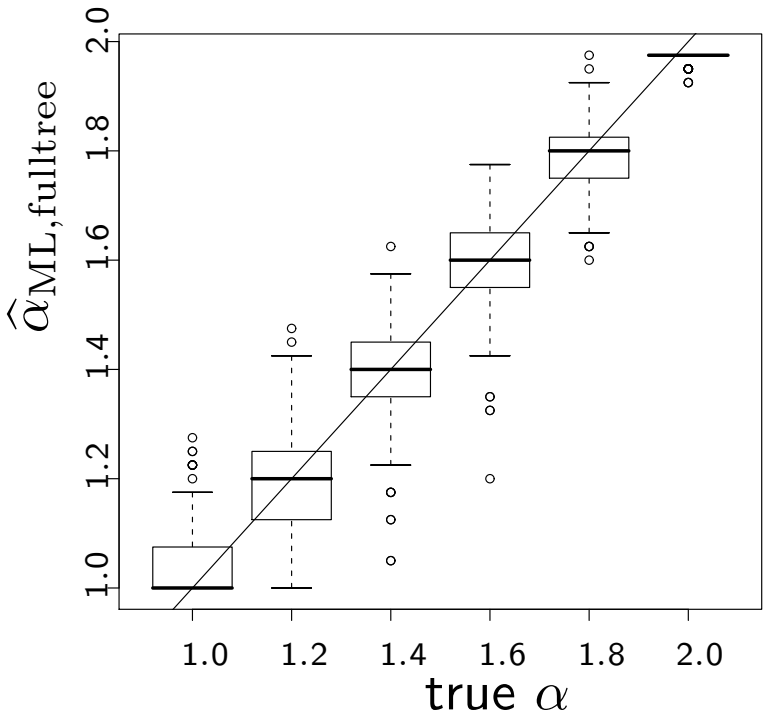


- $\mathrm{Beta}(2-\alpha,\alpha)$-coalescents appear as genealogies of α-stable continuous mass branching process (via a time-change).
- Scaling relation of mutation rate per generation relative to population size depends on α!

'Meta-mathematic' associations

Brownian motion	$\leftrightarrow$	Kingman's coalescent
$\cap$		$\cap$
Stable processes	$\leftrightarrow$	Beta$(2-\alpha, \alpha)$-coalescents
$\cap$		$\cap$
General Lévy processes	$\leftrightarrow$	General Λ-coalescents

Playing god with simulated "full trees"



ML estimates of α for simulted datasets with sample size $n = 100$, estimate based on *full genealogical tree*
(400 replicates for each value of α).

Consider n-Λ-coalescent with mutation rate r per line (and infinite alleles mutation model). $\mathbf{n} = (n_1, \ldots, n_\ell)$, possible type configuration

Theorem (Möhle 2005)

The probability $p(\mathbf{n})$ of observing a type configuration $\mathbf{n} = (n_1, \ldots, n_\ell)$ satisfies the recursion given by $p(1) = 1$ and

$$p(\mathbf{n}) = \frac{nr}{\sum_{k=2}^{n} \binom{n}{k} \lambda_{n,k} + nr} \sum_{\substack{j=1 \\ n_j=1}}^{\ell} \frac{1}{\ell} p(\tilde{\mathbf{n}}^{(j)})$$

$$+ \frac{1}{\sum_{k=2}^{n} \binom{n}{k} \lambda_{n,k} + nr} \sum_{k=2}^{n} \sum_{\substack{j=1 \\ n_j \geq k}}^{\ell} \binom{n}{k} \lambda_{n,k} \frac{n_j - k + 1}{n - k + 1} p(\mathbf{n} - (k-1)\mathbf{e}_j).$$

$(\tilde{\mathbf{n}}^{(j)} = (n_1, \ldots, n_{j-1}, n_{j+1}, \ldots, n_k))$

Infinitely many sites model

Model genetic locus as infinite sequence of completely linked sites, mutations always hit a new site.

Mathematical abstraction:

- a gene is $[0, 1]$
- a type is a configuration of points on $[0, 1]$

Ethier & Griffiths (1987) parametrisation:

- type space $E = [0, 1]^{\mathbb{N}}$
- mutation operator

$$Bf\big((x_1, x_2, \dots)\big) = r \int_0^1 f\big((u, x_1, x_2, \dots)\big) - f\big((x_1, x_2, \dots)\big)\, du$$

Asymptotics of the frequency spectrum

Consider an n-$\mathrm{Beta}(2-\alpha,\alpha)$-coalescent, mutations at rate r according to the *infinitely-many-sites* model (assuming known ancestral types). Let

$$\begin{aligned} M(n) &:= \#\text{total number of mutations in the sample,} \\ M_k(n) &:= \#\text{number of mutations affecting exactly } k \text{ samples,} \end{aligned}$$

$k = 1, 2, \ldots, n-1$.

Theorem (Berestycki, Berestycki & Schweinsberg 2007)

$$\frac{M(n)}{n^{2-\alpha}} \to r\frac{\alpha(\alpha-1)\Gamma(\alpha)}{2-\alpha}, \qquad \frac{M_k(n)}{n^{2-\alpha}} \to r\alpha(\alpha-1)^2\frac{\Gamma(k+\alpha-2)}{k!}$$

in probability as $n \to \infty$.

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in probability as $n \to \infty$.

Thus $M_1(n)/M(n) \approx 2-\alpha$ for n large, which suggests

$$\widehat{\alpha}_{\mathrm{BBS}} := 2 - \frac{M_1(n)}{M(n)} \qquad \text{as an estimator for } \alpha.$$

Infinitely-many-sites model

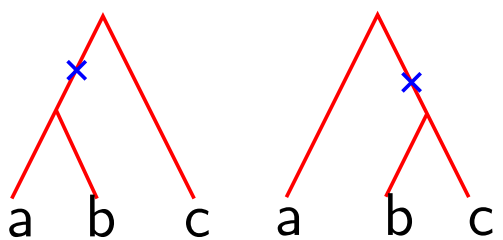
Model genetic locus as infinite sequence of completely linked sites, mutations always hit a new site

Example:

	segr. site			
Seq.	1	2	3	4
1	1	0	0	0
2	1	1	0	0
3	0	0	1	1
4	0	0	1	1
5	0	0	1	0

(0=wild type, 1=mutant
assume known ancestral types)

Obs. fit IMS $\iff$ no sub-matrix $\begin{matrix} 1 & 0 \\ 1 & 1 \\ 0 & 1 \end{matrix}$
(and no row permutation).



Infinitely-many-sites model, II

If the infinitely-many-sites model applies, the observations correspond to a unique rooted perfect phylogeny (or 'genetree').

Sequences,

	segr. site			
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1	1	0	0	0
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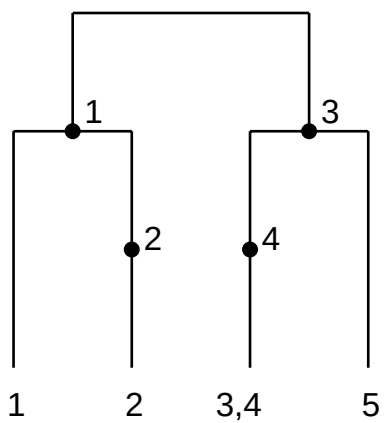
4	0	0	1	1
5	0	0	1	0

Genetree,



obs. types

type	multiplicity
(1, 0)	1
(2, 1, 0)	1
(4, 3, 0)	2
(3, 0)	1

Construct e.g. using GUSFIELD's (1991) algorithm.

Note: purely combinatorial, does not depend on a probabilistic model for the observations.

Simulating samples under the IMS model

The Ethier-Griffiths urn (1987) can be used to generate a random sample of size n under Kingman's coalescent
(with mutation rate r per line):

- Start with 2 leaves.
- When there are k leaves:

  Add a mutation to a leaf w. prob. $\frac{2r}{2r+(k-1)}$,

  split one leaf w. prob. $\frac{k-1}{2r+(k-1)}$

  (leaf picked uniformly among the k).
- Stop when $n+1$ leaves, delete last leaf.

Simulating samples under the IMS model: Λ-case

$(Y_t^{(n)})_{\geq 0}$ *block counting process* of Λ-coalescent starting from n blocks:

- Jump from i to $j \in \{1, 2, \ldots, i-1\}$ at rate $q_{ij} := \binom{i}{i-j+1} \lambda_{i,i-j+1}$.
- $\tau_1 := \inf\{t \geq 0 : Y_t^{(n)} = 1\}$.

$\widetilde{Y}_t^{(n)} := Y_{(\tau_1 - t)-}^{(n)}$ *time-reversed* block counting process

- $(\widetilde{Y}_t^{(n)} = \partial$ for $t \geq \tau_1)$.
- Jump rates $\widetilde{q}_{ji}^{(n)} = \frac{g_{ni} q_{ij}}{g_{nj}}$, $\widetilde{q}_{n\partial}^{(n)} = -q_{nn} = \sum_{j=1}^{n-1} q_{nj}$,
- $\mathbb{P}(\widetilde{Y}_0^{(n)} = k) = \mathbb{P}(Y_{\tau_1 -}^{(n)} = k) = g_{nk} q_{k1}$.

- $g_{ni} := \mathbb{E} \int_0^\infty \mathbf{1}(Y_t^{(n)} = i)\, dt$ is the Green function (in general, not known explicitly, but easy recursion).

Simulating samples under the IMS model: Λ-case, cont.

The n-Λ-"Ethier-Griffiths urn" (mutation rate r).

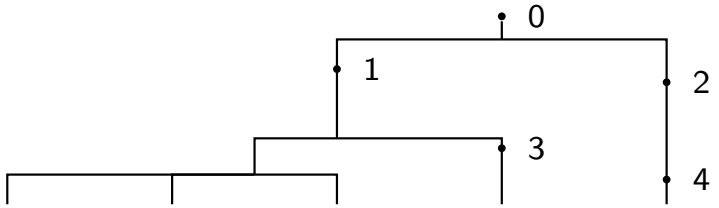
- Begin with K leaves, $\mathbb{P}(K = k) = \mathbb{P}(\widetilde{Y}_0^{(n)} = k)$.
- While there are k leaves:

Add a mutation to a leaf	w. prob.	$\frac{r}{kr - \widetilde{q}_{kk}^{(n)}}$,
split one leaf into ℓ	w. prob.	$\frac{\widetilde{q}_{k,k+\ell-1}^{(n)}}{\widetilde{q}_{kk}^{(n)}}$,
if $k = n$ goto stop	w. prob.	$\frac{-\widetilde{q}_{nn}^{(n)}}{kr - \widetilde{q}_{nn}^{(n)}}$

  (leaf picked uniformly among the k).
- Stop.

Recursion for tree probabilities

Can calculate $\mathbb{P}_{(r,\Lambda)}\big(\text{observed sequence data } (\mathbf{t},\mathbf{n})\big) =: p(\mathbf{t},\mathbf{n})$ via



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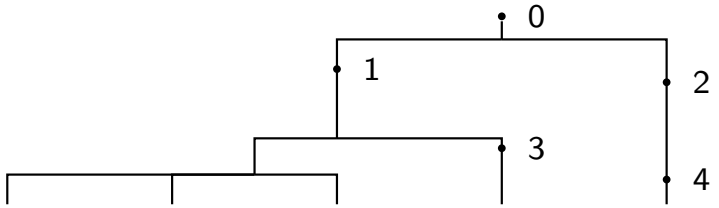


$$p(\mathbf{t},\mathbf{n}) = \frac{1}{rn+\lambda_n}\sum_{i:n_i\geq 2}\sum_{k=2}^{n_i}\binom{n}{k}\lambda_{n,k}\frac{n_i-k+1}{n-k+1}p\big(\mathbf{t},\mathbf{n}-(k-1)\mathbf{e}_i\big)$$
$$+\frac{r}{rn+\lambda_n}\sum_{\substack{i:n_i=1,x_{i0}\text{unique},\\ \mathfrak{s}(\mathbf{x}_i)\neq\mathbf{x}_j\,\forall j}} p\big(\mathfrak{s}_i(\mathbf{t}),\mathbf{n}\big)$$
$$+\frac{r}{rn+\lambda_n}\frac{1}{d}\sum_{\substack{i:n_i=1,\\ x_{i0}\text{unique}}}\sum_{j:\mathfrak{s}(\mathbf{x}_i)=\mathbf{x}_j}(n_j+1)p\big(\mathfrak{r}_i(\mathbf{t}),\mathfrak{r}_i(\mathbf{n}+\mathbf{e}_j)\big).$$

Extends Ethier & Griffiths (1987) to Λ-coalescents and Möhle's recursion (2005) to IMS model.

Compute probabilities

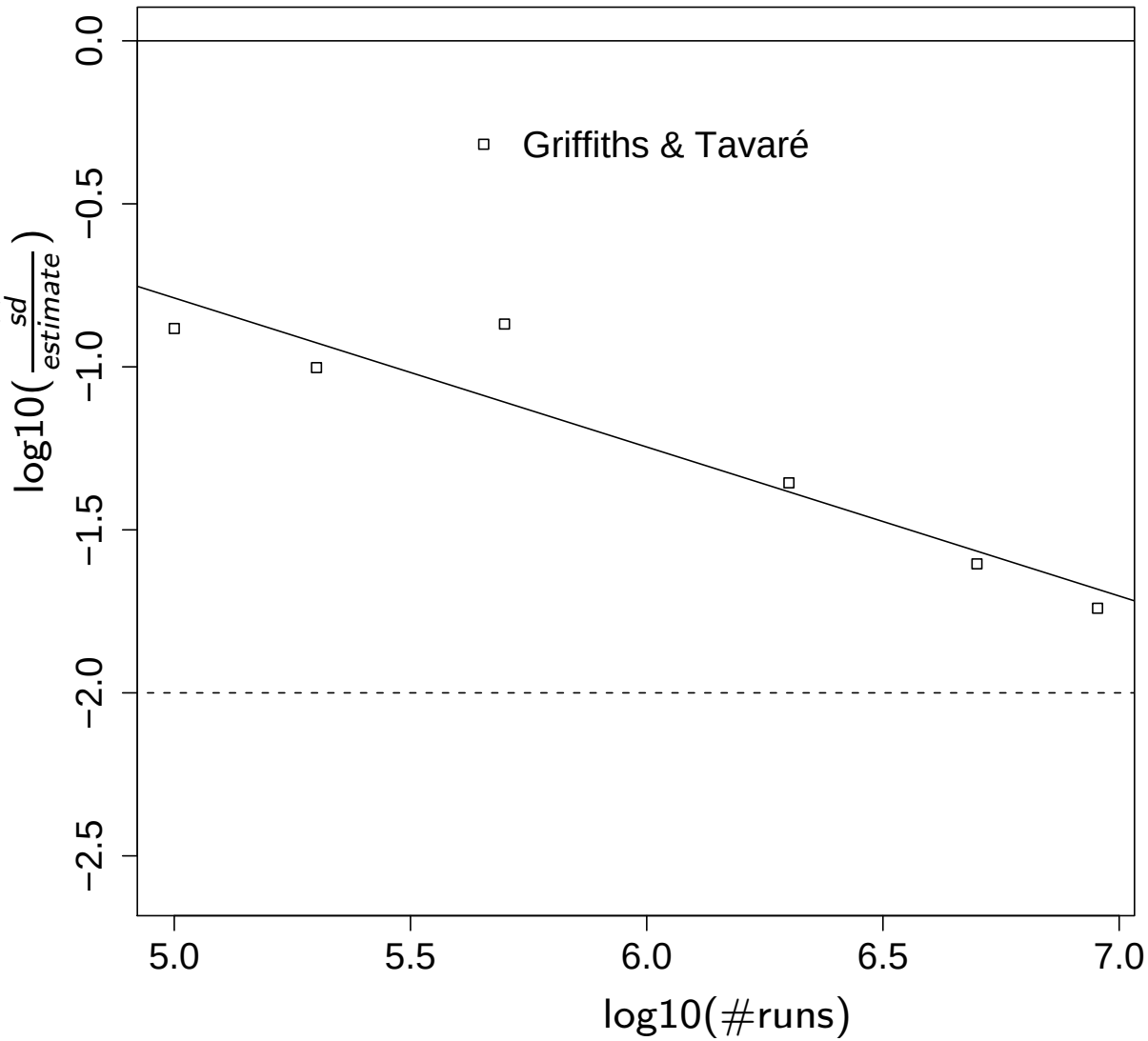
Use exact recursions for moderate sample complexities.
Approach more complex samples by version of Griffiths & Tavaré's (1994)

Monte Carlo method

$$p(\mathbf{t}, \mathbf{n}) = \mathbb{E}_{(\mathbf{t},\mathbf{n})}\Big[\prod_{i=0}^{\tau-1} f_{(r,\Lambda)}(X_i)\Big]$$

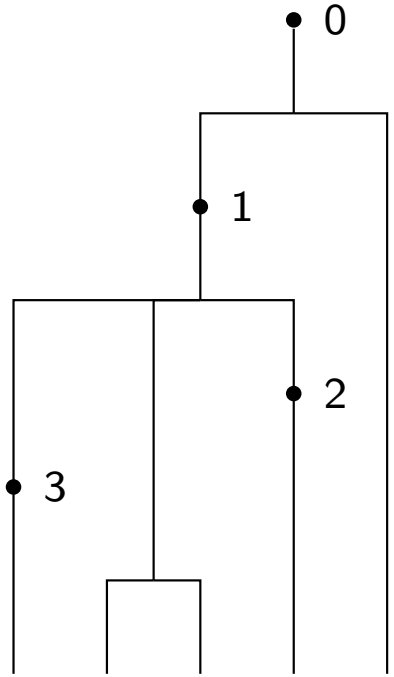
- For suitable Markov chain X_i on sample configurations.
- Estimate expectation via empirical mean of independent runs.
- extension to Λ-coalescents by B. & Blath (2008)

Artifical sample of size 12 analysed with $r = 1$ and $\alpha = 1.5$:



Histories

Interpret genealogy as sequency of historical states:
$\mathcal{H} = \left(H_{-\tau} = ((1),(0)), H_{\tau-1}, \ldots, H_{-1}, H_0 = (\mathbf{t}, \mathbf{n})\right)$



$$\Big(\big((3,1,0),(1,0),(2,1,0),(0)\big),(1,2,1,1)\Big)$$

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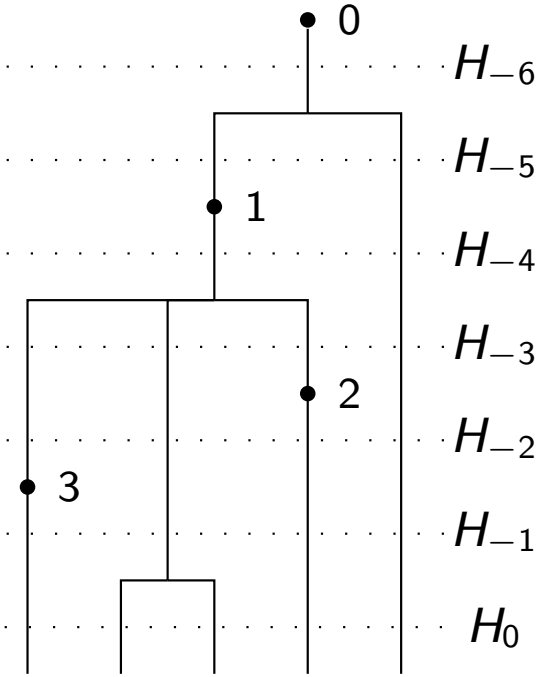

$$\Big(((3,1,0),(1,0),(2,1,0),(0)),(1,2,1,1)\Big)$$

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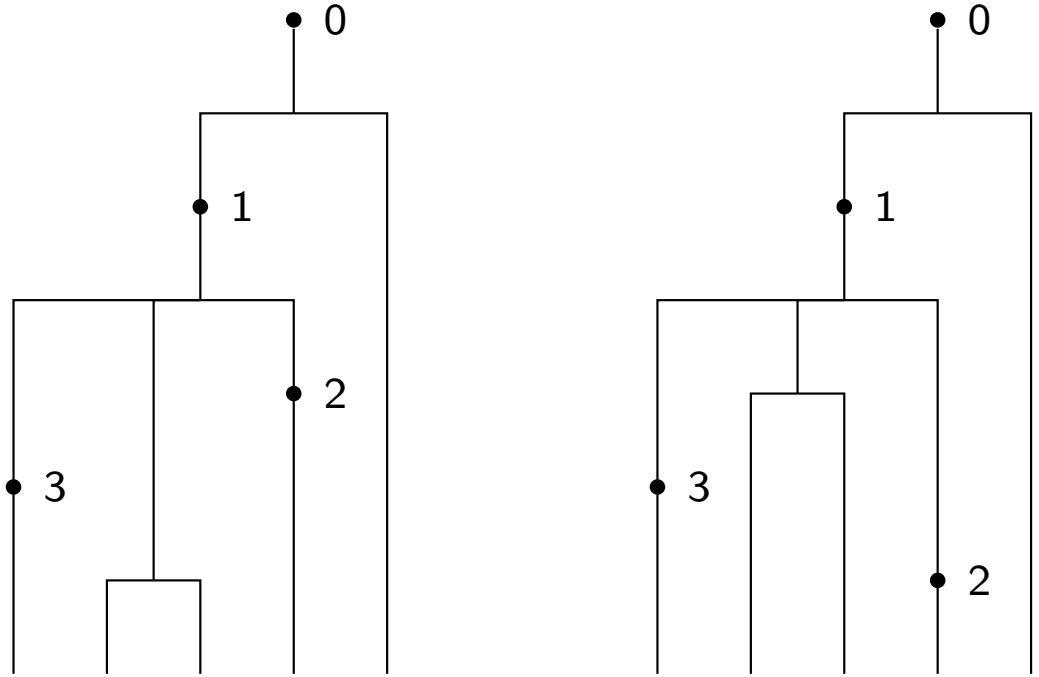

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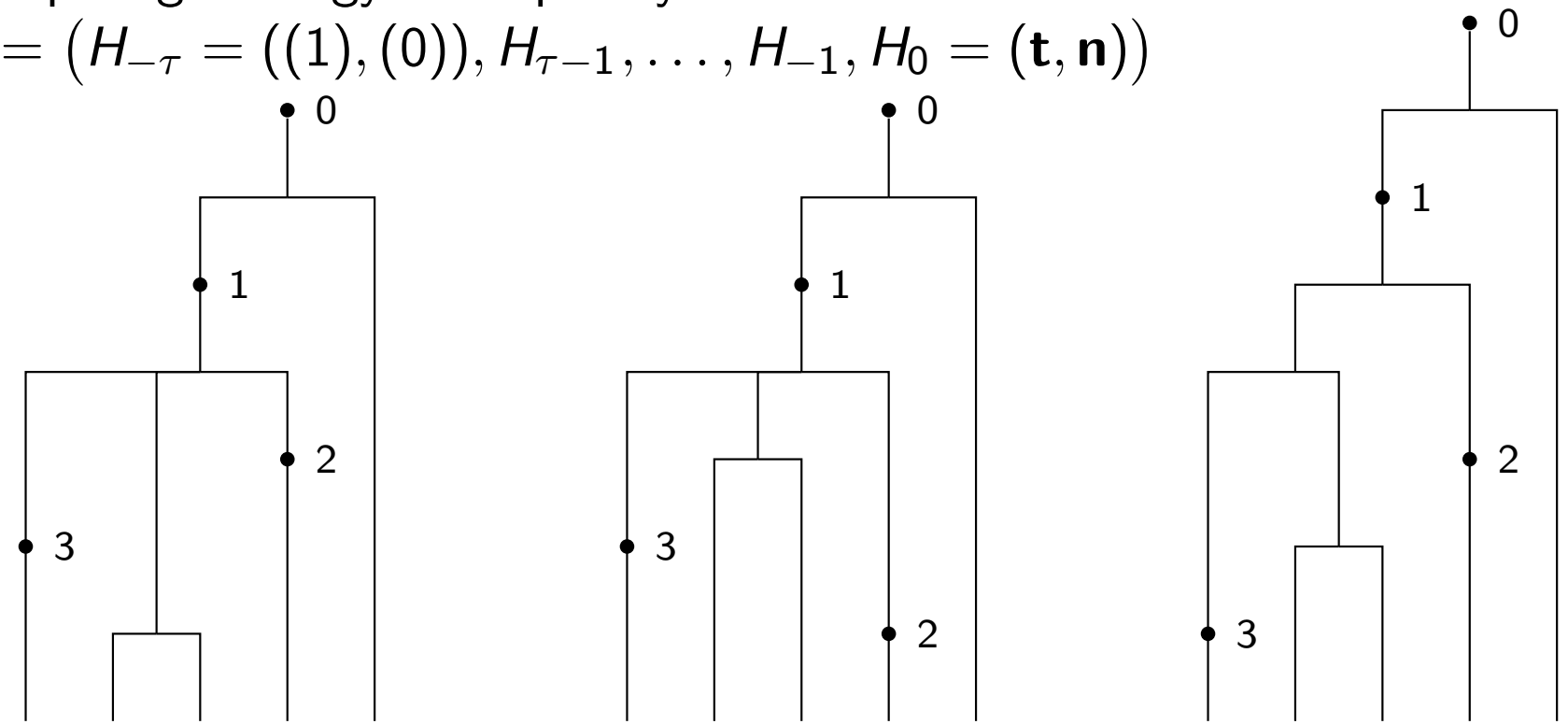

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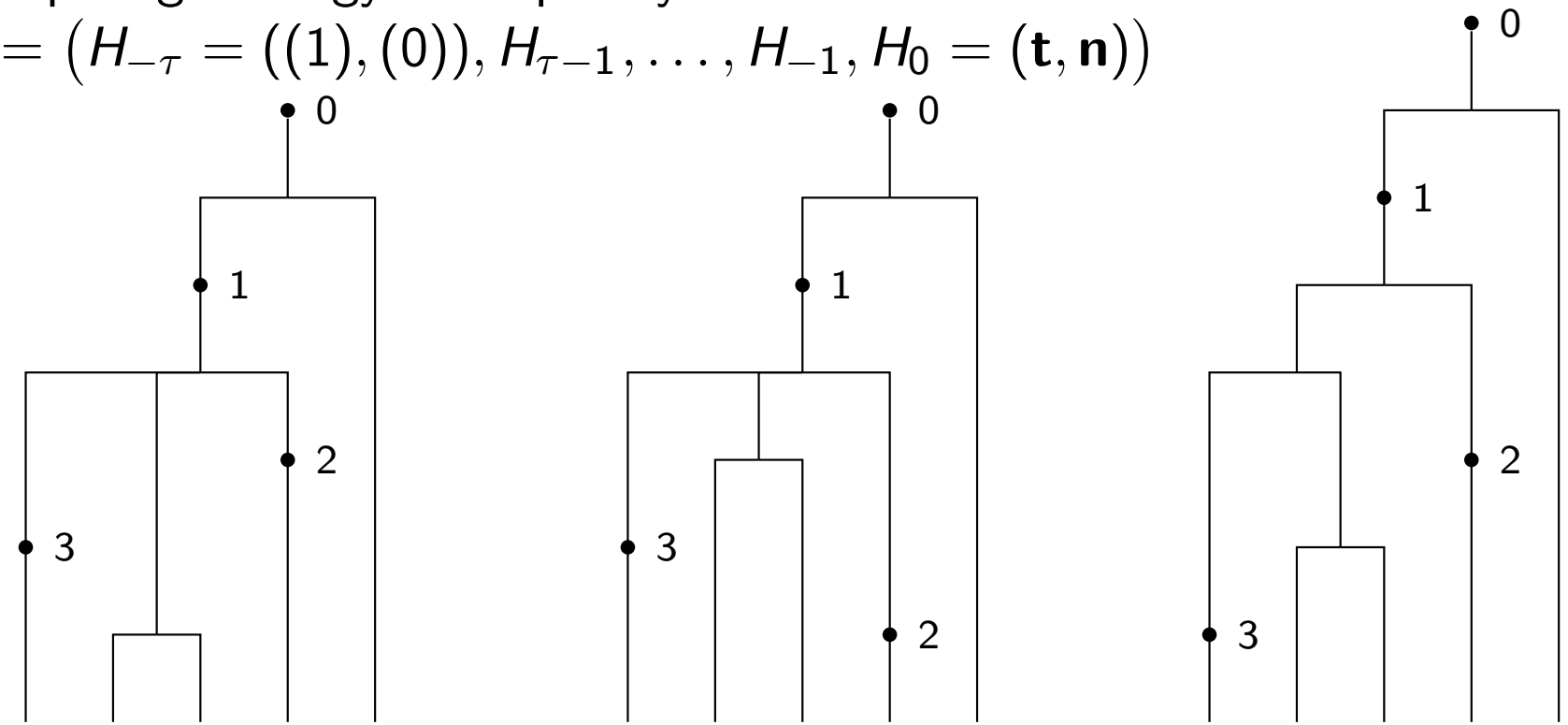


different histories can lead to same sample

$$\Big(\big((3,1,0),(1,0),(2,1,0),(0)\big),(1,2,1,1)\Big)$$

Importance sampling

We have

$$p(\mathbf{t},\mathbf{n}) = \mathbb{P}_{(r,\Lambda)}\big(H_0 = (\mathbf{t},\mathbf{n})\big) = \sum_{\mathcal{H}:H_0=(\mathbf{t},\mathbf{n})} \mathbb{P}_{(r,\Lambda)}\big(\mathcal{H}\big)$$

$$= \sum_{\mathcal{H}:H_0=(\mathbf{t},\mathbf{n})} \underbrace{\frac{\mathbb{P}_{(r,\Lambda)}\big(\mathcal{H}\big)}{\mathcal{Q}\big(\mathcal{H}\big)}}_{\substack{=:w(\mathcal{H}) \\ \text{importance weight}}} \mathcal{Q}(\mathcal{H}),$$

for any law $\mathcal{Q}$ on histories s.th. $\mathbb{P}_{(r,\Lambda)}\Big|_{\{H_0=(\mathbf{t},\mathbf{n})\}} \ll \mathcal{Q}$.

Thus,

$$p(\mathbf{t},\mathbf{n}) \approx \frac{1}{R}\sum_{i=1}^{R} w(\mathcal{H}^{(i)}),$$

where $\mathcal{H}^{(1)},\ldots,\mathcal{H}^{(R)}$ are independent samples from $\mathcal{Q}$

(Theoretical) optimal solution

$$p(\mathbf{t},\mathbf{n}) = \sum_{\mathcal{H}:H_0=(\mathbf{t},\mathbf{n})} \frac{\mathbb{P}_{(r,\Lambda)}(\mathcal{H})}{\mathcal{Q}(\mathcal{H})}\mathcal{Q}(\mathcal{H}) \approx \frac{1}{R}\sum_{i=1}^{R} w(\mathcal{H}^{(i)})$$

$\mathcal{Q}_{\mathrm{opt}}(\cdot) := \mathbb{P}_{(r,\Lambda)}\big(\,\cdot\,\big|H_0 = (\mathbf{t},\mathbf{n})\big)$ is optimal (Stephens & Donnelly 2000):

- Variance of estimator is zero since $w(\mathcal{H}^{(i)}) \equiv p(\mathbf{t},\mathbf{n})$.
- Finding $\mathcal{Q}_{\mathrm{opt}}$ is as hard as the original problem.
- $H_0, H_{-1}, \ldots$ is Markov chain under $\mathcal{Q}_{\mathrm{opt}}$.

Remark: Transistion probabilities $q_{\mathrm{GT}}(H_i|H_{i+1}) \propto \mathbb{P}_{(r,\Lambda)}(H_{i+1}|H_i)$ gives (Λ-)Griffiths-Tavaré method.

Stephens and Donnelly's (2000) IMS candidate

Kingman case: Choose individual uniformly:

- If type is unique in sample, remove "outmost" mutation,
- if at least two individuals with this type, merge two lines.

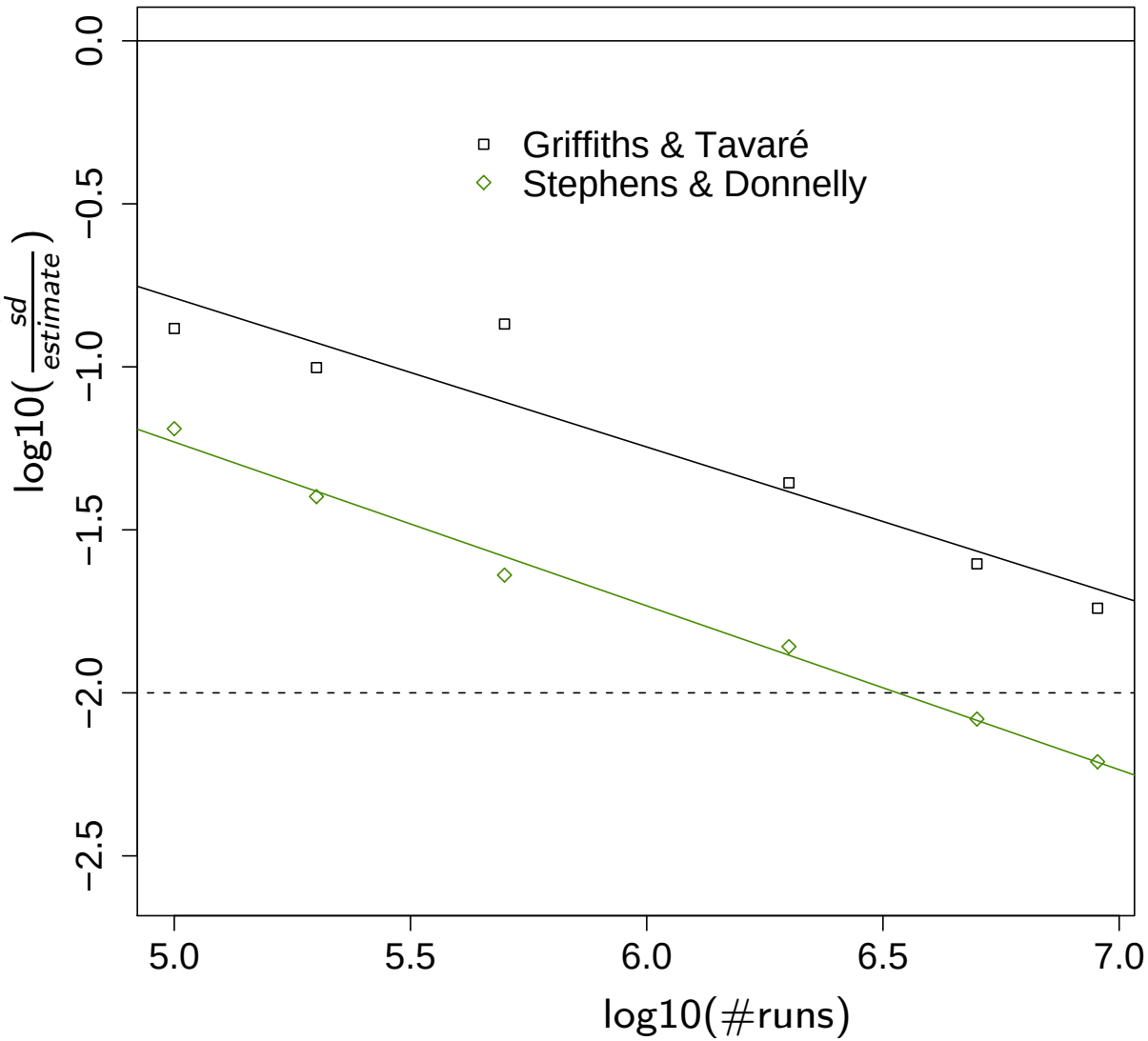
(this *would be* optimal for parent-independent mutations)

Heuristic extension to Λ case:

$$(\mathbf{t},\mathbf{n}) \to \begin{cases} \left(\mathfrak{s}_i(\mathbf{t}),\mathbf{n}\right) & \text{w.p. } \propto 1 \text{ if } n_i = 1, x_{i0} \text{ unique, } \mathfrak{s}_i(\mathbf{x}_i) \neq \mathbf{x}_j \forall j \\ \left(\mathfrak{r}_i(\mathbf{t},\mathfrak{r}_i(\mathbf{n}+\mathbf{e}_j)\right) & \text{w.p. } \propto 1 \text{ if } n_i = 1, x_{i0} \text{ unique, } \mathfrak{s}_i(\mathbf{x}_i) \neq \mathbf{x}_j \\ \left(\mathbf{t},\mathbf{n}-(k-1)\mathbf{e}_i\right) & \text{w.p. } \propto n_i \bar{q}_{n_i}(k) \text{ if } 2 \leq k \leq n_i, \end{cases}$$

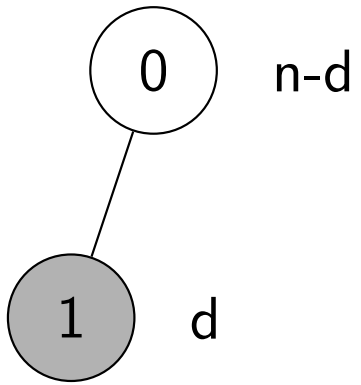
where $\bar{q}_{n_i}(k) = \frac{q_{n,n-k+1}}{\sum_{l=2}^{n_i} q_{n,n-l+1}}$, jump probabilities of block counting process.

Artifical sample of size 12 analysed with $r = 1$ and $\alpha = 1.5$:



Hobolth, Uyenoyama & Wiuf's (2008) idea

Sample of size n where exactly one mutation is visible (in d copies).



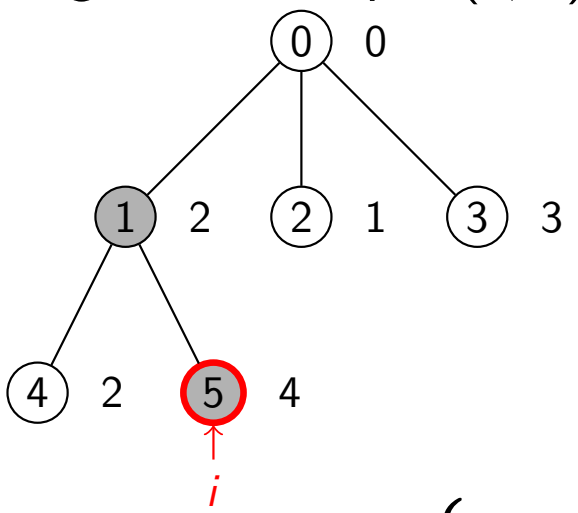
$$p^{(1)}_{(r,\Lambda)}(n,d) = \mathbb{P}_{(r,\Lambda)}\left\{\begin{array}{l}\text{most recent event involves indi-}\\ \text{vidual bearing mutation}\end{array}\right\}$$

Probability can be computed

- Kingman case: explicit formula (HUW (2008))
- Λ case: numerically, using recursion

Hobolth, Uyenoyama & Wiuf's (2008) idea contd.

For a general sample $(\mathbf{t}, \mathbf{n})$



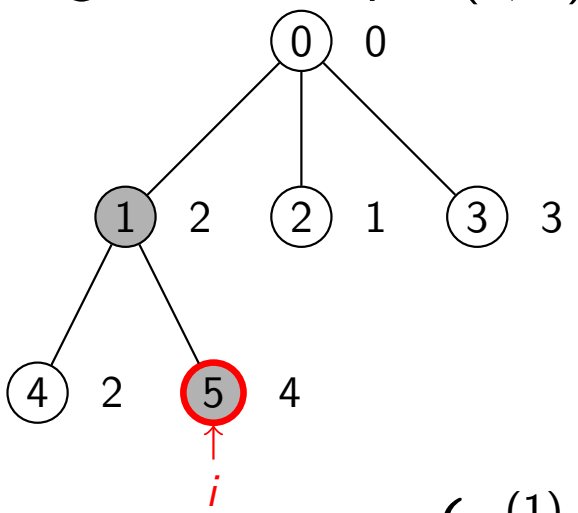
put

$$u_{i,m} = \begin{cases}$$

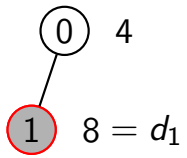
where mutation m is present in d_m individuals.

Hobolth, Uyenoyama & Wiuf's (2008) idea contd.

For a general sample $(\mathbf{t}, \mathbf{n})$



carrying:



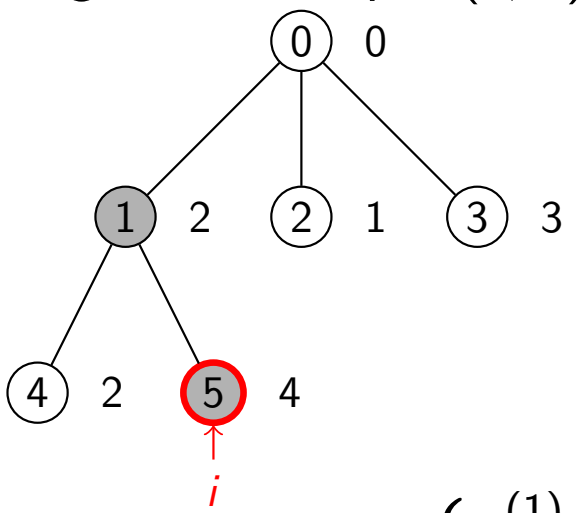
put

$$u_{i,m} = \begin{cases} p^{(1)}_{(r,\Lambda)}(n, d_m) \cdot \frac{n_i}{d_m} & \text{if } i \text{ bears } m \\ \end{cases}$$

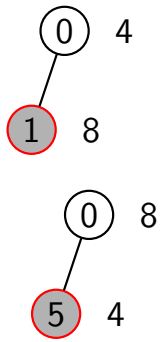
where mutation m is present in d_m individuals.

Hobolth, Uyenoyama & Wiuf's (2008) idea contd.

For a general sample $(\mathbf{t}, \mathbf{n})$



carrying:



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Hobolth, Uyenoyama & Wiuf's (2008) idea contd.

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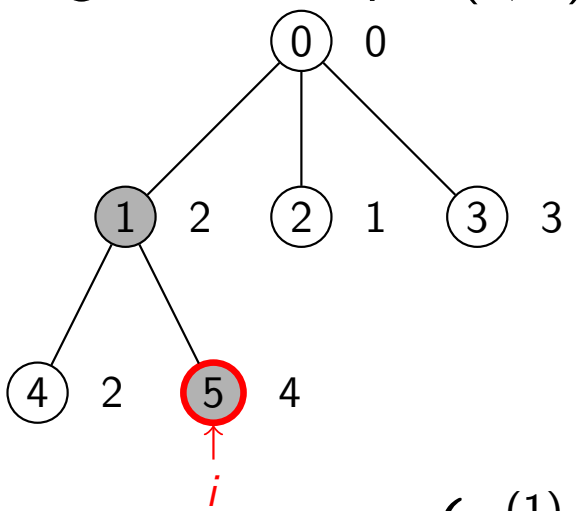

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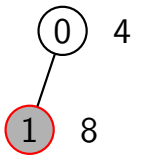
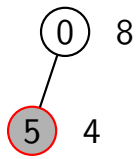
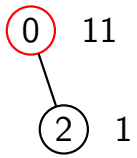




not carrying:



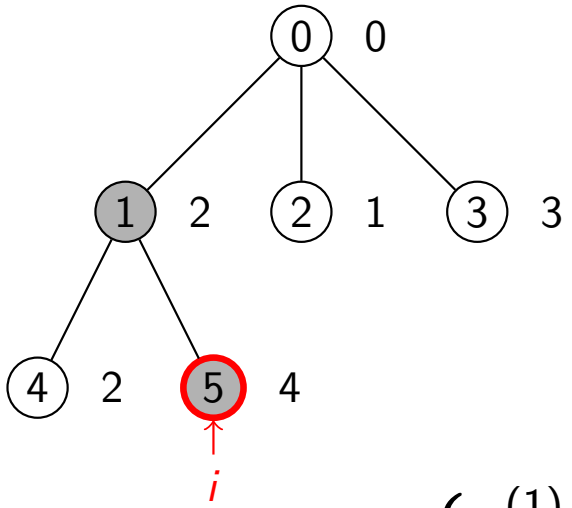
put

$$u_{i,m} = \begin{cases} p^{(1)}_{(r,\Lambda)}(n, d_m) \cdot \frac{n_i}{d_m} & \text{if } i \text{ bears } m \\ \left(1 - p^{(1)}_{(r,\Lambda)}(n, d_m)\right) \cdot \frac{n_i}{n - d_m} & \text{otherwise,} \end{cases}$$

where mutation m is present in d_m individuals.

Hobolth, Uyenoyama & Wiuf's (2008) idea contd.

For a general sample $(\mathbf{t}, \mathbf{n})$



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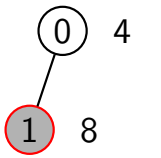

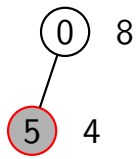

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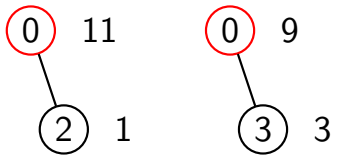

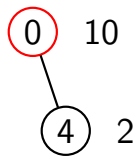

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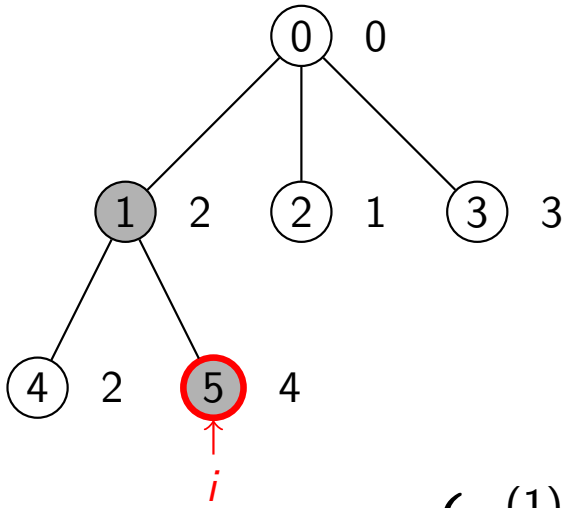

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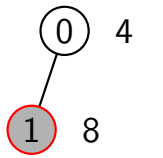

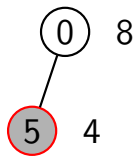

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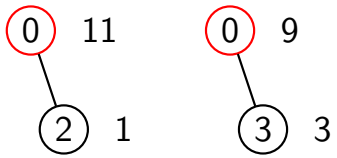

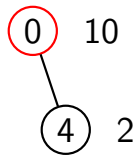

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where mutation m is present in d_m individuals. Propose type i according to

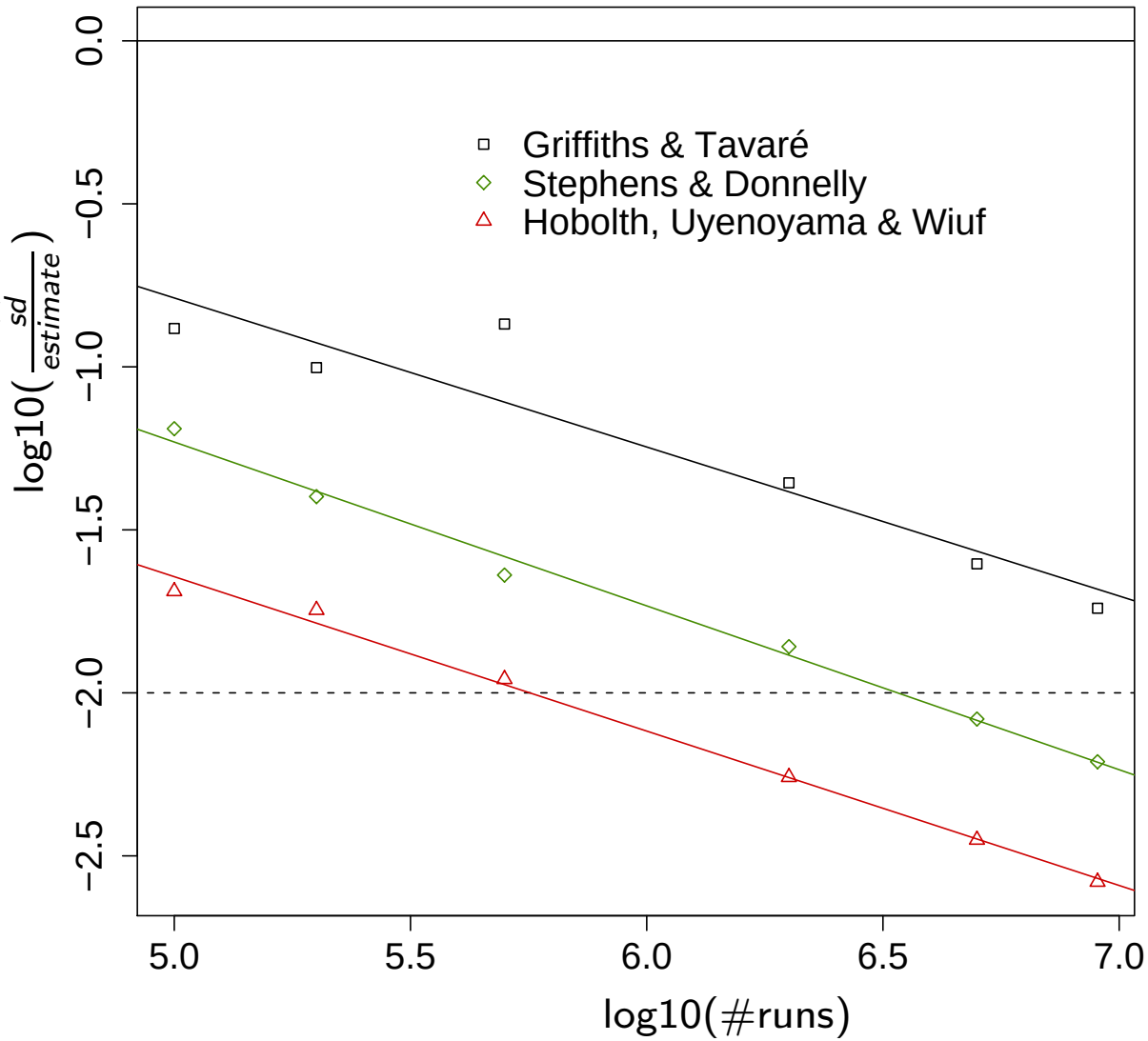
$$q_{\Lambda\text{-HUW}}\left(i|(\mathbf{t}, \mathbf{n})\right) \propto \begin{cases} \sum_m u_{i,m} & \text{if } i \text{ is allowed to act} \\ 0 & \text{otherwise.} \end{cases}$$

Hobolth, Uyenoyama & Wiuf's (2008) idea contd.

If proposed type i

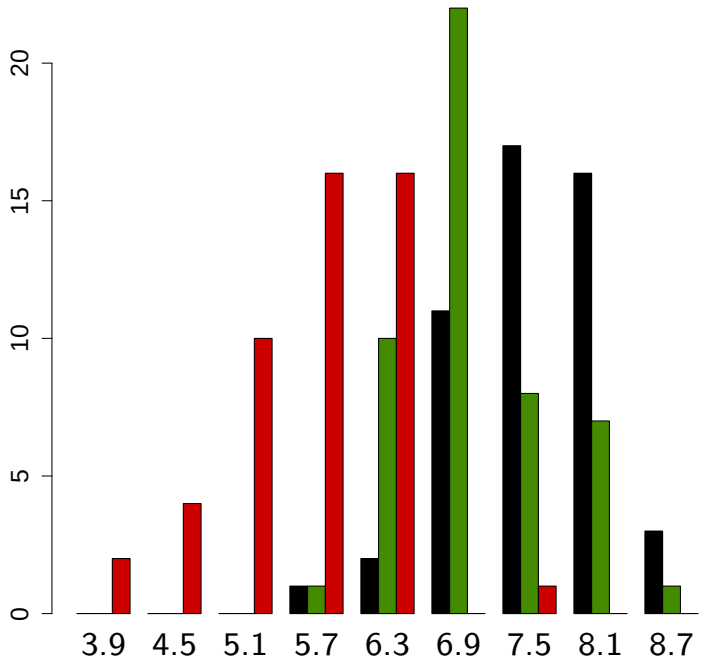
- is singleton: remove "outmost" mutation,
- has $n_i \geq 2$: merger inside type i.
  - Kingman case: merge two lines
  - Λ-case: propose $\ell + 1$-merger w.p. $\propto \mathbb{P}_{r,\Lambda}\left\{ \begin{array}{c|c} \begin{array}{cc} 0 & n \\ 1 & d_o - l \end{array} & \begin{array}{cc} 0 & n \\ 1 & d_o \end{array} \end{array} \right\}$

Artifical sample of size 12 analysed with $r = 1$ and $\alpha = 1.5$:

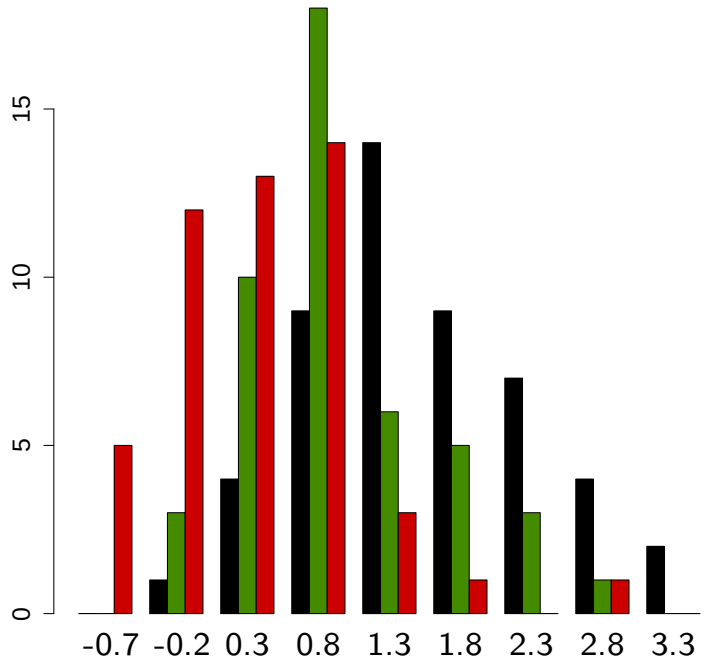


Performance

Simulated 50 samples of size 15 with $r = 2$ and $\alpha = 1.5$. Analysed with $r = 1$ and $\alpha = 1.5$. Time needed to get relative error below 0.01:



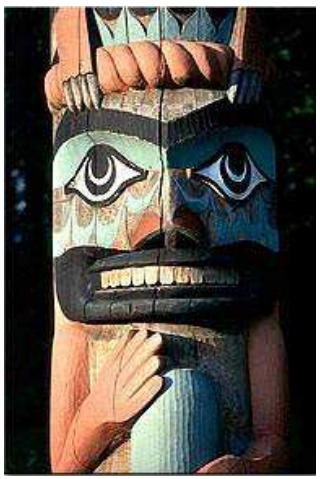
(a) measured in log10(# runs of MC)

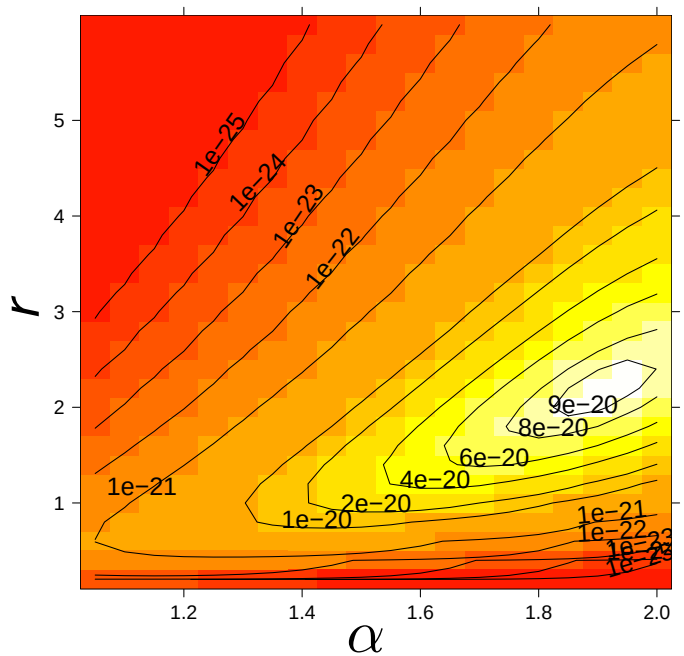


(b) measured in log10(seconds)

Dataset from Ward et al, Extensive Mitochondrial Diversity Within a Single Amerindian Tribe, *PNAS* 1991

Analysis with Beta-Coalescent:

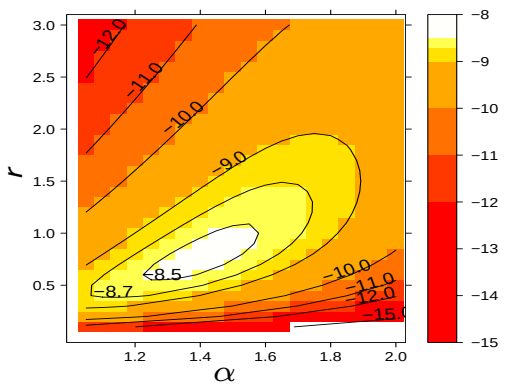




Mitochondrial control region from 55 female Nuu-Chah-Nulth:
$\widehat{\alpha}_{\mathrm{ML}} = 1.9$, $\widehat{r}_{\mathrm{ML}} = 2.2$
(Sample as edited in Griffiths & Tavaré, *Stat. Sci.*, 1994)

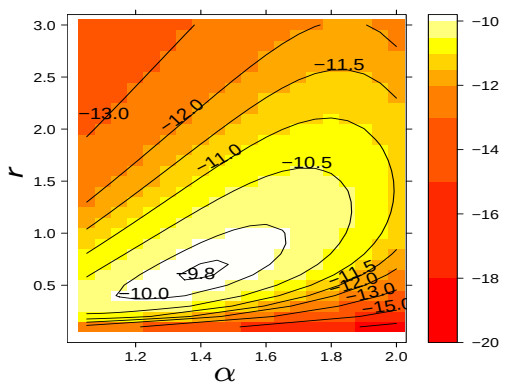
Genetic variation at the mitochondrial cyt *b* locus of Atlantic cod: log-likelihood surfaces

Carr & Marshall 1991



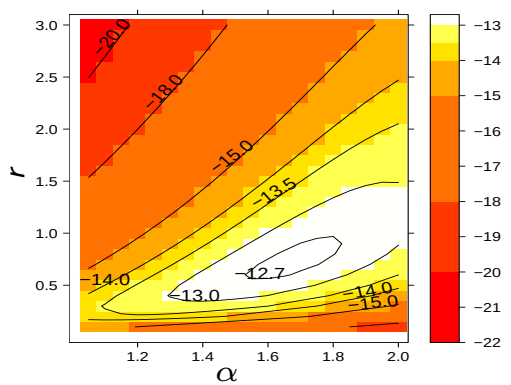
$\widehat{\alpha}_{\mathrm{ML}} = 1.4, \widehat{r}_{\mathrm{ML}} = 0.8, \widehat{\alpha}_{\mathrm{BBS}} = 1.4$

Pepin & Carr 1993



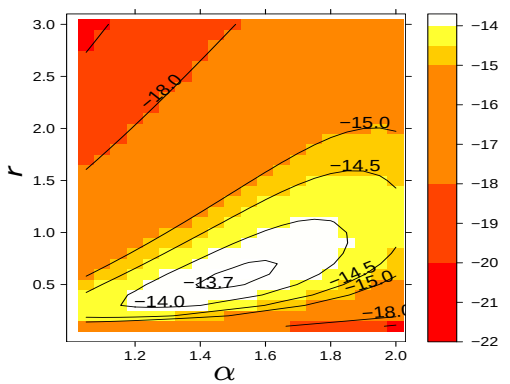
$\widehat{\alpha}_{\mathrm{ML}} = 1.4, \widehat{r}_{\mathrm{ML}} = 0.6, \widehat{\alpha}_{\mathrm{BBS}} = 1.5$

Árnason & Palsson 1996



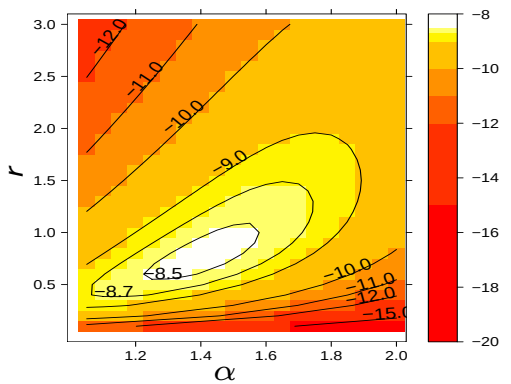
$\widehat{\alpha}_{\mathrm{ML}} = 1.65, \widehat{r}_{\mathrm{ML}} = 0.7, \widehat{\alpha}_{\mathrm{BBS}} = 1.5$

Árnason et al 1998



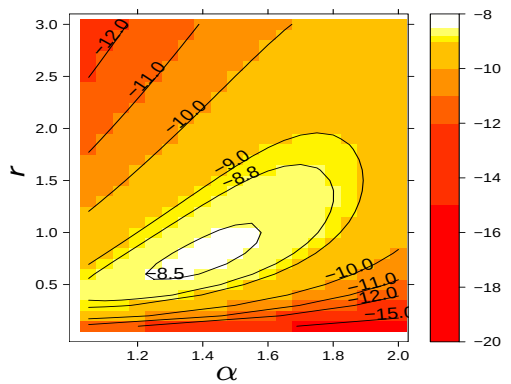
$\widehat{\alpha}_{\mathrm{ML}} = 1.55, \widehat{r}_{\mathrm{ML}} = 0.6, \widehat{\alpha}_{\mathrm{BBS}} = 1.8$

Árnason et al 2000



$\widehat{\alpha}_{\mathrm{ML}} = 1.4, \widehat{r}_{\mathrm{ML}} = 0.8, \widehat{\alpha}_{\mathrm{BBS}} = 1.5$

Sigurgíslason & Árnason 2003



$\widehat{\alpha}_{\mathrm{ML}} = 1.4, \widehat{r}_{\mathrm{ML}} = 0.8, \widehat{\alpha}_{\mathrm{BBS}} = 1.44$

"α-effective population size" — do the figures make sense?

In Schweinsberg's model, we have

$$\text{pair coalescence prob. } c_N \sim C \times N^{1-\alpha}$$

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Using $\mu = 250 \times 1.85 \cdot 10^{-7}$ (Árnason, 2004), $\widehat{\alpha} = 1.5$, $\widehat{r} = 1$ (and, ad hoc, $m = 2$), this gives

$$\widehat{N}_{\text{eff},\alpha=1.5} \approx 3.2 \cdot 10^8$$

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By contrast, using a Wright-Fisher model and $N_{\text{eff},\alpha=2} \times \mu = r$, we have (using $\widehat{r}_{\alpha=2} = 2$): $$\widehat{N}_{\text{eff},\alpha=2} \approx 4.3 \cdot 10^4.$$

Summary & Outlook

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> For many species, *the* coalescent with multiple mergers might be a better null model than Kingman's coalescent.

- For panmictic fixed-size discrete generations populations, haploid neutral one-locus theory is "mathematically complete".
- Tools for estimation exist, results point towards "non-Kingman-ness" in certain cases.
- Statistical properties of estimators?
- speed-up of computer-intensive methods?
  - combinations between IS-methods possible
  - "Double-HUW" scheme: ask all pairs of mutations what to do
- A good class of alternative models? In particular, true diploid models?
- Application to scenarios with selection?

Thank you for your attention!