ABCDE Approximate Bayesian Computations Done Exactly: Experiments with the Site Frequency Spectrum

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- **Solution**: Approximate Inference from Summaries of $\mathcal{D}_o$

Outline

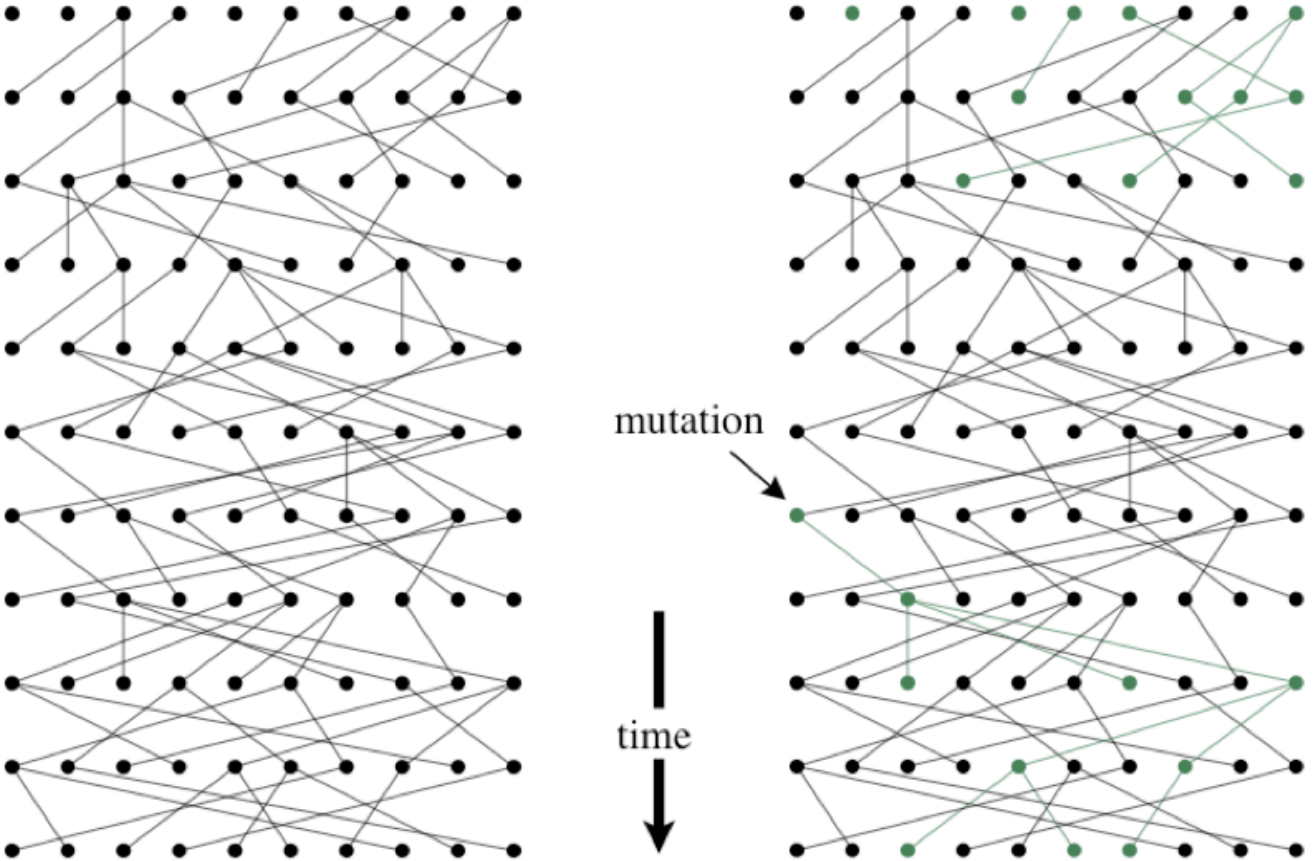
- Wright-Fisher Model – vanilla version
- The n-Coalescent Approximation
- Computationally Intensive Likelihoods
- A Paritllay-ordered Coalescent Experiments Graph
- Unlabeled n-Coalescent
- Likelihood of SFS
- Controlled Lumped Coalescent
- Results
- Summary
- Acknowledgments

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  : ...
```

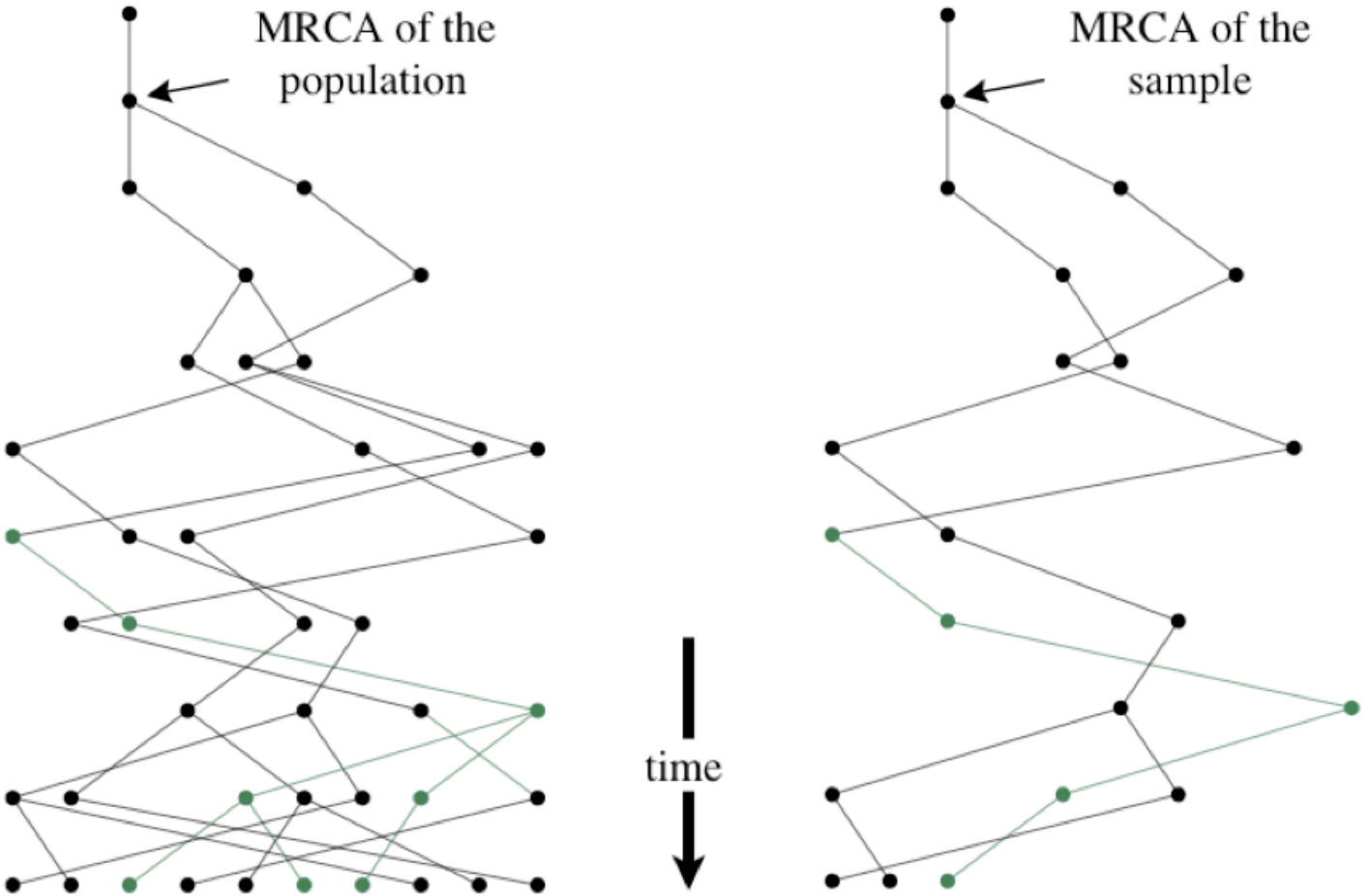


The Wright-Fisher Model – 2

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 $t_i, i \in \{3,2\}$.

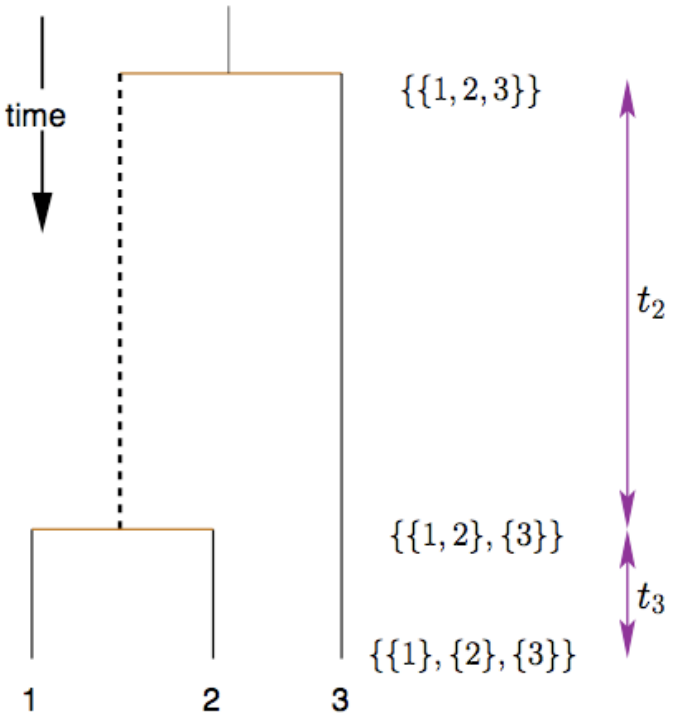
- Offspring "choose" parents uniformly and independently in W-F model
- $\Pr(2 \text{ lineages coalesce in } 1 \text{ generation}) = 1/N$
- $\Pr(2 \text{ lins. are distinct} > g \text{ gens.}) = (1-1/N)^g$
- Rescaled time t is g in units of N gens. Then, $\Pr(2 \text{ lins. remain distinct} > t)$ is

$$(1-1/N)^{\lfloor Nt \rfloor} \overset{N\to\infty}{\longrightarrow} e^{-t}$$

- 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.



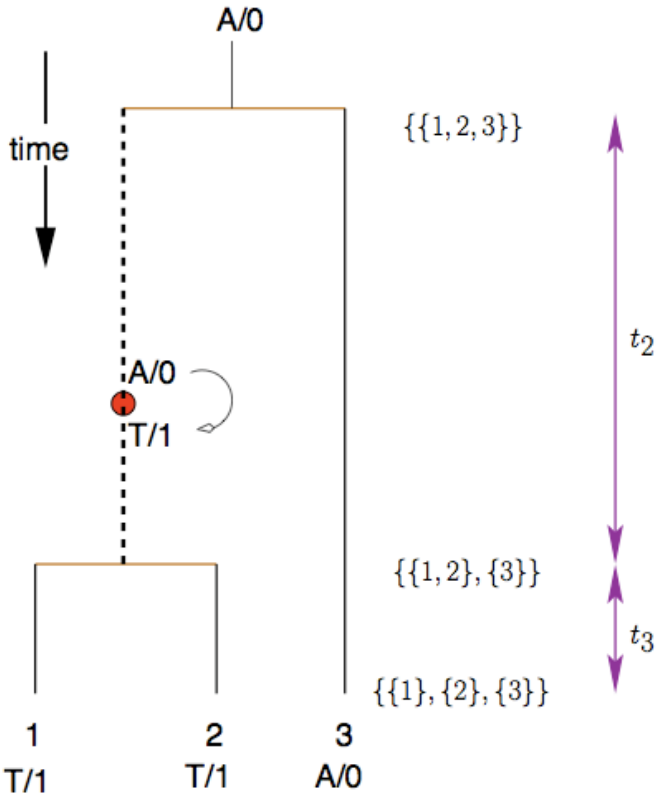
The Coalescent Approximation of the Wright-Fisher (W-F) Model (Kingman, 1982)

- The n-Coalescent is a continuous time Markov Chain on $\mathbb{C}_n \equiv \cup_{i=1}^{n} \mathbb{C}_n^i$, the set partitions of $\{1, \ldots, n\}$, 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 $c = (c_n, c_{n-1}, \ldots, c_1) \in \mathcal{C}_n$

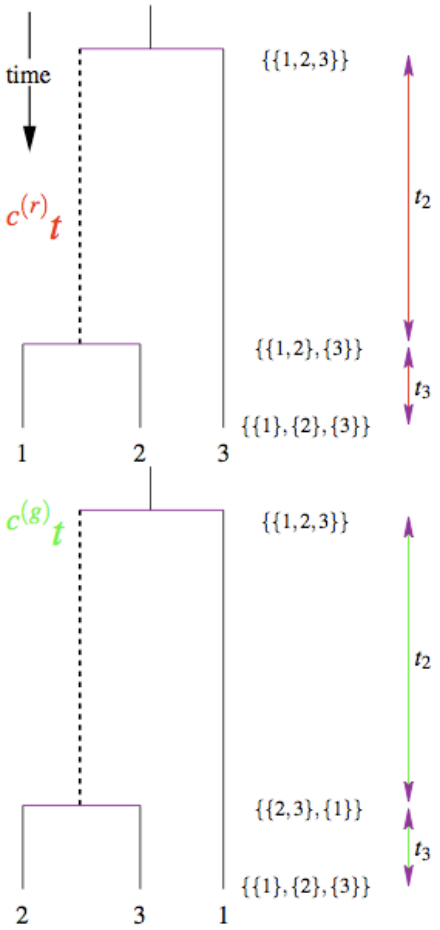


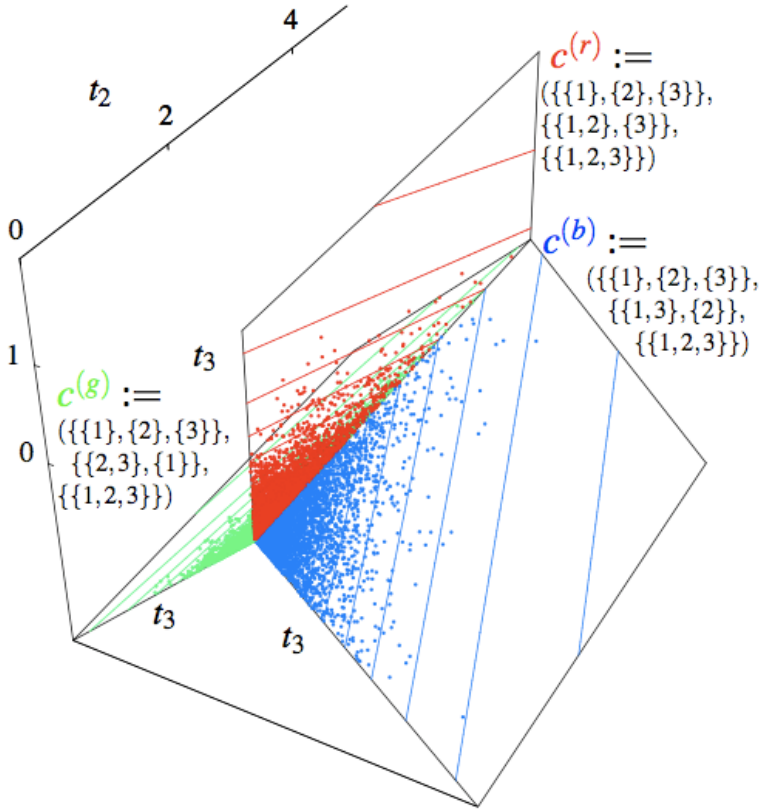
- Superimpose indep. mutations $\sim Poisson(\theta/2 \equiv 2N\mu)$

∞-many-sites mutation model

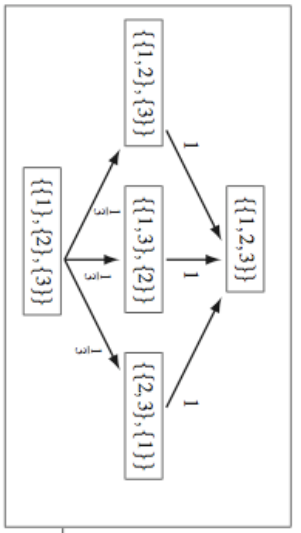
The n-Coalescent for $n = 3$

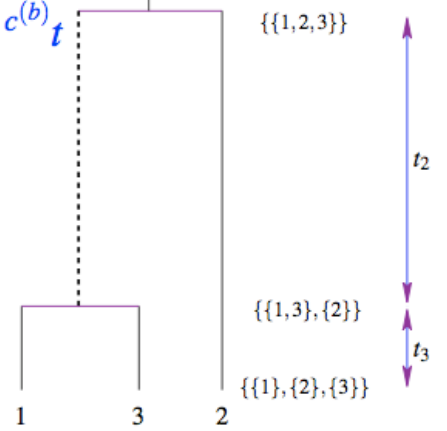
One Parameter: $\phi := (\theta) \in \Phi$, $\theta = 4N_e\mu$



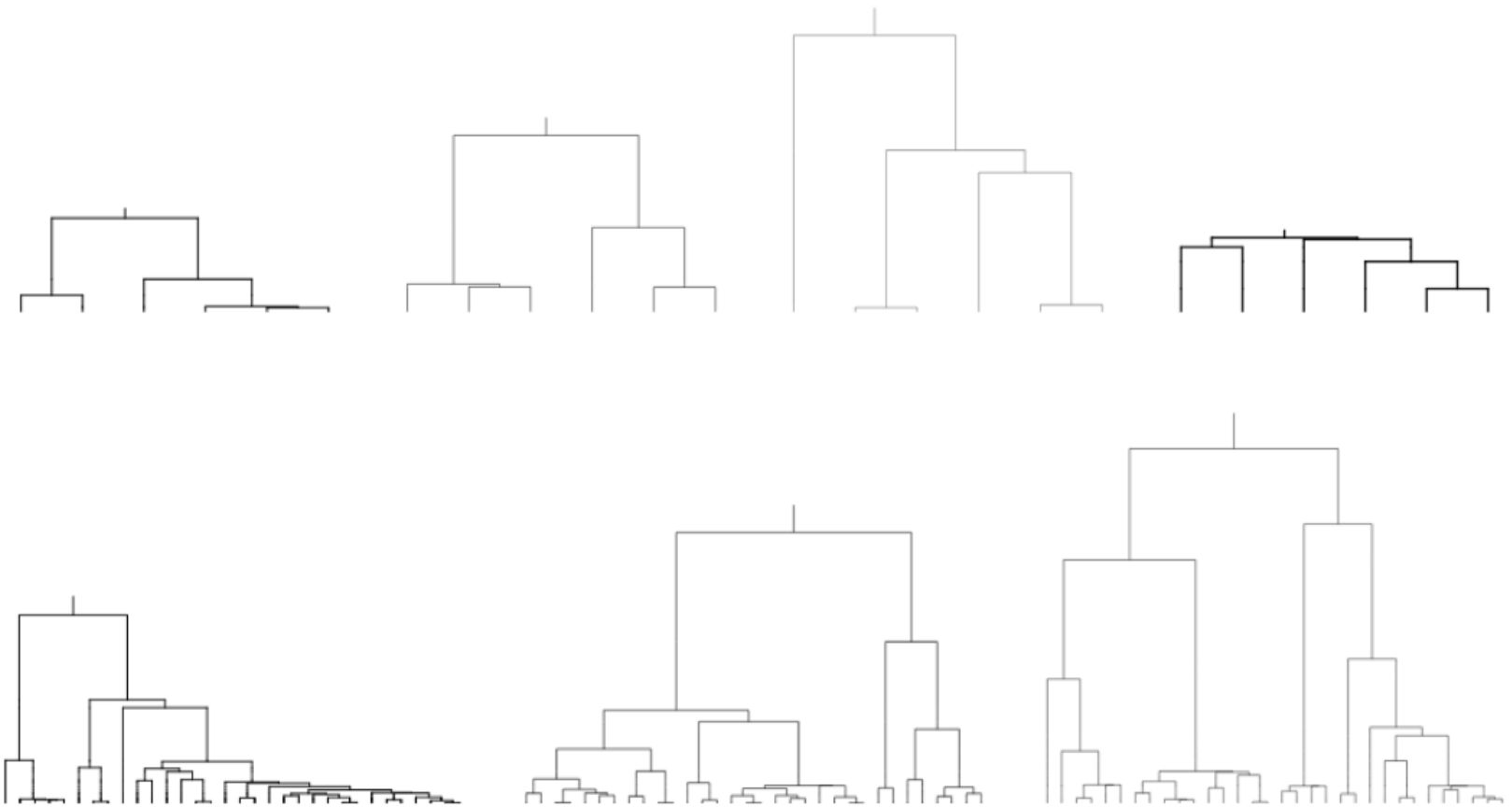


$$\mathscr{C}_3\mathbb{T}_3 := \mathscr{C}_3 \otimes \mathbb{T}_3 = \mathscr{C}_3 \otimes (0,\infty)^2$$





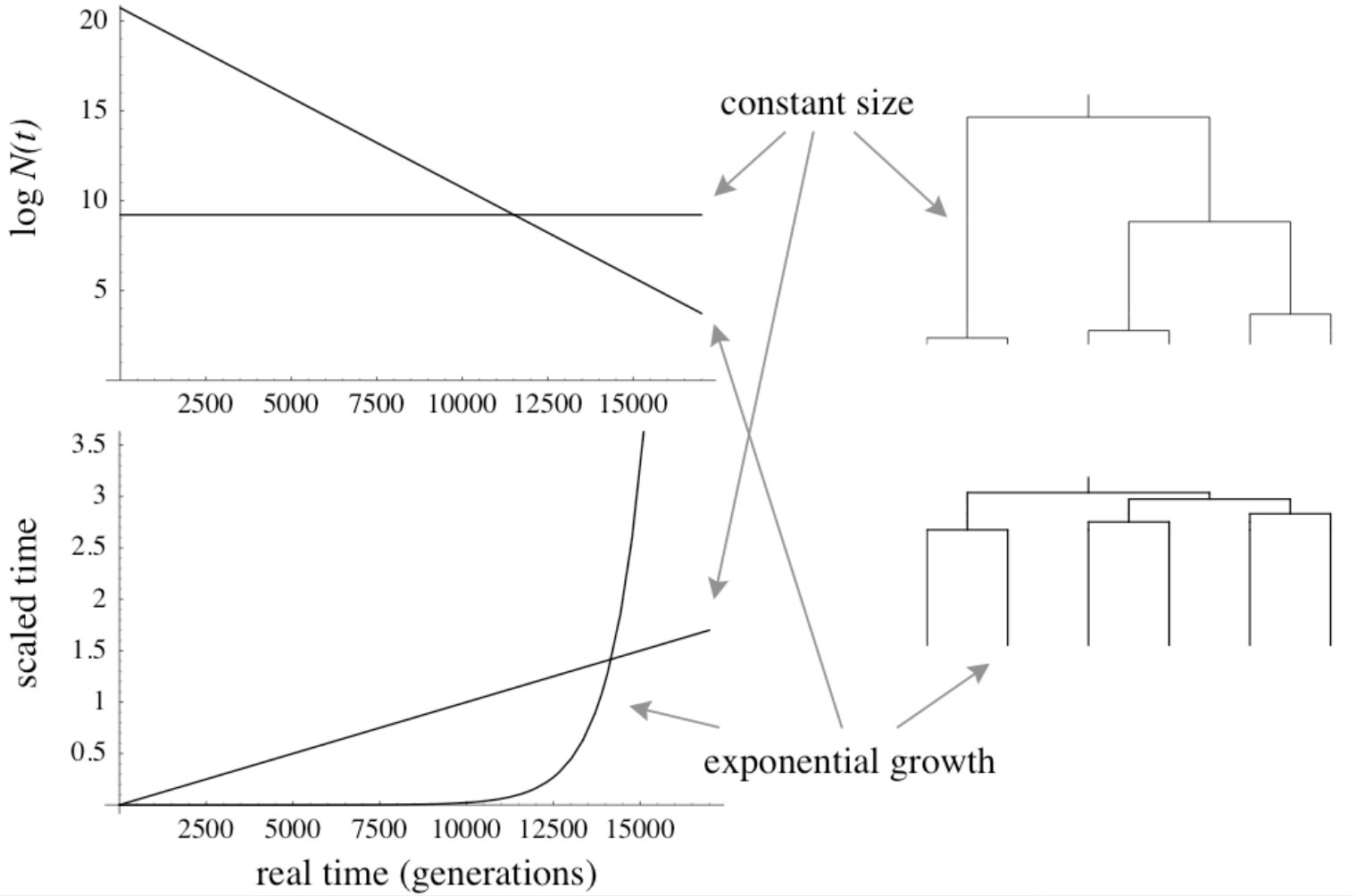
Realisations from the n-Coalescent for $n = 6$ and $n = 32$



The Coalescent with Exponential Growth – Model 2

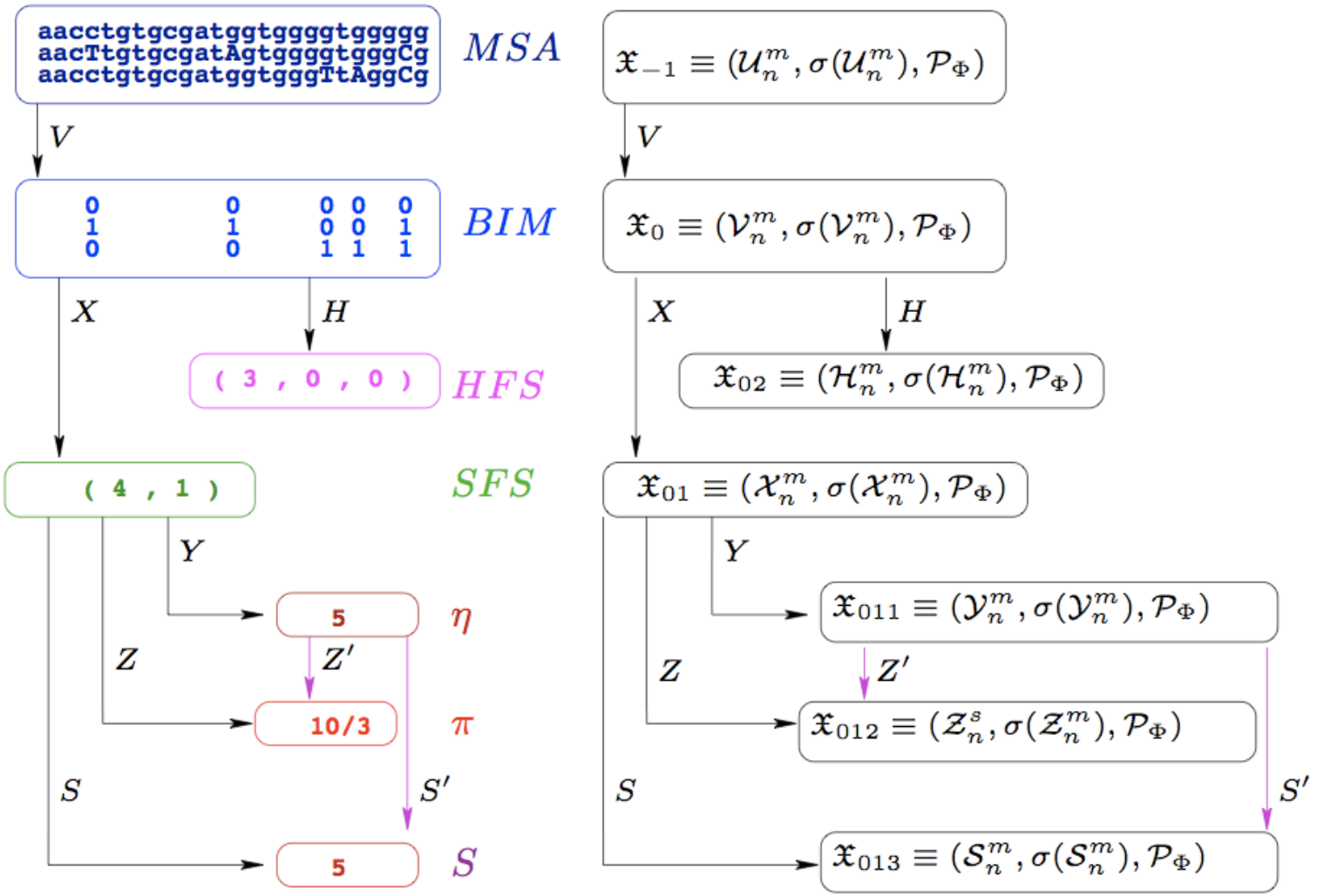
Random Mating, Exponential Growth, No Recombination/Selection

Two Parameters: $\phi := (\theta, \nu) \in \Phi$, $\theta = 4N_e\mu$



Figures 1-6 of M. Nordburg, Coalescent Theory, 2000

Partially Ordered Coalescent Experiments Graph



(1) Every directed acyclic subgraph of the POEG indexes a Martingale

(2) Each node of the POEG is a tri-sequential asymptotic family of Experiments

Likelihood

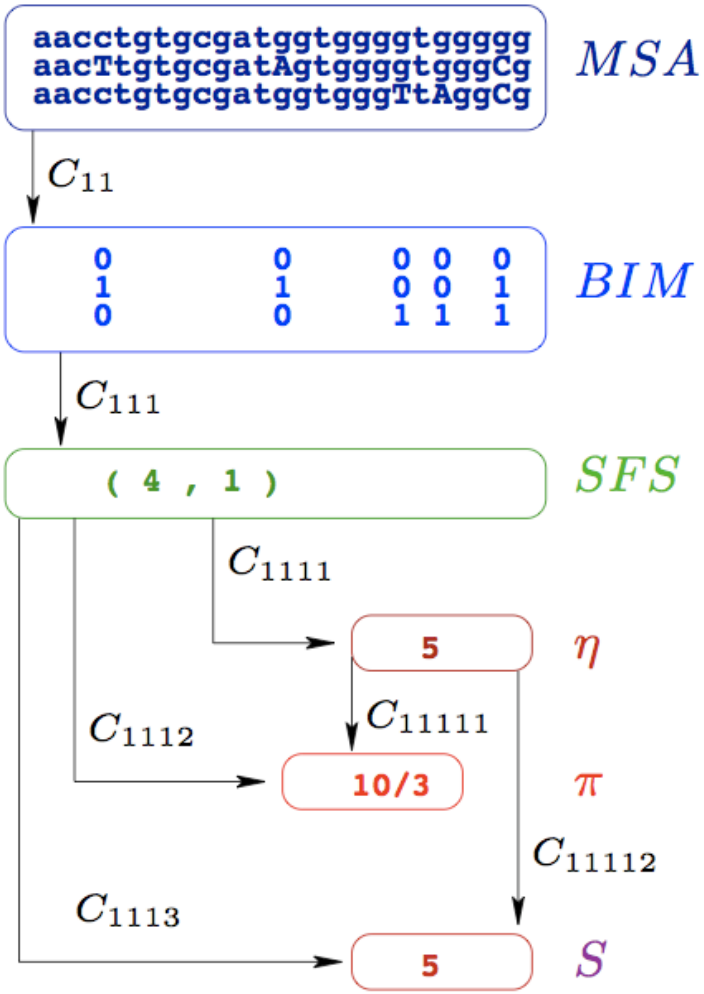
Likelihood, $P(D|\phi)$, is computed by Integrating Missing-Data:

$$\sum_{c \in \mathcal{C}_n} \int_{t \in (0,\infty)^{n-1}} P(D|c,t,\phi) P(c,t|\phi) dt \; dc$$

Cardinalities of the state spaces of the standard n-coalescent on $\mathbb{C}_n$ and the unlabeled n-coalescent on $\mathbb{F}_n$ (to be seen in the sequel).

n	4	10	30	60	90
$\lvert\mathbb{C}_n\rvert$	15	1.2×10^5	8.5×10^{23}	9.8×10^{59}	1.4×10^{101}
$\lvert\mathbb{F}_n\rvert$	5	42	5.6×10^3	9.7×10^5	5.7×10^7
$\lvert\mathbb{F}_n\rvert / \lvert\mathbb{C}_n\rvert$	0.33	3.6×10^{-4}	6.6×10^{-21}	9.9×10^{-55}	4.0×10^{-94}

Likelihood is computationally prohibitive for MSA/BIM



- Exact Methods :

  MSA $10,000$ Auto-validating i.i.d. Posterior Samples in MRS SY2006 – novel (3/4 leaved phylogenetic tree spaces) ≈ 200 CPU sec for $n <= 3$, :-($\rightarrow$ impractical for $n > 4$

  BIM Complete Recursion in PTREE G1980 (1 Locus, $\theta = 10$, C-Model 1) :-($\rightarrow$ out of stack for $n > 4$

- Approximate Methods :

  MSA MCMC in COALESCE KYF1998 : $n < 200$ & heuristic

  BIM SIS in GENETREE GT1994 : $L(\theta|v) \approxeq 4$ CPU hrs / θ

- The Bottom Line: Exact Genome Scanning at fine DNA resolution is currently impractical for $n > 4$

- A Solution: Inference at coarser empirical resolutions, eg. SFS and its sub-experiments – novel

A Currently Popular Alternative is ABC

Algorithm 3 A Simple ABC/ALC Algorithm

input:

1. a samplable distribution $P(v|\phi)$ over $\mathscr{V}_n^m$ indexed by $\phi \in \boldsymbol{\Phi}$
2. a samplable prior $P(\phi)$
3. observed data $v_o \in \mathscr{V}(v)_n^m$ and summaries $r_o = R(v_o) \in \mathscr{R}_n^m$
4. tolerance $\varepsilon \geq 0$
5. a map $\mathfrak{m} : \mathscr{R}_n^m \times \mathscr{R}_n^m \to \mathbb{R}_+$
6. a large positive integer `MAXTRIALS` $\in \mathbb{N}$

output: a sample $U \sim P(\phi|\mathbf{r}_\varepsilon(r_o)) \approxeq P(\phi|r_o) \approxeq P(\phi|v_o)$ or $\{\}$, where, $\mathbf{r}_\varepsilon(r_o) := \{r : \mathfrak{m}(r, r_o) \leq \varepsilon\}$.

initialize: `TRIALS` $\leftarrow 0$, `SUCCESS` $\leftarrow$ `false`, $U \leftarrow \{\}$

repeat

  $\phi \leftarrow P(\phi)$ {DRAW from Prior}

  $v \leftarrow P(v|\phi)$ {SIMULATE data}

  $r \leftarrow R(v)$ {SUMMARIZE data}

  if $\mathfrak{m}(r, r_o) \leq \varepsilon$ **then** {COMPARE summaries and ACCEPT/REJECT parameter}

    $U \leftarrow \phi$, `SUCCESS` $\leftarrow$ `true`

  end if

  `TRIALS` $\leftarrow$ `TRIALS` $+ 1$

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8: **if** $\mathfrak{m}(r, r_o) \leq \varepsilon$ **then** {COMPARE summaries and ACCEPT/REJECT parameter}
9: $U \leftarrow \phi$, `SUCCESS` $\leftarrow$ `true`
10: **end if**
11: `TRIALS` $\leftarrow$ `TRIALS` $+ 1$
12: **until** `TRIALS` $\geq$ `MAXTRIALS` or `SUCCESS` $\leftarrow$ `true`
13: **return:** U

- PROBLEM 1: but what is approximately sufficient?

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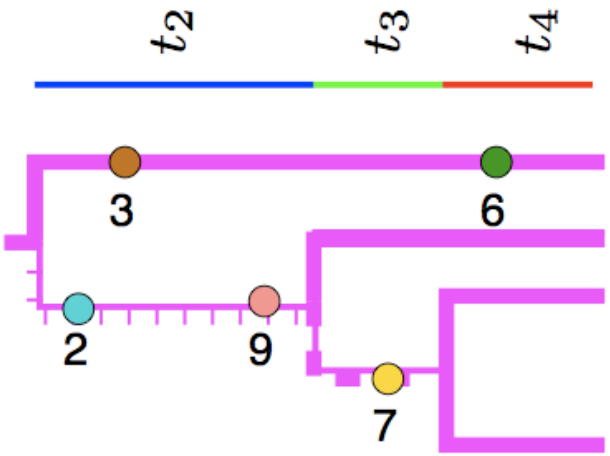
return: U

- PROBLEM 1: but what is approximately sufficient?
- PROBLEM 2: the "epsilon-dilemma" —ABCDE Fixes 1 & 2

∞-many-sites M-Model: BIM $v \in \mathcal{V}_n^m \to$ SFS $x \in \mathcal{X}_n^m$

Let $v \in \mathcal{V}_n^m \equiv \{0,1\}^{n \times m}$ be a BIM, then the SFS
$x \equiv (x_1, \ldots, x_{n-1}) \in \mathcal{X}_n^m \equiv \{x \in \mathbb{Z}_+^{n-1} : \sum_{i=1}^{n-1} x_i \leq m\}$

$$x_i = N_i(v^T \cdot (1,1,\ldots,1)), \qquad N_i(y_1, y_2, \ldots, y_s) = \sum_{j=1}^{s} \mathbf{1}_{\{i\}}(y_j), \qquad i = 1, \ldots, n-1.$$

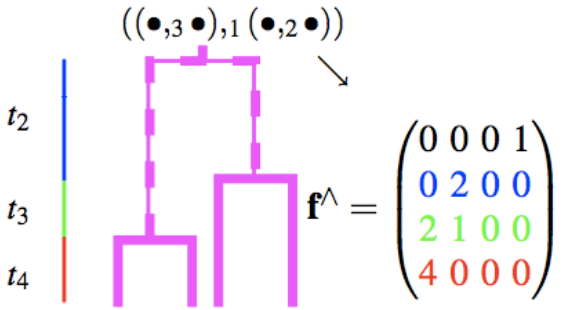


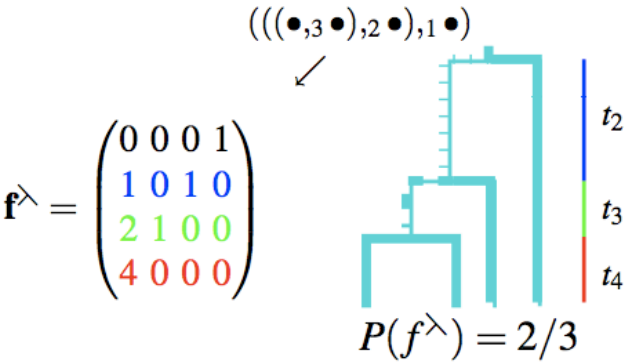
BIM $v \in \mathcal{V}_4^9$

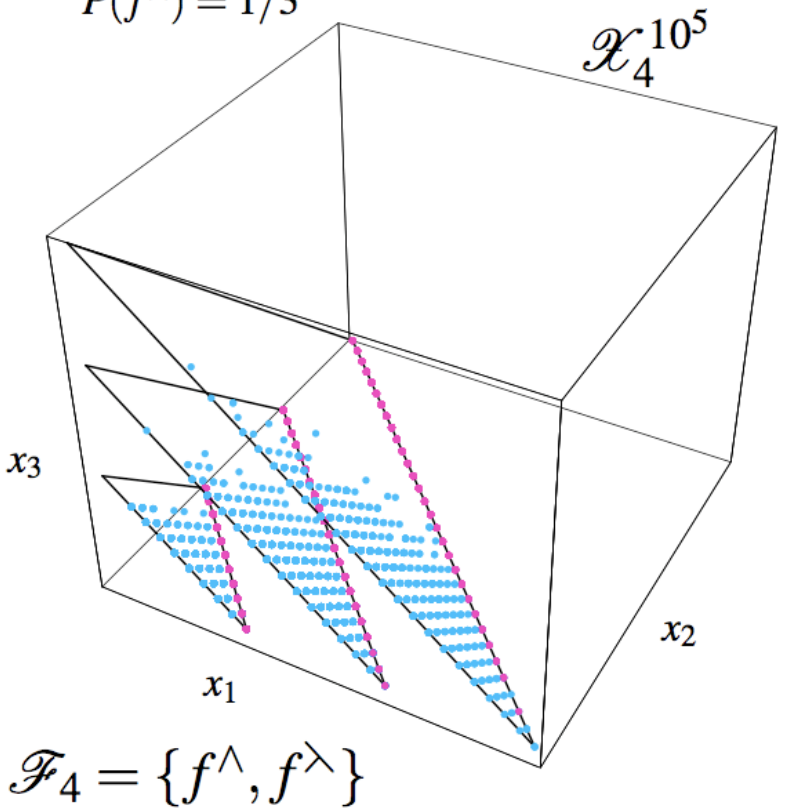
SITES:	1	2	3	4	5	6	7	8	9
IND 1:	0	0	1	0	0	1	0	0	0
IND 2:	0	1	0	0	0	0	0	0	1
IND 3:	0	1	0	0	0	0	1	0	1
IND 4:	0	1	0	0	0	0	1	0	1
COL +:	0	3	1	0	0	1	2	0	3

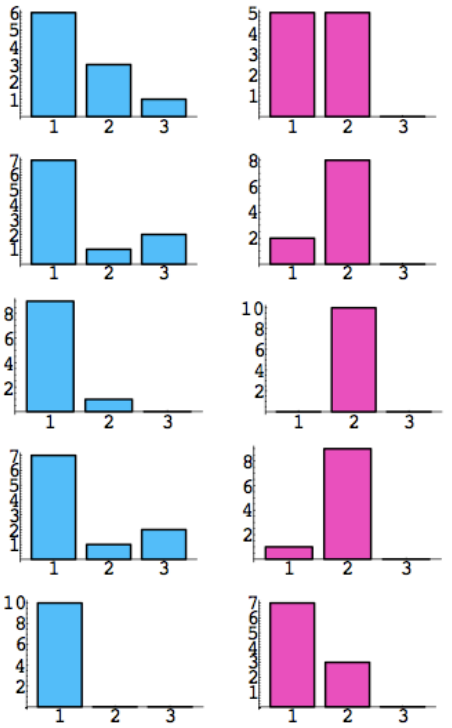
SFS $x = (x_1, x_2, x_3) = (2, 1, 2) \in \mathcal{X}_4^9$

Coalescent Tree Shape, f-Sequence and SFS



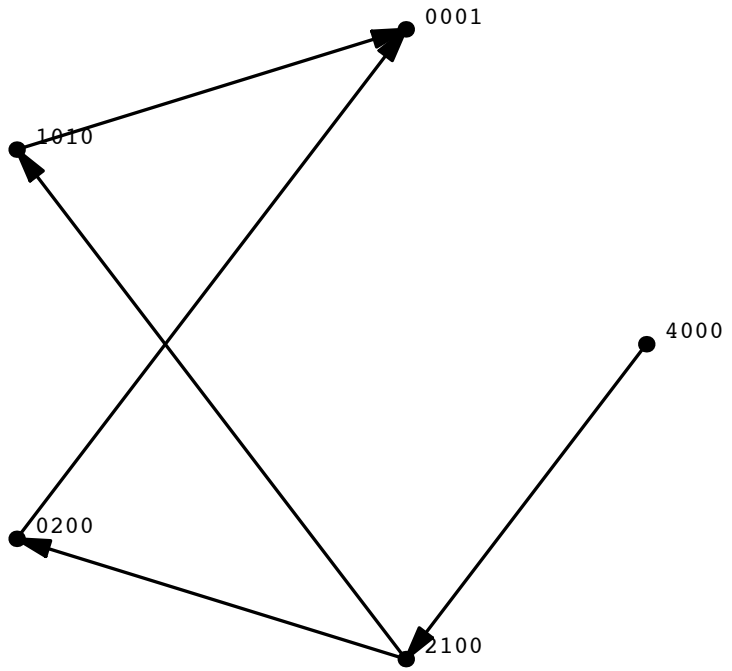




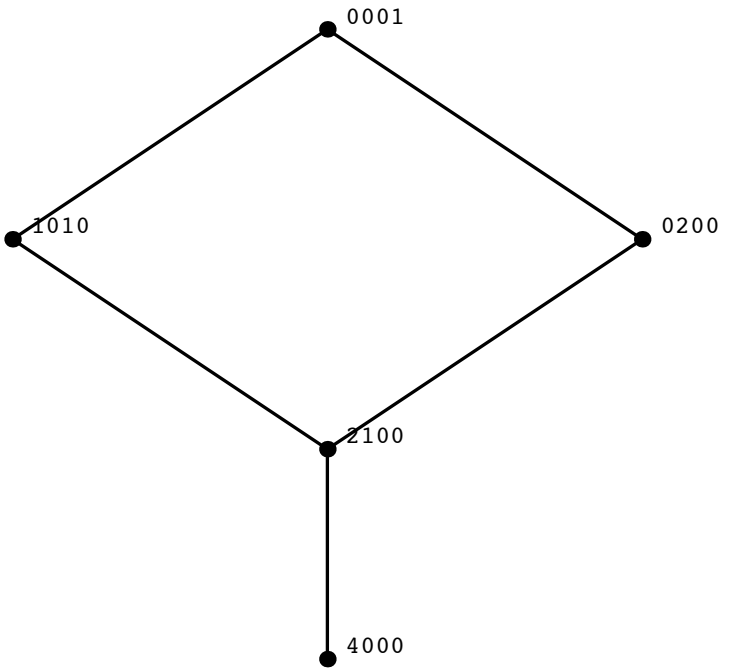


Examples of c-sequence $\rightarrow$ f-sequence, when $n = 4$

Transition-Diagram

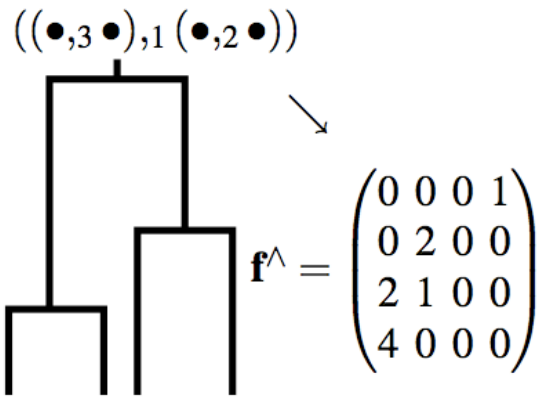


Hasse-Diagram

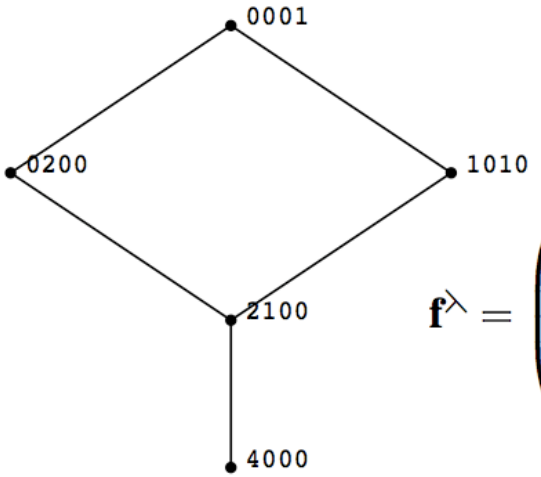


Ex 1:
$[\{1\},\{2\},\{3\},\{4\}], [\{1,2\},\{3\},\{4\}], [\{1,2,3\},\{4\}], [\{1,2,3,4\}] \rightarrow$
$[(4,0,0,0), (2,1,0,0), (1,0,1,0), (0,0,0,1)]$
Ex 2:
$[\{1\},\{2\},\{3\},\{4\}], [\{1,2\},\{3\},\{4\}], [\{1,2\},\{3,4\}], [\{1,2,3,4\}] \rightarrow$
$[(4,0,0,0), (2,1,0,0), (0,2,0,0), (0,0,0,1)]$

Transition Diagram for realisations in $\mathcal{F}_n$ $(n = 4)$



$$\mathbf{f}^{\wedge} = \begin{pmatrix} 0 & 0 & 0 & 1 \\ 0 & 2 & 0 & 0 \\ 2 & 1 & 0 & 0 \\ 4 & 0 & 0 & 0 \end{pmatrix}$$



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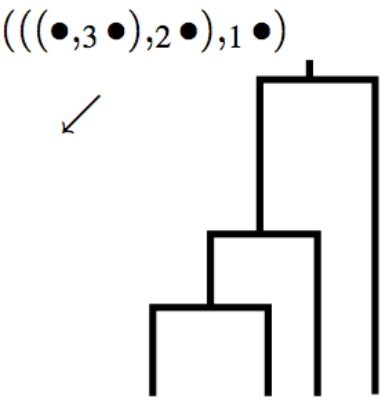
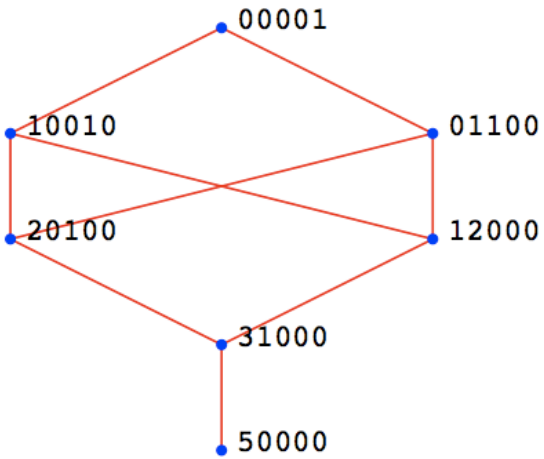
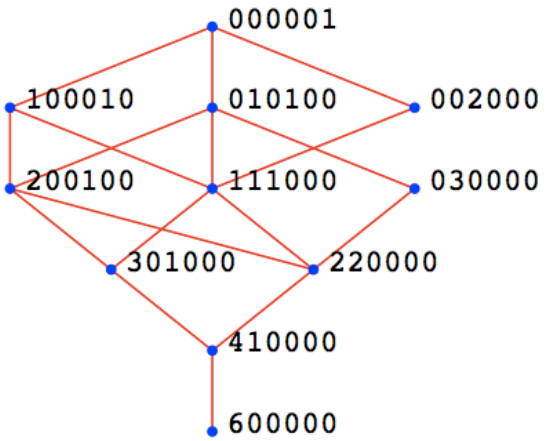
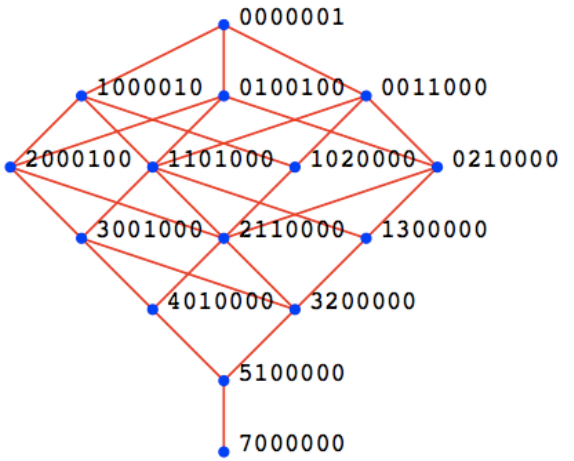
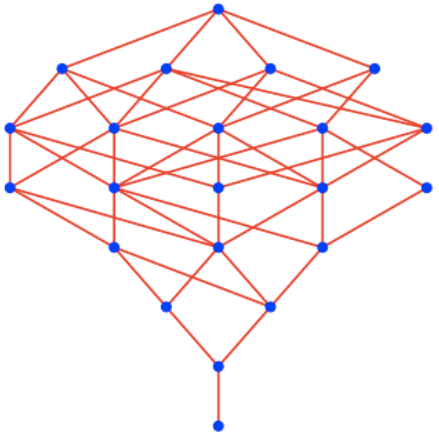


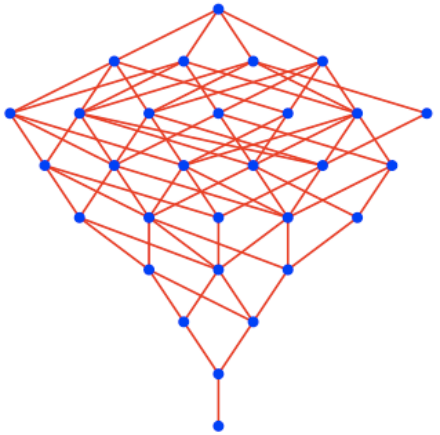
Hasse Diagram of the Poset making $\mathcal{F}_n$ $(n = 4, \ldots, 9)$

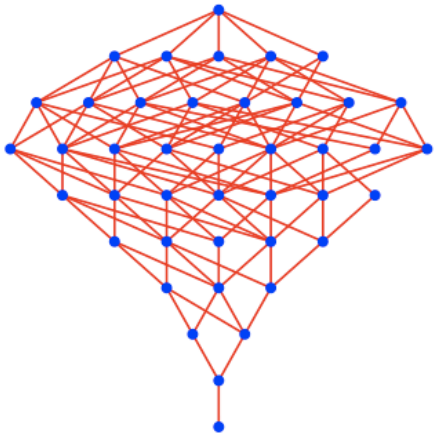












Kingman's Unlabeled n-Coalescent

Consider, the integer partitions of n with i blocks:

$$\mathbb{F}_n^i \equiv \{f_i \equiv (f_{i,1}, f_{i,2}, \ldots, f_{i,n}) \in \mathbb{Z}_+^n : \sum_{j=1}^{n} j f_{i,j} = n, \sum_{j=1}^{n} f_{i,j} = i\}.$$

where $f_{i,j}$ is the number of lineages subtending j leaves at the i-th epoch.

Theorem (Kingman's Unlabeled n-coalescent)

It is the continuous time Markov chain on $\mathbb{F}_n \equiv \cup_{i=1}^{n} \mathbb{F}_n^i$, the set of integer partitions of n, whose infinitesimal generator $\mathbf{q}(f_h|f_g)$ for any two states $f_g, f_h \in \mathbb{F}_n$ is:

$$\mathbf{q}(f_h|f_g) = \begin{cases} -i(i-1)/2 & : \text{if} \quad f_g = f_h,\ f_g \in \mathbb{F}_n^i \\ f_{g,j} f_{g,k} & : \text{if} \quad f_h = f_g - e_j - e_k + e_{j+k},\ j \neq k,\ f_g \in \mathbb{F}_n^i,\ f_h \in \mathbb{F}_n^{i-1} \\ (f_{g,j})(f_{g,j}-1)/2 & : \text{if} \quad f_h = f_g - e_j - e_k + e_{j+k},\ j = k,\ f_g \in \mathbb{F}_n^i,\ f_h \in \mathbb{F}_n^{i-1} \\ 0 & : \text{otherwise} \end{cases}$$

Initial state: $f_n = (n, 0, 0, \ldots, 0)$ and absorbing state: $f_1 = (0, 0, \ldots, 1)$.

Any realization of the chain is an f-sequence: $f = (f_n, f_{n-1}, \ldots, f_1) \in \mathcal{F}_n$.

Simulating f-sequences: for SFS, Shape Stats, ...

1: **input:**

   1. scaled mutation rate θ
   2. sample size n

2: **output:** a SFS sample x from the n-coalescent

3: generate an f-sequence under the unlabeled n-coalescent

4: draw $t \sim T = (T_2, T_3, \ldots, T_n)$, where T_i's are independently distributed as $\text{Exponential}\left(\binom{i}{2}\right)$

5: $l \leftarrow t^{\mathrm{T}} \cdot \mathrm{f}$ and $l_\bullet = \sum_{i=1}^{n-1}$

6: draw x from Poisson-Multinomial distribution $e^{-\theta l_\bullet}(\theta l_\bullet)^{\sum_{i=1}^{n-1} x_i} \prod_{i=1}^{n-1} \bar{l}_i^{x_i} / \prod_{i=1}^{n-1} x_i!$

7: **return:** x

Likelihood of a Site Frequency Spectrum

Theorem (Likelihood of SFS)

Let c, f and t be the c-sequence, f-sequence, and epoch times of tree a, then

$$l := (l_1, \ldots, l_{n-1}) = t^{\mathrm{T}} f = \left(\sum_{i=2}^{n} t_i f_{i,1}, \ldots \sum_{i=2}^{2} t_i f_{i,n-1} \right), \quad l_\bullet \equiv \sum_{i=2}^{n} l_i, \quad \bar{l}_i \equiv \frac{l_i}{l_\bullet}$$

where l is lineage lengths subtending $1, 2, \ldots, n-1$ leaves. Then:

$$P(x|\phi, a) = P(x|\phi, l = t^{\mathrm{T}} f) = e^{-\theta l_\bullet} (\theta l_\bullet)^S \prod_{i=1}^{n-1} \bar{l}_i^{x_i} / \prod_{i=1}^{n-1} x_i!$$

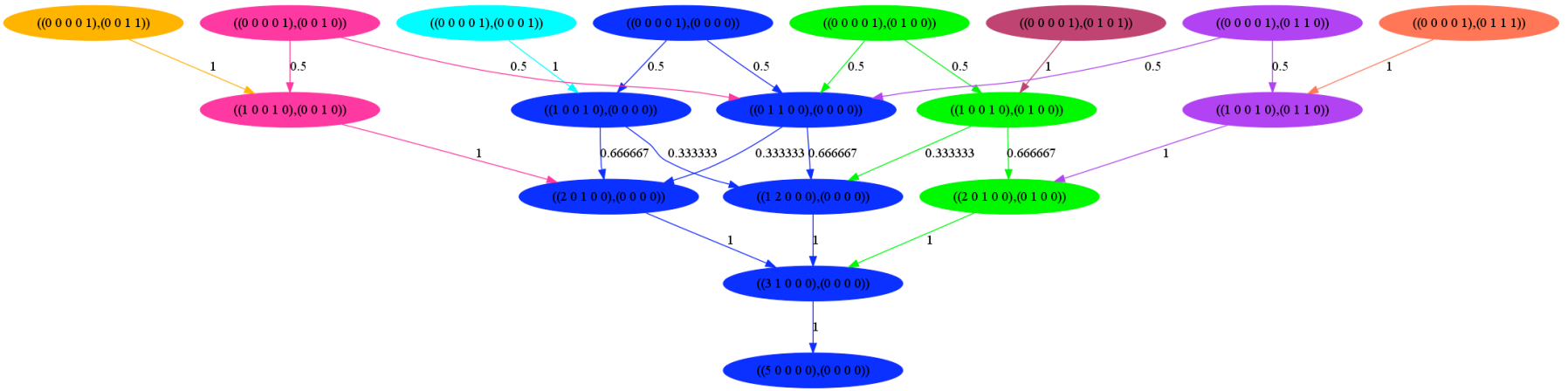
$$P(x|\phi, a) = P(x|\phi, l = t^{\mathrm{T}} f) = e^{-\theta l_\bullet} (\theta l_\bullet)^S \prod_{i=1}^{n-1} \bar{l}_i^{x_i} / \prod_{i=1}^{n-1} x_i!$$

$$P(x|\phi) = \frac{1}{\prod_{i=1}^{n-1} x_i!} \sum_{f \in F_n^c(x^\circledast)} P(f) \left(\int_{t \in (0,\infty)^{n-1}} \left(e^{-\theta l_\bullet} (\theta l_\bullet)^S \prod_{i=1}^{n-1} \bar{l}_i^{x_i} \right) P(t|\phi) \right)$$

$$\text{where,} \quad F_n(x^\circledast) \equiv \bigcup_{\{h : x_h^\circledast = 1\}} \{f \in \mathcal{F}_n : \sum_{i=1}^{n} f_{i,h} = 0\}$$

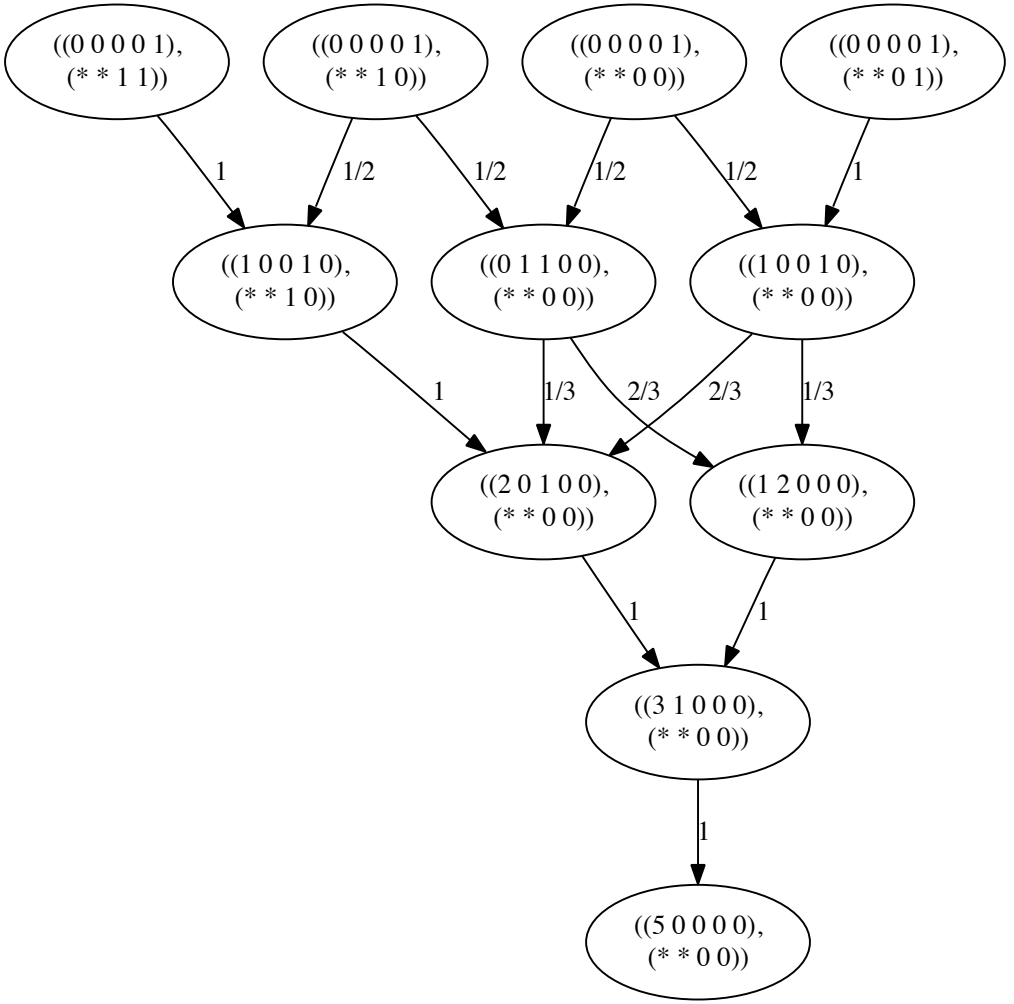
$$X^\circledast(x) = x^\circledast \equiv (x_1^\circledast, \ldots, x_{n-1}^\circledast) \equiv (\mathbf{1}_{\mathbb{N}}(x_1), \ldots, \mathbf{1}_{\mathbb{N}}(x_{n-1})) \in \{0,1\}^{n-1}$$

Transition diagram of $\{F^{\lfloor x^{\circledast}}(k)\}_{k\in[5]_+}$



Transition diagram of $\{F^{\lfloor x^{\circledast}}(k)\}_{k\in[5]_+}$ over states in $\mathbb{F}_n^{x^{\circledast}}$. The simplified diagram replaces the states that do not affect the transitions, namely, $x_1^{\circledast}$ and $x_2^{\circledast}$, with $* \in \{0, 1\}$.

Transition diagram of $\{F^{\lfloor x^{\circledast}}(k)\}_{k\in[5]_+}$



Transition diagram of $\{F^{\lfloor x^{\circledast}}(k)\}_{k\in[5]_+}$ over states in $\mathbb{F}_n^{x^{\circledast}}$. The simplified diagram replaces the states that do not affect the transitions, namely, $x_1^{\circledast}$ and $x_2^{\circledast}$, with $* \in \{0, 1\}$.

An Importance Sampler over $F_n^c(x^{\circledast})$

Theorem (A Proposal over $F_n^c(x^{\circledast})$)

For a given $x \in \mathcal{X}_n^m$, consider the following discrete time Markov chain $\{F^{\downarrow x^{\circledast}}(k)\}_{k\in[n]_+}$ on the augmented state space $\mathbb{F}_n \times \{0,1\}^{n-1} \ni (f_h, z_h)$:

$$P^*((f_h,z_h)|(f_g,z_g)) = \begin{cases} P(f_h|f_g)/\Sigma(f_g,z_g) & : \text{if} \quad (f_h,z_h) \prec_{f,z} (f_g,z_g), \\ 0 & : \text{otherwise} \end{cases}$$

where,

$$\Sigma(f_g,z_g) = \sum_{(j,k)\in H(f_g,z_g)} P(f_g - e_{j+k} + e_j + e_k | f_g),$$

$$H(f_g,z_g) = \{(j,k) : f_{g,j+k} > 0,\ 1 \le j \le \max\{\min\{\hat{g}, j+k-1\}, \lceil \frac{j+k}{2} \rceil\} \le k \le j+k-1\},$$

$$\hat{g} = \max\{i : z_{g,i} = 1\},$$

$$(f_h,z_h) \prec_{f,z} (f_g,z_g) \Leftrightarrow f_h = f_g + e_j + e_k - e_{j+k},\ z_h = z_g - \mathbf{1}_{\{1\}}(z_{g,j})\, e_j - \mathbf{1}_{\{1\}}(z_{g,k})\, e_k$$

where, the initial state is $(f_1, X^{\circledast}(x)) = ((0,0,\ldots,1), x^{\circledast})$ and the final absorbing state is $(f_n, (0,0,\ldots,0)) = ((n,0,\ldots,0),(0,0,\ldots,0))$.

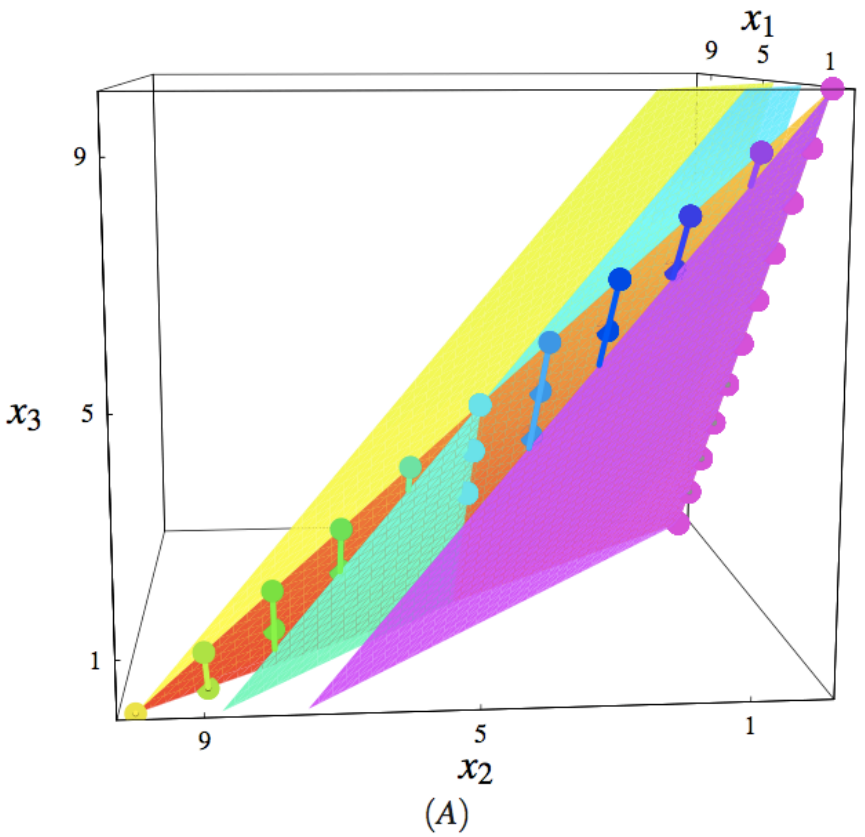
On Dangers of Topology-free Genome Scans

Table 1 10^4 loci were simulated under each hypothesised model $H_0, H_1, \ldots H_8$ and tested for the extremeness of the observed Tajima's D statistic with and without conditioning on the observed $x^{\circledast}$ in an attempt to reject the null hypothesis H_0 at significance level $\alpha = 5\%$.

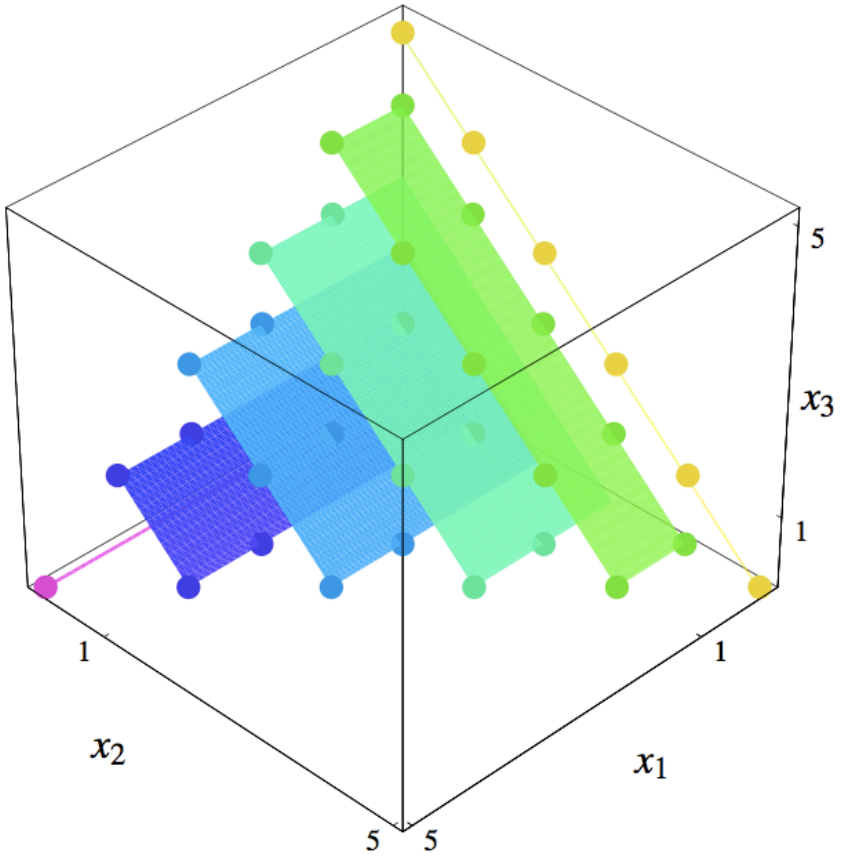
Model: parameters	Proportion of loci rejected by null distribution of test statistics			
$H_i : (m\phi_1, \phi_2, \rho)$	$P_{H_0}(D \geq d)$	$P_{H_0}(D \geq d \mid x^{\circledast})$	$P_{H_0}(D \leq d)$	$P_{H_0}(D \leq d \mid x^{\circledast})$
$H_0 : (100, 0, 0)$	0.0495	0.0501	0.0499	0.0501
$H_1 : (100, 0, 10)$	0.0074	0.8640	0.0061	0.0017
$H_2 : (100, 0, 100)$	0.0000	0.9999	0.0000	0.0000
$H_3 : (100, 10, 0)$	0.0000	0.0019	0.0326	0.1759
$H_4 : (100, 10, 10)$	0.0001	0.2023	0.0135	0.0797
$H_5 : (100, 10, 100)$	0.0000	0.5559	0.0006	0.0180
$H_6 : (100, 100, 0)$	0.0000	0.0000	0.1696	0.6882
$H_7 : (100, 100, 10)$	0.0000	0.0002	0.1580	0.6668
$H_8 : (100, 100, 100)$	0.0000	0.0020	0.1321	0.6617

Computational Commutative Algebra – another 1/2

Population Genetic Fibers from Markov bases of polytopes in SFS lattices

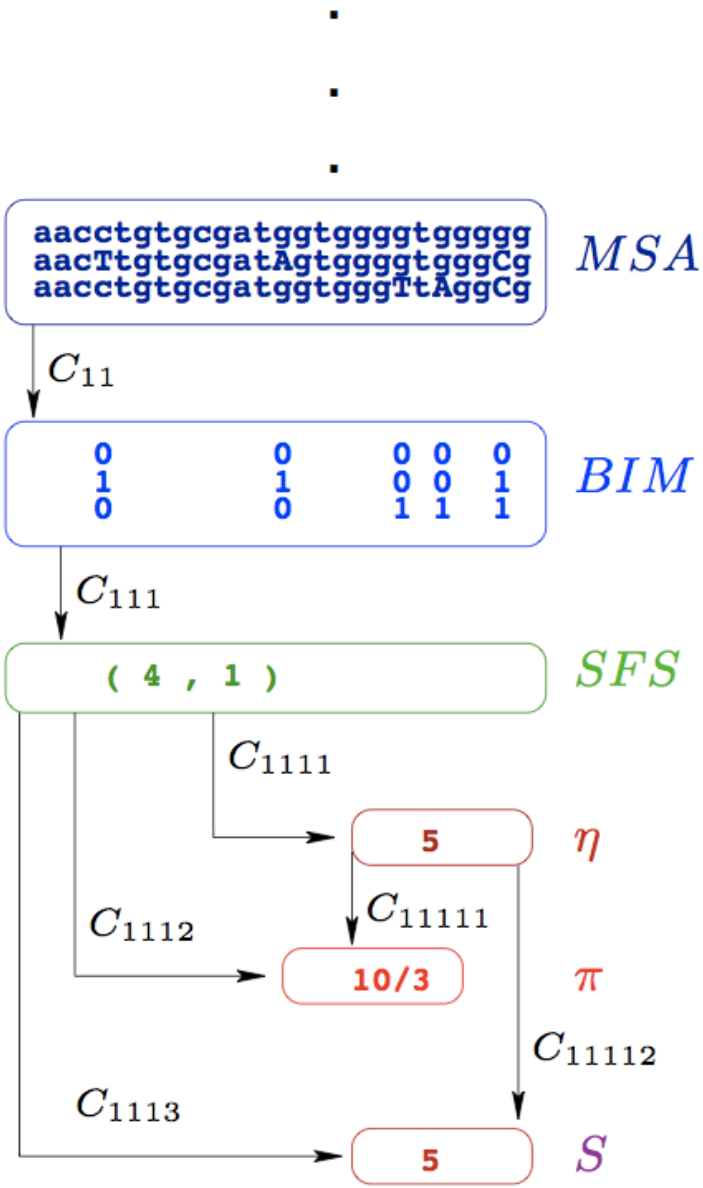


(A)



(B)

Summary



- Limits on Inference from Finest Empirical Resolutions
- Inference from Coarser Site Frequency Spectrum is Possible via a Collapsed Kingman's n-coalescent Markov chain
- Algebraic Geometry is useful to infer from classical summaries of SFS.
- MSEs are smaller – the exponential growth model
- Helps speed-up intensive SIS methods (Particle filtering on Experiment Graph)
- Topological unfolding of SFS and D $\Rightarrow$ Tree-less Genome Scans are essentially meaningless
- A Decision-theoretic formalism – partially-ordered coalescent experiments graph
- Possible to generalize
- Saves electricity and slows down global warming!

The End

- Many thanks to:
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  - Allan Wilson Centre Summur Studentship to Jenny Harlow
  - Simon Tavare and Michael Nussbaum for discussions on Approximate Sufficiency

For the Full Story See:

R. Sainudiin, K. Thornton, J. Harlow, J. Booth, M. Stillman, R. Yoshida, R. Griffiths, G. McVean and P. Donnelly *Experiments with the Site Frequency Spectrum,* Bulletin of Mathematical Biology, Algebraic Biology Special Edition, pp. 1-44, 2010. `http://www.springerlink.com/content/074896671675348 4/`.

R. Sainudiin, K. Thornton, J. Harlow and B. Bycroft, *LCE: a C++ Class Library for Lumped Coalescent Experiments*, GPL licensed, available from `http://www.math.canterbury.ac.nz/~r.sainudiin/codes/lce`, 2010.