Multiple-merger coalescents - extended models, inference methods & evidence

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joint works w.
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UNIVERSITY OF HOHENHEIM

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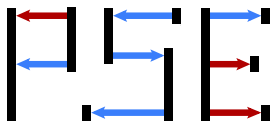

PROBABILISTIC STRUCTURES IN EVOLUTION

DFG SPP 1590

Probabilités et évolution biologique, Luminy, 28.06.2018

What do we want to infer?

Data:

Sample of size n of present-day genetic data (DNA sequences) from a population of a single species

- Can we pinpoint loci under positive selection?
- Can we infer the evolutionary history of the processes?

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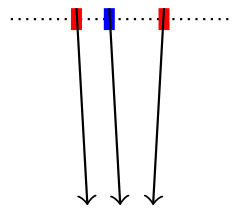
- Can we pinpoint loci under positive selection? Search for deviation of data from selectively neutral model (includes ALL other processes affecting genetic diversity)
- Can we infer the evolutionary history of the processes? Model selection between biologically reasonable models

Model the genetic diversity of n DNA SNP sequences

genetic locus (no recomb.)



0 1 1

0 1 0

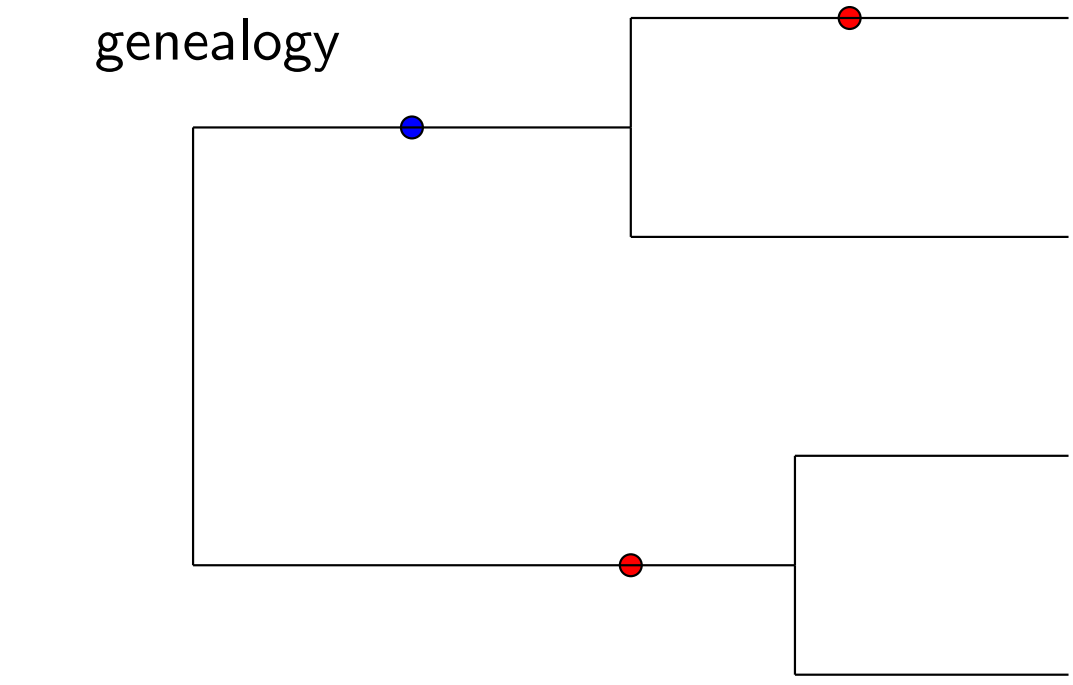
1 0 0

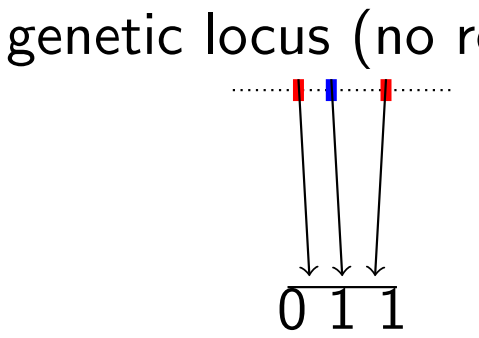
1 0 0

observed

Model the genetic diversity of n DNA SNP sequences

- Genealogy: random tree w. n leaves
- Mutation: Poisson PP w. rate $\frac{\theta}{2}$, infinite-sites m.
- Mutation is neutral: independent of genealogy





not observed

observed

Which evolutionary forces affect the genealogy?

Standard null model: Kingman's n-coalescent $\mathbb{KM}$

- Strictly bifurcating $\Leftrightarrow$ no multiple mergers
- Assumptions (robust to small deviations): Sample from large, randomly mating fixed size population, offspring distributions non-skewed (e.g. offspring/parent has bounded variance), no selection

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- Moderate population size fluctuations (e.g. exponential growth)
- Population structure
- Moderate positive selection (affects locally)
- Seed banks
- (Recombination & HGT)

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May lead to multiple mergers

- Extreme, repeated bottlenecks
- Skewed offspring distributions (Reproduction sweepstakes)
- Rapid selection
- Recurrent selective sweeps

Genealogy: (Λ-)n-coalescents with multiple mergers

Random tree: n leaves, random branch lengths. Goes backwards in time.

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1 2 3 4 5

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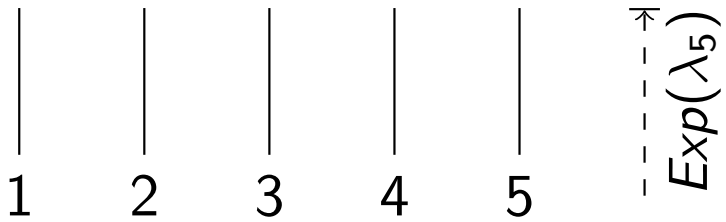

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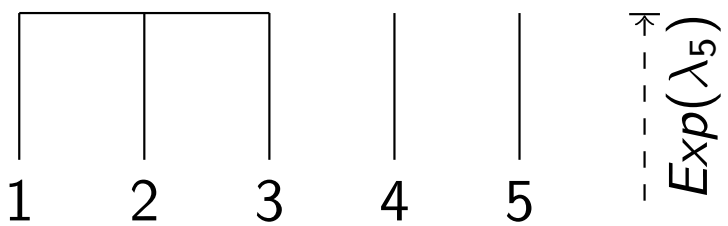

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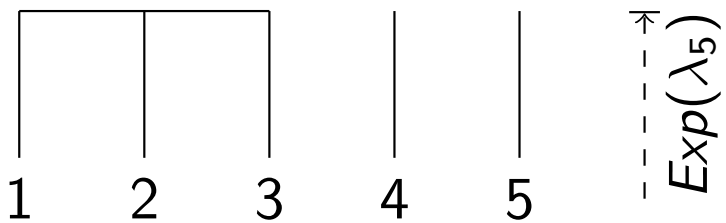

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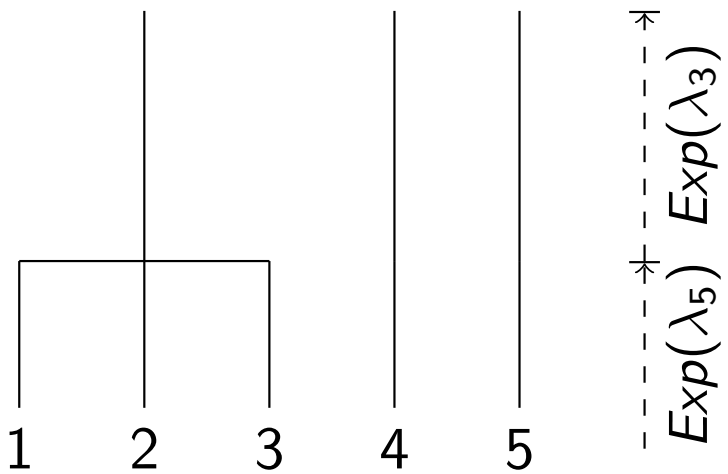

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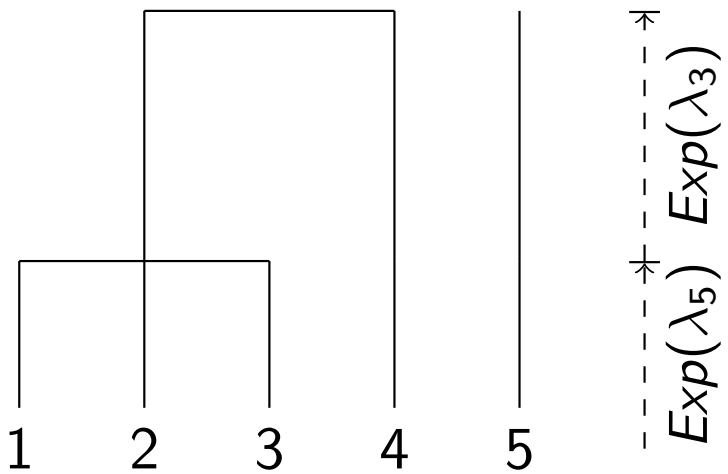

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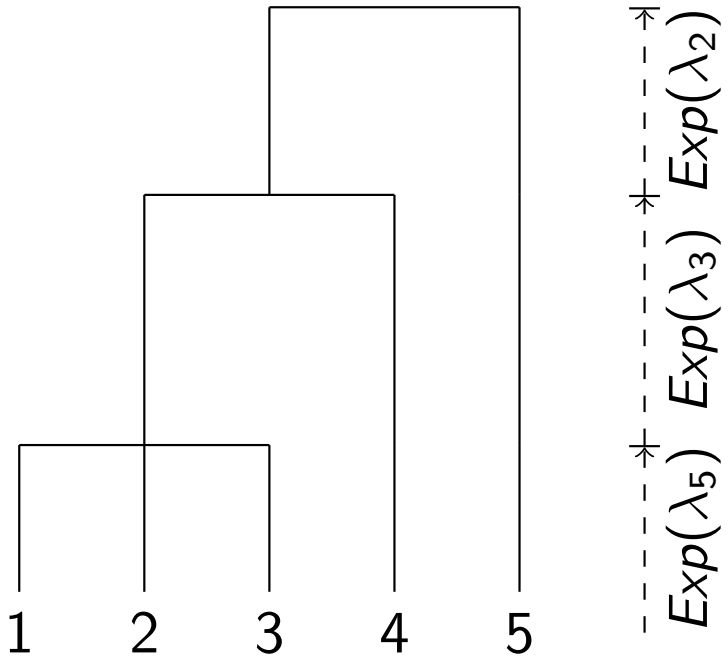

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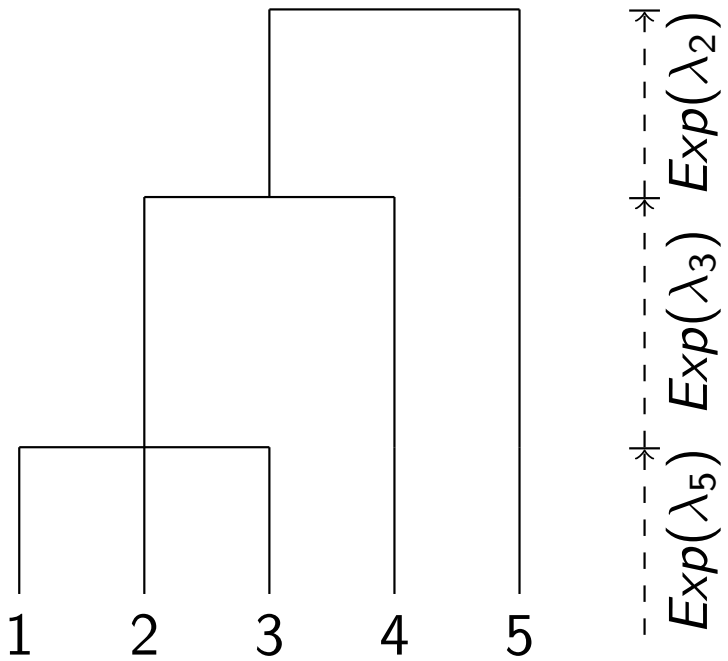

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$\lambda_{n,k} = \int x^k (1-x)^{n-k} x^{-2} \Lambda(dx)$, Λ finite measure on $[0,1]$

Beta-n-coalescents $\mathbb{BETA}$ $\Lambda = \mathcal{B}(2-\alpha, \alpha)$, $1 \leq \alpha \leq 2$

Dirac-n-coalescents $\mathbb{DIRAC}$ $\Lambda = \delta_p$ (point mass in $p \in (0,1]$)

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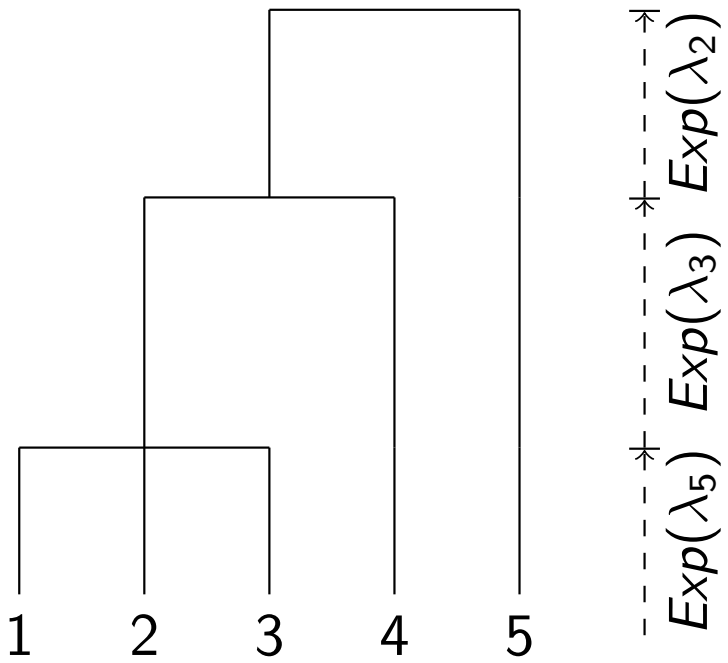

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$$\lambda_{n,k} = \int x^k (1-x)^{n-k} x^{-2} \Lambda(dx),\ \Lambda = \mathcal{B}(2-\alpha, \alpha),\ \alpha \in \{0, 1\}$$

$\alpha = 1$: Bolthausen-Sznitman n-coalescent $\mathbb{BSZ}$

$\alpha = 2$: Kingman's n-coalescent ($\Lambda = \delta_0$)$\mathbb{KM}$

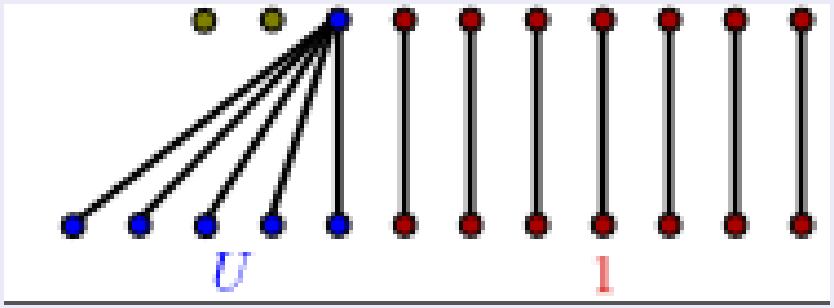
Some models with Λ-n-coalescent genealogy (Population size $N \to \infty$)

- $\mathbb{BSZ}$ (w. $+1$ to all external branch lengths): Clonal interference of equal-effect mutations [DWF13],[Sch17]
- $\mathbb{BSZ}$: Fixed-size population with increasing fitness given by a travelling wave, e.g. [BBS13],[BD13], [NH13]
- $\mathbb{BETA}$: Random sampling from a supercritical Galton-Watson process (offspring distribution heavy-tailed) [Sch03]
- $\mathbb{DIRAC}$: Modified Moran models ("lucky" individual produces 2 or U offspring) with fixed $U = \Psi N$ [EW06]
- Recurring extinction-recolonisation pattern (as # demes $\to \infty$) [TV09]

Any Λ-n-coalescent: limit genealogy of a family of modified Moran models (for $N \to \infty$) [HM13]

Adding exponential growth to multiple mergers

[MHAJ17]



from [MHAJ17]

Eldon-Wakeley model + exponential growth

- Population size back k generations: $N_k = \lfloor (1 - \frac{\Psi^2}{N^\gamma})^k \rfloor$
- Large N: $U_{N_k} = N_k \Psi 1_{\{BIG\}} + 2 \cdot 1_{\{small\}}$, $P(BIG) = 1 - P(small) = N_k^{-\gamma}$, $\Psi \in (0,1)$

For $N \to \infty$, $\gamma \in (0,2)$: Genealogy converges to a time-changed Dirac-n-coalescent $(\Pi_{\mathcal{G}_t})_{t \geq 0}$ w. $\Lambda = \delta_\Psi$ and $\mathcal{G}_t = (\rho\gamma)^{-1}(e^{\rho\gamma t} - 1)$ if one scales time in the discrete models by c_N^{-1} w. $c_N = P_N$(1,2 share parent) from the fixed model.

Proof idea: Use [Möh02]

- For the modified Moran models with changing pop. sizes, we want to lump # generations given by the pseudo-inverse $\mathcal{G}_N^{-1}(t)$ of $\sum_{r=1}^{[s]} c_{N,r}$, $c_{N,r} = P(1,2 \text{ have same parent})$ to end up at coalescent time t

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- Convergence of the time-scaled discrete models follows if

$$\lim_{N\to\infty} \sum_{r=1}^{\mathcal{G}_N^{-1}(t)} \Phi_l^{(N)}(r; a_1, \ldots, a_l) < \infty$$

$\Phi_l^{(N)}(r; a_1, \ldots, a_l) = P_{\text{gen -r,}\sum_i a_i\text{ind.}}((a_i \text{ ind. common parent})_i)$. If it has the form $q_{a_1,\ldots,a_l} t$, the limit is a time-homogeneous Markov process with rates q.

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For the modified Dirac coalescents, one gets the only non-zero limit $\lim_{N\to\infty} \sum_{r=1}^{\mathcal{G}_N^{-1}(t)} \Phi_l^{(N)}(r; a_1, \ldots, a_l) = \Psi^{k-2} t = \int x^{k-2}(1-x)^0 \delta_\Psi(dx)$ for $l = 1$ and $a_1 \geq 2$.

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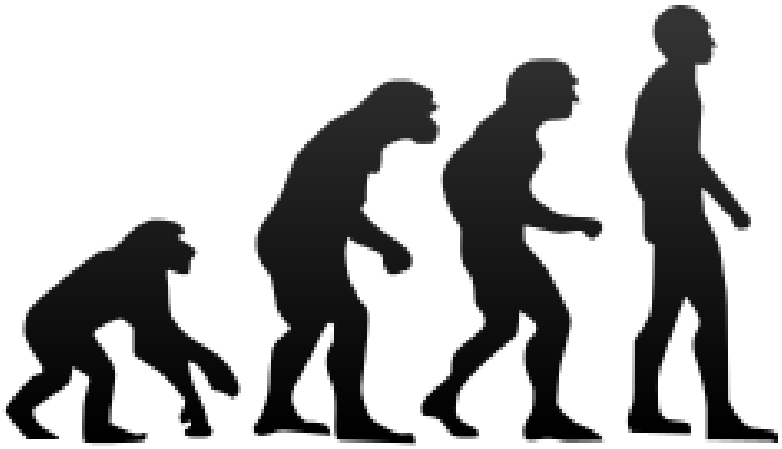
Works for other modified Moran models, too

w. S. Matuszewski, M. Lapierre, E. Kerdoncuff, A. Lambert, J. Jensen, G. Achaz, in prep.

- [HM13]: The fixed-size modified Moran model w. $P(U_N = j) = \binom{N}{j} \frac{B(j-\alpha,\alpha+N-j)}{B(2-\alpha,\alpha)}$, $j \geq 2$, has a Beta$(2-\alpha,\alpha)$-n-coalescent genealogy for $N \to \infty$
- Analogously, adding exponential growth ($N_k \sim N(1 - \frac{\rho}{N^\alpha})^k$) leads to a time-changed Beta coalescent genealogy, scaling with c_N^{-1} from the fixed N model
- [Sch03] (Fixed N): Each individual produces independent X_i offspring (heavy-tailed, $P(X_i \geq k) \sim Ck^{-\alpha}$). Next gen. randomly sampled from these.
- Adding exponential growth $N_k \sim N\left(1 - \frac{\rho}{N^{\alpha-1}}\right)^r$ again leads to a time-changed Beta$(2-\alpha,\alpha)$-n-coalescent $(\Pi_{\mathcal{G}_t})_{t\geq 0}$ with $\mathcal{G}_t = c^{-1}(e^{ct} - 1)$ for a constant c

Genealogy models $\leftrightarrow$ species

Species with non-skewed offspring distribution: Mammals, most plants,...



pictures from Wikimedia commons (users Tkgd2007,MrFrosty2)

Should lead to a bifurcating genealogy of (short) neutral loci ($\mathbb{KM}$,+growth,+pop. struct.). *Do they?*

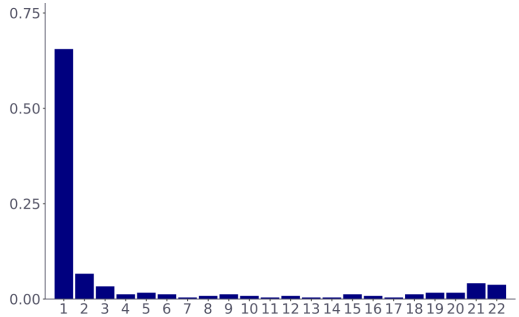
Genealogy models $\leftrightarrow$ species

Reproduction sweepstakes ($\mathbb{BETA}$):

Japanese sardine [NNY16]

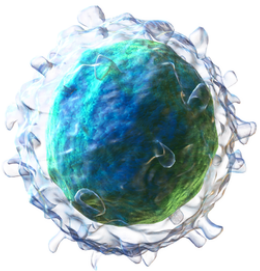
Atlantic cod [ÁH14]

with exp. growth:

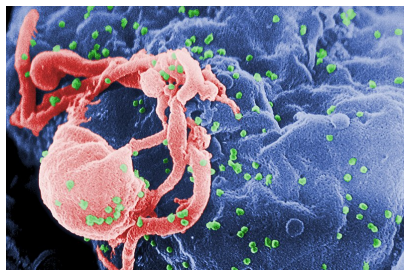


copy numbers in cancer cells [KVS$^+$17]

Candidate populations for rapid selection ($\Lambda = U_{[0,1]}$):



B-cells under HIV [NOŁ$^+$18]



HIV [ZBT$^+$15]

SeaFIC; H. Hillewaert; Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2); CDC/ C. Goldsmith, P. Feorino, E. L. Palmer, W. R. McManus

How to distinguish genealogy models

Usually, we would be interested in inferring the true (best-fitting) genealogy model, while we treat θ as a nuisance parameter

Inference approaches

- (Nearly) Full likelihood on SNP data (MCMC-based for moderate n) [SBB13],[BG00],[KJS15]...
  Slow, does not scale well w. large data sets
- Based on the site-frequency spectrum (SFS)
  $\xi_i^{(n)} :=$ # SNPs with derived allele frequency $\frac{i}{n}$, $i \in [n-1]$
  Quicker, but needs approximations and/or simulations

SFS-based inference between n-coalescents

Pseudo-likelihood approach [EBBF15], $s = \sum_i \eta_i$

Base approximate LRT on

$PsL(\xi_i^{(n)} = k_i, i \in [n-1])$

$= \frac{s!}{k_1! \cdots k_{n-1}!} \prod_{i=1}^{n-1} \left(\frac{E(\xi_i^{(n)})}{E(\sum_{j=1}^{n} \xi_j^{(n)})} \right)^{k_i}$

Assumptions:

fixed-s, $\frac{\xi_i^{(n)}}{\sum_{j=1}^{n} \xi_j^{(n)}} \approx \frac{E(\xi_i^{(n)})}{E(\sum_{j=1}^{n} \xi_j^{(n)})}$

$E(\xi_i^{(n)})$ can be computed analytically [SKS16],[PK03]

Multiple loci: Add up SFS

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Multiple loci: Add up SFS

Monte Carlo Likelihood approach [Kos17]

Perform approximate LRT for

$$\left(\frac{\xi_1^{(n)}}{\sum_{j=1}^n \xi_j^{(n)}}, \frac{\sum_{i=k}^{n-1} \xi_i^{(n)}}{\sum_{j=1}^n \xi_j^{(n)}} \right),$$

estimating the two-dimensional kernel density via simulation

Multiple loci: Use average over loci for LRT, estimate density of average

For distinguishing coalescent models, both methods are very robust if models tested misspecify θ

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Monte Carlo Likelihood approach [Kos17]

Perform approximate LRT for

$$\left(\frac{\xi_1^{(n)}}{\sum_{j=1}^n \xi_j^{(n)}}, \frac{\sum_{i=k}^{n-1} \xi_i^{(n)}}{\sum_{j=1}^n \xi_j^{(n)}} \right),$$

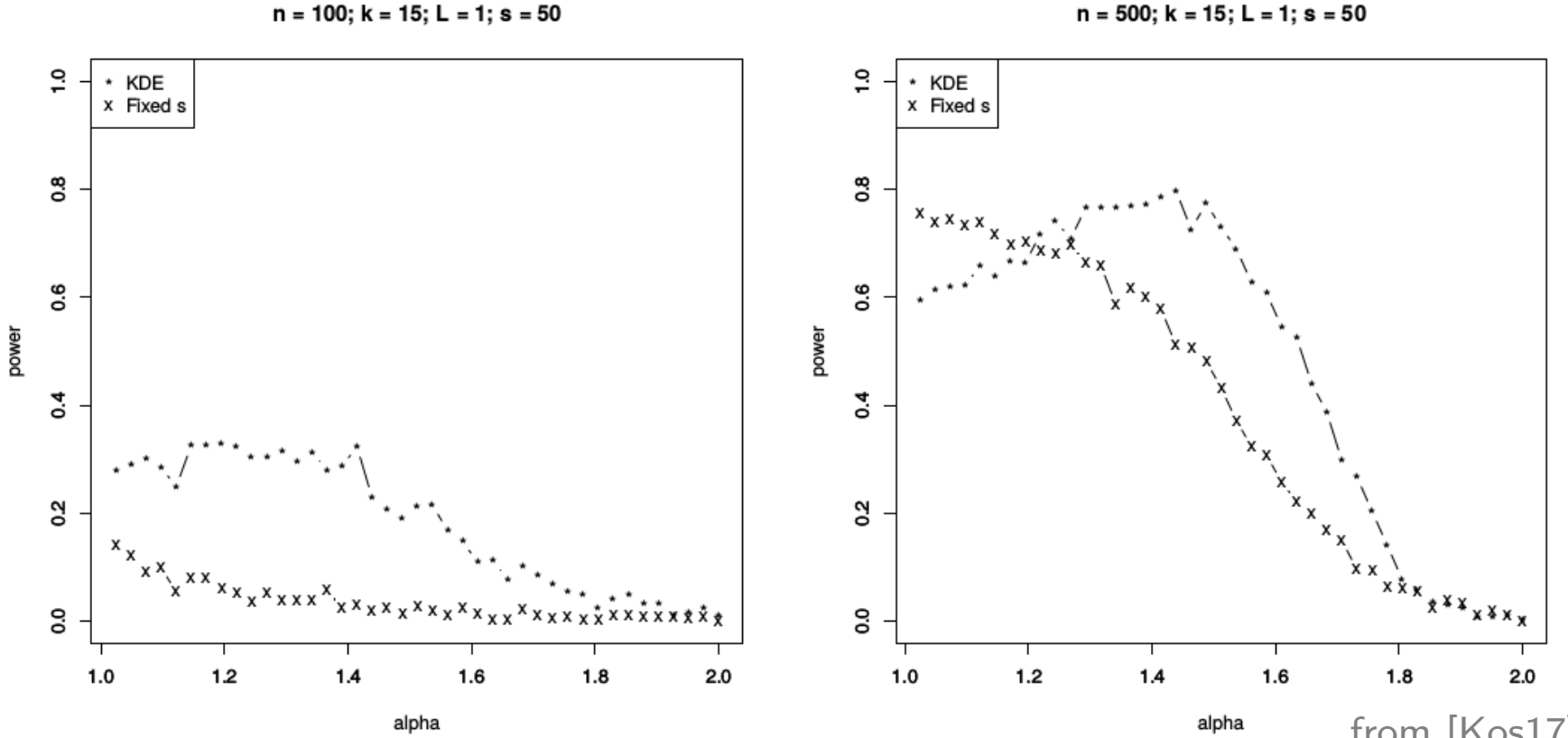
estimating the two-dimensional kernel density via simulation

Multiple loci: Use average over loci for LRT, estimate density of average

For distinguishing coalescent models, both methods are very robust if models tested misspecify θ

[Kos17] Using KDE is superior, more loci is better

H_0 : $\mathbb{KM}$ w. exp. growth, $g \in [0, 1000]$, $+.1$ near 0, $+10$ for $g \geq 40$
H_1 : Beta$(2-\alpha,\alpha)$-n-coalescent, $\alpha \in \{1, 1.025, \ldots, 2\}$



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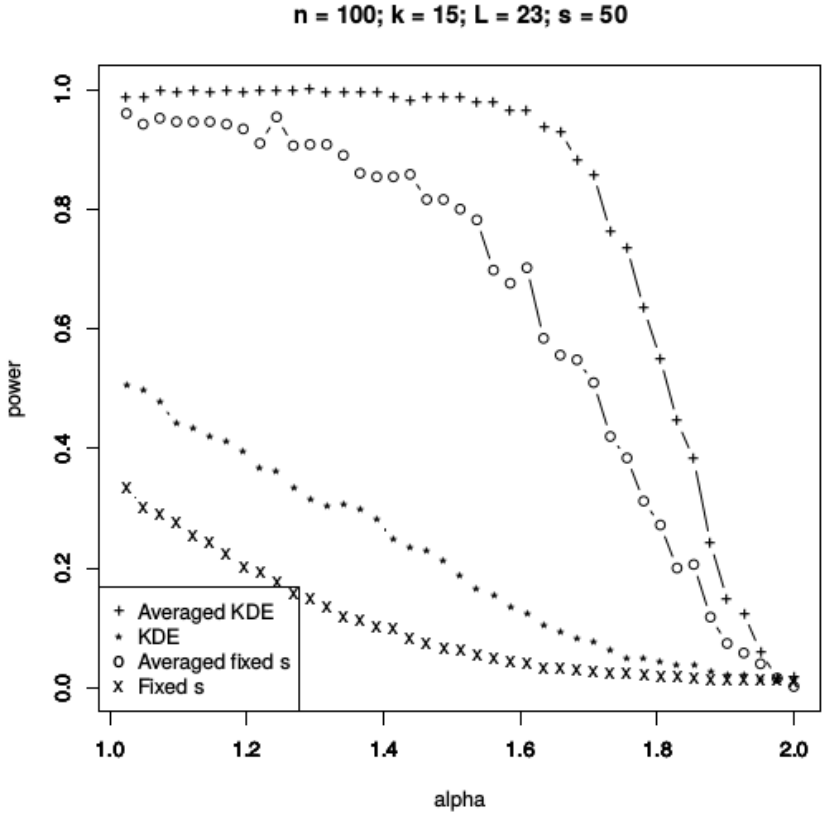

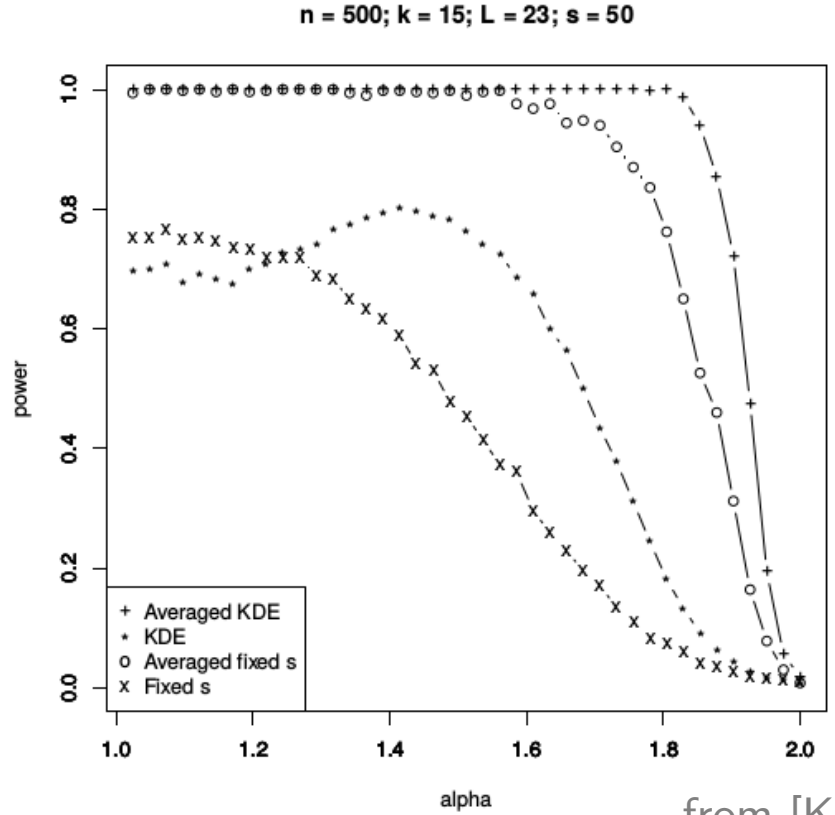

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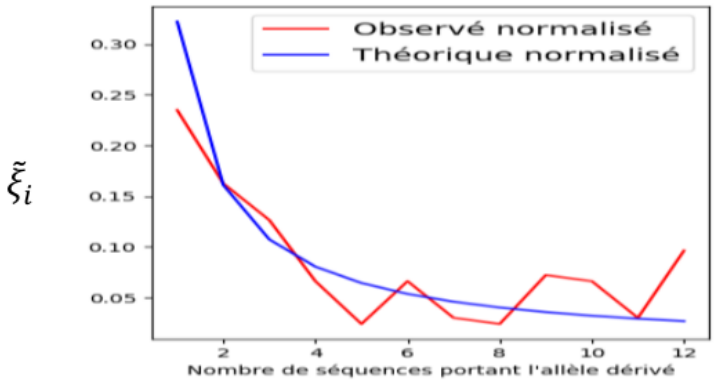
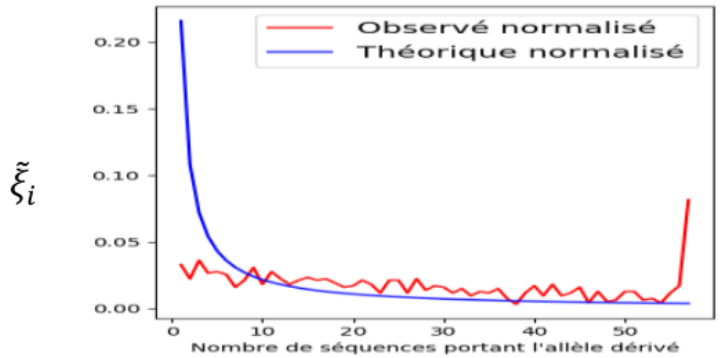
U-shaped SFS vs. genealogy models

- Collection of U/J-shaped SFS from G. Achaz' group in a diverse set of species: pill-bug, *E. coli*, *Helicobacter pylori*, cuttlefish, *A. thaliana*, shark, *Drosophila melanogaster*, humans... ($18 \leq n \leq 1214$)



Caenorhabditis elegans



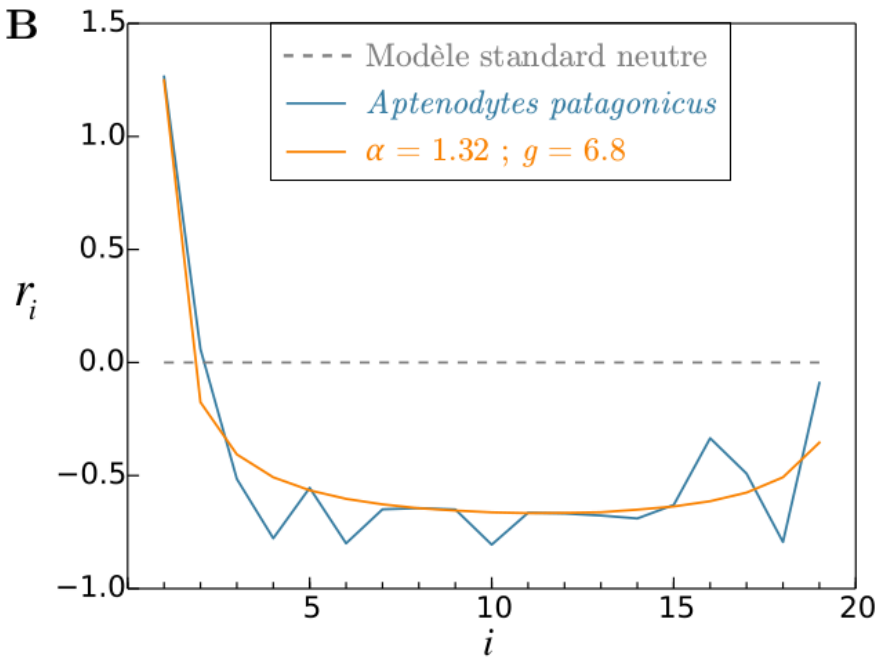
Glyphis garricki

(Graphs by R. Clodion)

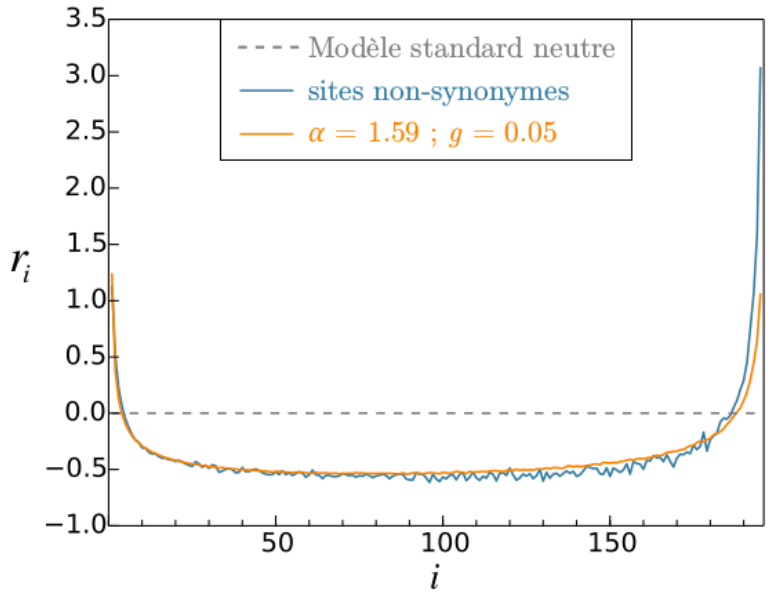
- Plots of $E(nSFS)$: expected scaled SFS $\tilde{\xi}_i := \frac{\xi_i^n}{\sum_j \xi_j^{(n)}}$
- [Lap17] Possible contributions to U/J-shape: Confusing derived and ancestral alleles (misidentification, *MI*), selection, demography, biased gene conversion, multiple-merger,...

E(nSFS) corrected for *MI*, fit to $\mathbb{BETA}$+exp. g.

- [Lap17] Correct $E(nSFS)$ for *MI*: Via outgroup, estimate *MI* prob. x, use $((1-\hat{x})\tilde{\xi}_i - \hat{x}\tilde{\xi}_{n-i})/(1-2\hat{x})$
- [Lap17], R. Clodion, E. Kerdoncuff: Multiple-merger coalescents (with exp. growth/decline) can match (*MI*-corrected) E(nSFS) rather well



D. melanogaster



$$r_i = (x_i - E_{\mathbb{KM}}(\xi_i^{(n)}))/E_{\mathbb{KM}}(\xi_i^{(n)}),$$

minimize $\sum_i \frac{(E_{\mathbb{B}exp}(\tilde{\xi}_i^{(n)}) - E_{\mathbb{KM}}(\tilde{\xi}_i^{(n)}))^2}{E_{\mathbb{KM}}(\tilde{\xi}_i^{(n)})}$

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w. S. Matuszewski, M. Lapierre, E. Kerdoncuff, A. Lambert, J. Jensen, G. Achaz

Inference using few loci: Use more statistics?

w. A. Siri-Jégousse

- SFS-based inference for few (1) loci is very noisy
- [KVS+17] report very low misclassification probabilities in an ABC approach for (essentially) $\mathbb{BETA}$+exp. growth vs. $\mathbb{KM}$+ exp. growth if additional statistics are used
  - Number of segregating sites
  - Quantiles .1,.3,.5,.7,.9 of allele frequencies
  - Quantiles .1,.3,.5,.7,.9 of pairwise Hamming distances (mismatch count)
  - Quantiles .1,.3,.5,.7,.9 of LD measured as squared correlation r^2 between SNP allele frequencies
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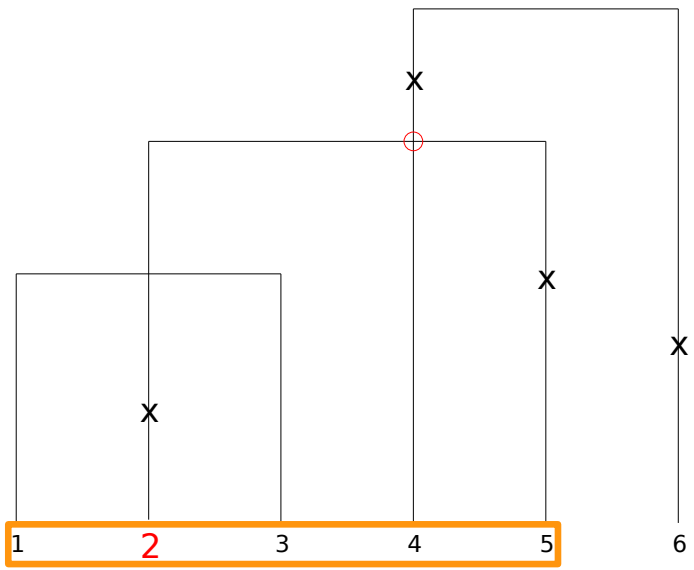
  - Quantiles .1,.3,.5,.7,.9 of total branch length of reconstructed phylogeny (e.g. neighbor-joining tree)
- Partly, low misclassification rates stem from models using identitical θ ranges (which can lead to stark differences in # segregating sites)
- If we compare models with comparable # segregating sites, do we see the same effect? Which statistics help to distinguish?

We also add a further statistic



$O_n(2)$=5

- $O_n(i) :=\#$ individuals sharing all non-private mutations of i
  Smallest family of i which can be genetically distinguished

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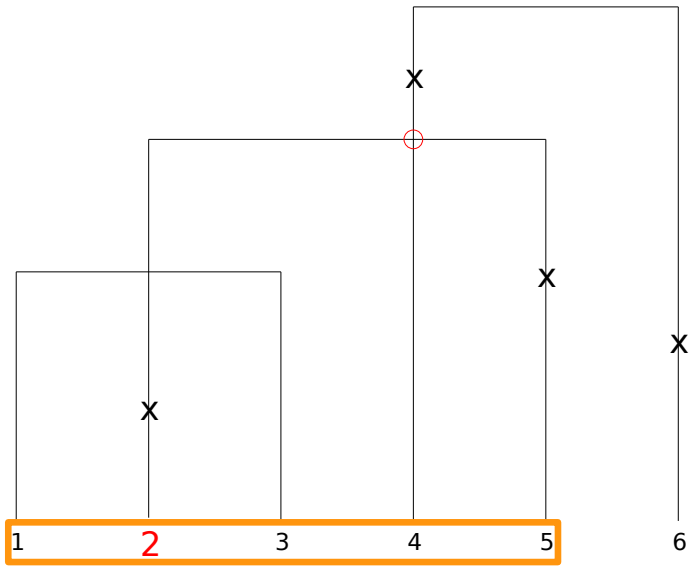

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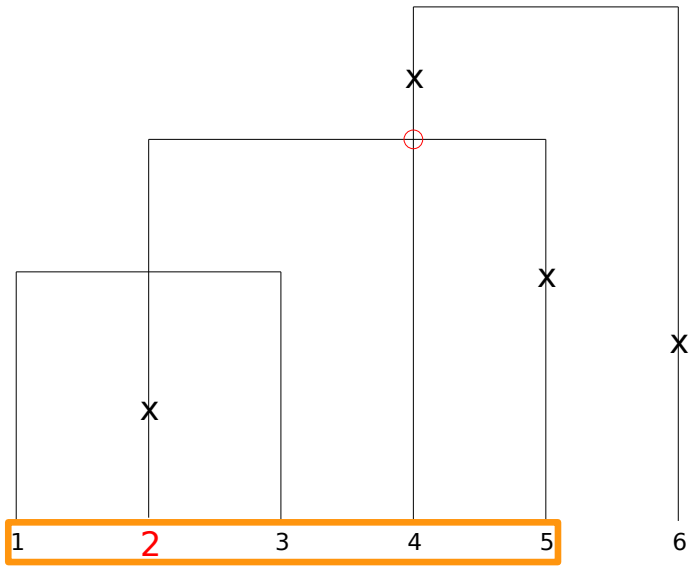

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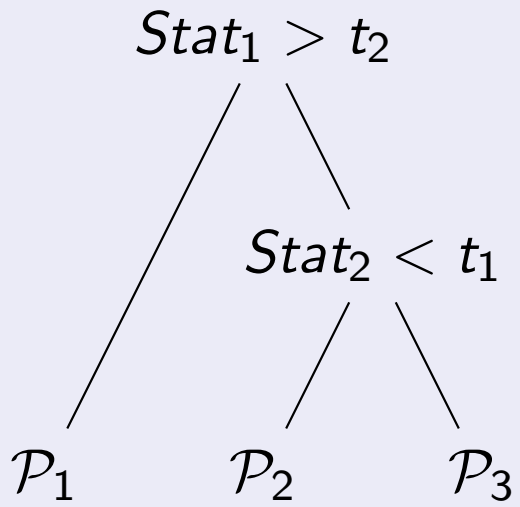
- $\Leftrightarrow$ # descendants of the youngest ancestor of i with a mutation on the branch above it
- Use quantiles .1,.3,.5,.7,.9, the harmonic mean, sample mean and s.d.

Model selection via ABC with random forests

Using many test statistics: Curse of dimension, added noise

Random forest-based ABC [PME+15]

1) Build decision trees (CART) using bootstrap samples of simulated stats S (w. prior) to sort the latter into bins $\mathcal{P}_i$ from the same model.
2) For each tree, sort S_{obs} to $\mathcal{P}_i$



Randomised CART

At node, take stat from random subset w. minimal misclassification (Gini index)

- Misclassification measure: Out-of-the-bag error
- Model selection a) % trees: $S_{obs} \rightarrow$ model M b) Posterior probability
- Importance of stat S_i: Decrease in misclassification by all nodes of S_i, averaged over RF

Which statistics distinguish genealogy models?

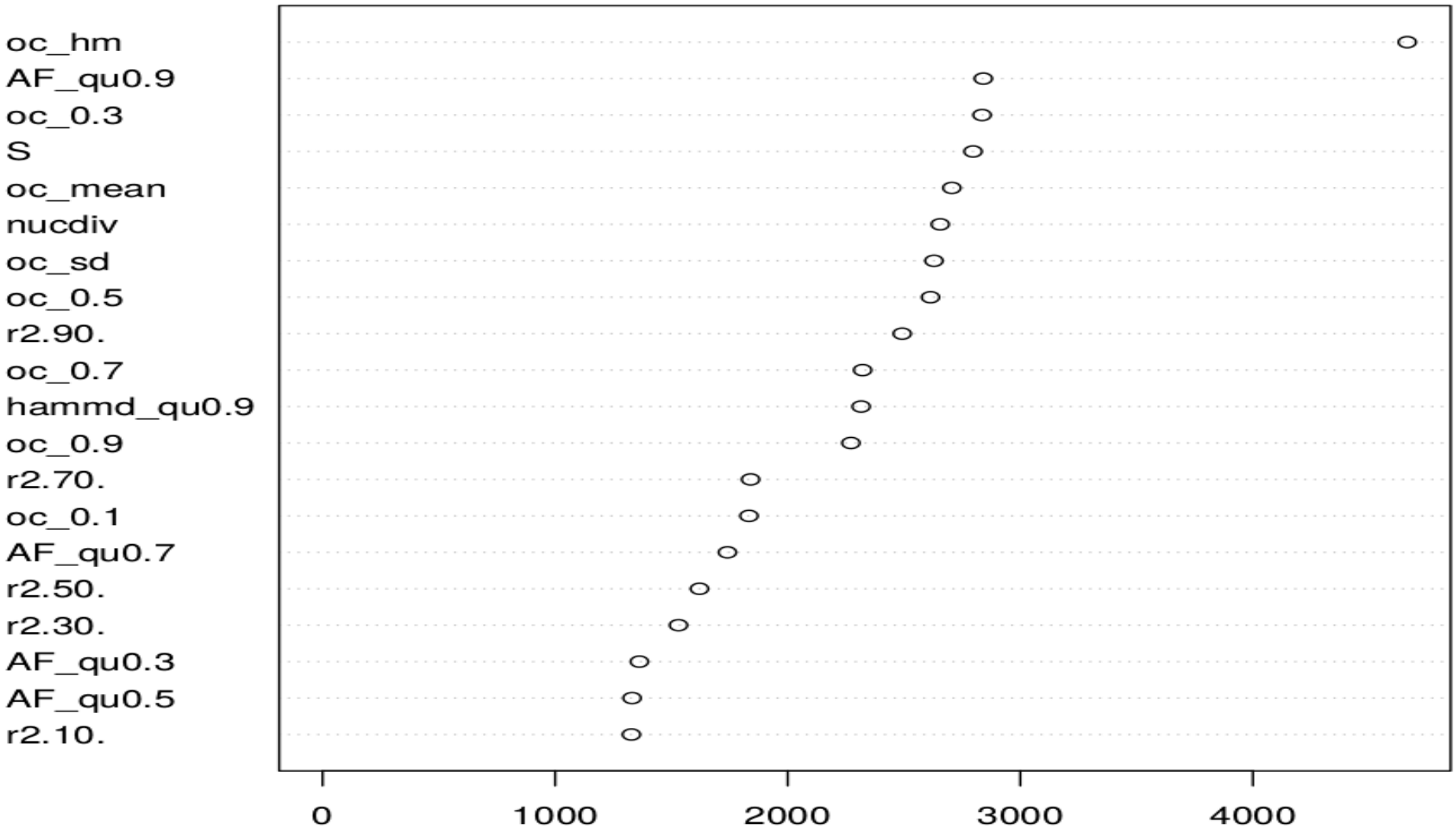
$M1 : \mathbb{KM}$ + exp. growth, $g \in \{0, .5, 1, 2.5, 4, 7, 10, 25, 50, 75, 100, 500, 1000\}$
$M2 : \mathbb{BETA}$, $\alpha \in \{1, 1.1, \ldots, 2\}$

$n = 100$, $\theta = 2s/E$(total coalescent length) for $s \in \{15, 20, 30, 40, 60, 75\}$, 175K sims/model (1x replicated), flat prior

Statistics: O_n, allele frequencies (SFS,fSFS), Hamming distances, r^2, phylogenetic branch lengths, nucleotide diversity π, # mutations S

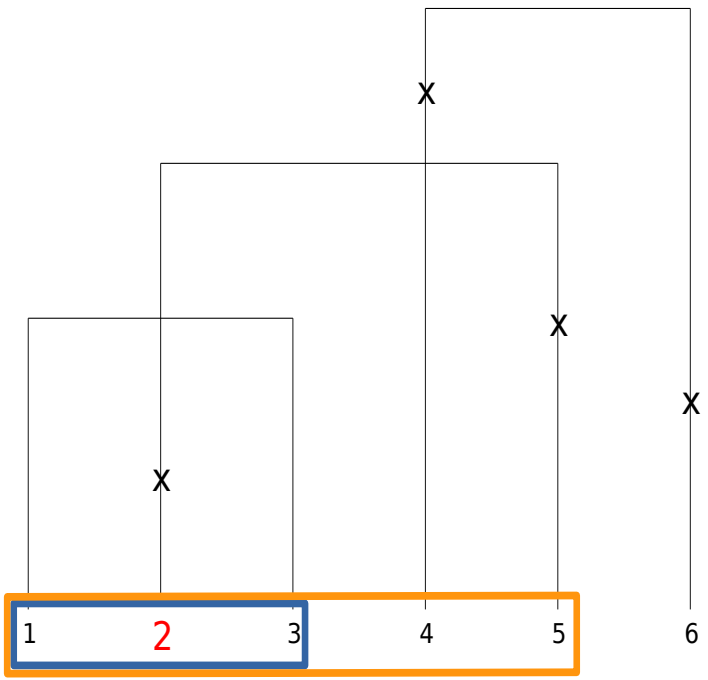
Stats	% $\mathbb{BETA}$ misclassified	% $\mathbb{KM}$+growth misclassified
All	16.9/16.8 %	23.2/23.3 %
No O_n	18.2/18.2 %	26.2/26.2 %
No r^2, phylo	17.2/17 %	23.3/23.5 %
AF, π, S	21.9/22.1 %	33.9/34.1 %
SFS, π, S	19.1/19.2 %	30.7/30.4 %
+ O_n, Hamming	17.7/17.6 %	23.8/23.6 %
fSFS, π, S	23.2/23.2 %	33/33.2 %
+ Hamming	19.8/20 %	27.6/27.5 %
+ r^2, phylo	19/19 %	26.6/26.7 %

Importance of statistics (full set)



measured by average decrease in Gini index over nodes of the statistic in the trees of the RF

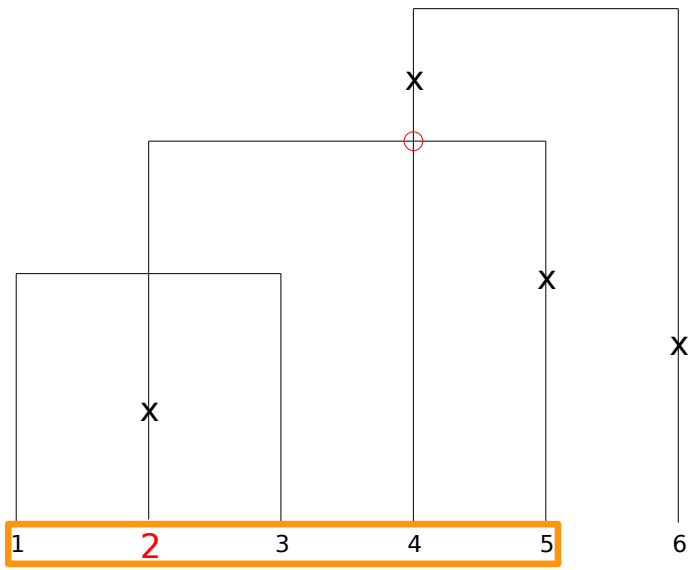
Why is the harmonic mean of $(O_n(i))_{i\in[n]}$ distinguishing well?



- $M_n(i)$: smallest family of i, # descendants of the most recent ancestor of i
- $M_n(i) \leq O_n(i)$, equality for $\theta \to \infty$
- $M_n(i)$ tends to be bigger for MMC than for KM [BF05], [FSJ14], [SJY16]
- $M_n(i)$'s law not changed if we make a time-change (to model pop.size changes)

Mathematical properties of O_n

n-coalescents: Processes in the partitions of $\{1, ..., n\}$
At time t: partition blocks = offspring of ancestral lines at t



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- $O_n(i) := B_i^{(n)}(E_n(i) + T_n(i))$, where
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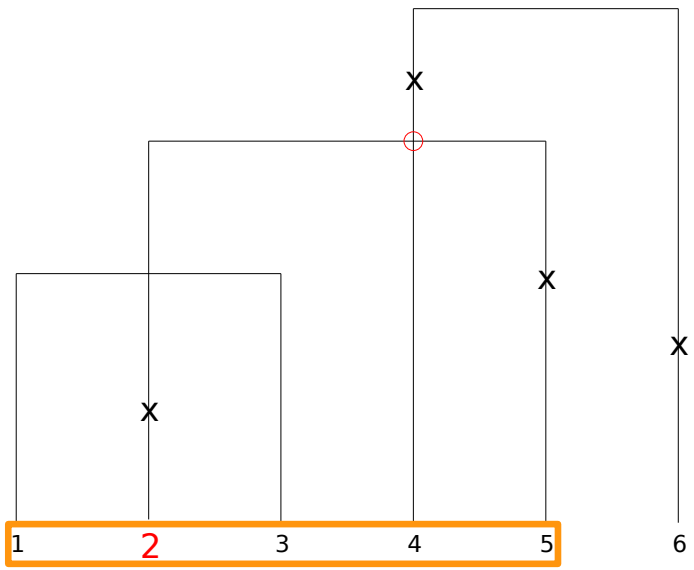

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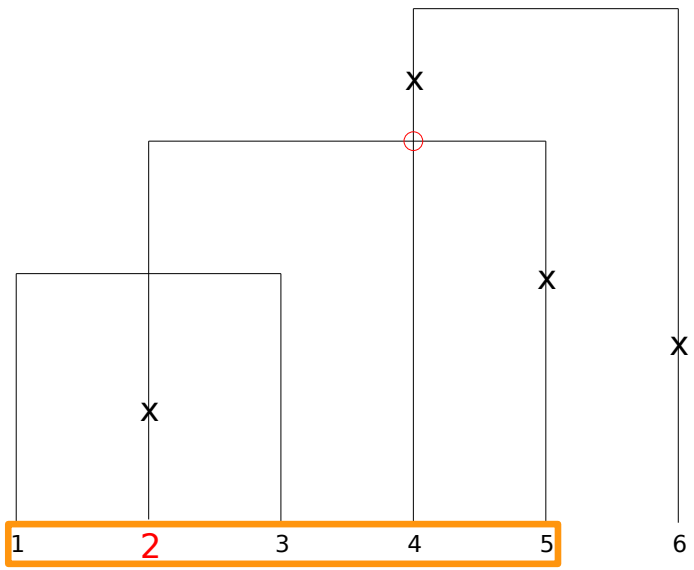

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- All moments of $O_n(1)$ can be computed recursively for any Λ-n-coalescent

Asymptotics of $O_n(i)$ for $\mathbb{BETA}$, $n \to \infty$

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$E_n(1) \xrightarrow{d} Exp(\mu_{-1})$, $n \to \infty$

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$\mu_{-1} = \infty$, dust-free for Λ-coalescents

- $f_1(t) := \lim_{n\to\infty} n^{-1} B_1(t)$
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- $E[(f_1(T(1)))^k] = 1 - \sum_{r=2}^{k+1} a_{k,r} \frac{\theta/2}{\lambda_r + \theta/2}$, where λ_r is the total rate of the Λ-coalescent in a state with r blocks and $a_{k,r}$ is a rational function of $\lambda_2, \ldots, \lambda_k$.
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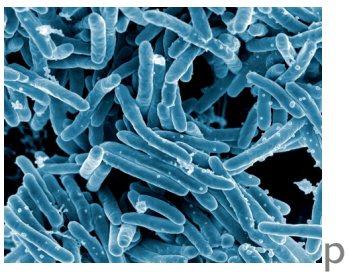
- $\mathbb{BSZ}$ $f_1(T(1)) \stackrel{d}{=} Beta\left(\frac{1}{1+\frac{\theta}{2}}, \frac{\frac{\theta}{2}}{1+\frac{\theta}{2}}\right)$

Mycobacterium tuberculosis - multiple-merger genealogy?

- Bacterial agent of tuberculosis, haploid



pic from NIAID

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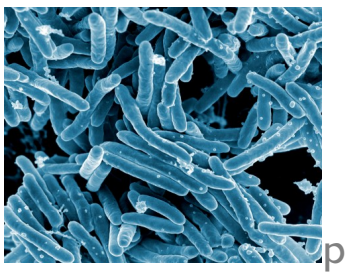
- Clonal reproduction (gen.$\approx$ 15-20 h), rather small 4 Mb genome, very few recombination events $\Rightarrow$ treated as a single locus



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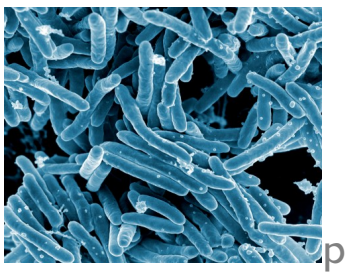

pic from NIAID

Mycobacterium tuberculosis - multiple-merger genealogy?

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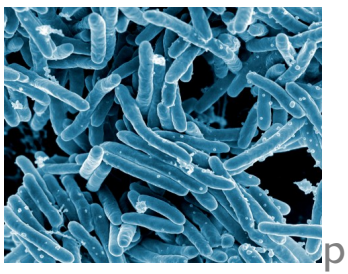

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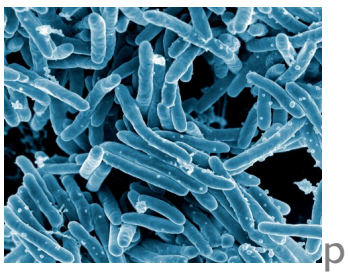

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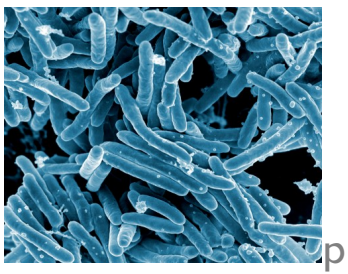

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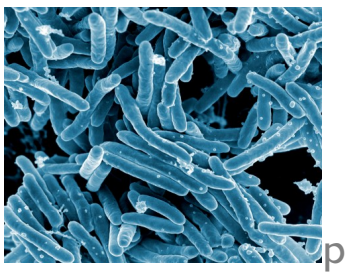
- Reproduction also potentially skewed* $\Rightarrow \mathbb{BETA}$, other multiple-merger coalescents
- We use data sets from outbreaks and local samples to control population structure
- Genealogy model (usually) proposed in the literature: Kingman's n-coalescent with exponential growth



pic from NIAID

ABC with random forest approach w. F. Menardo, in prep.

Models

$\mathbb{KM}$ + exp. growth, $g \in \{0, \ldots, 5000\}, \{0, \ldots, 20000\}$
$\mathbb{BETA}$ $\alpha \in \{1, 1.025, \ldots, 1.975, 0.\}$
$\mathbb{DIRAC}$ $\Psi \in \{0.025, 0.05, \ldots, 0.975\}$

Setup

- $\theta \in [\hat{\theta}_w/5, 5\hat{\theta}_w]$
- Sequential ABC (2x) to fit growth range
- ABC w. RF can also be used for parameter estimation
- Many mutations, large samples: Misclassification $\leq 5\%$

PROBLEM: We treat the sequences as sampled at the same time!

ABC with random forest results w. F. Menardo, in prep.

sample	n	S_{obs}	best model (post. prob.)	.1/.9 quant. posterior g, α
(Inuit, '11,'13	147	454	$\mathbb{BETA}$ (1)	1.2/1.425
Hamburg, 99-'10	61	74	$\mathbb{BETA}$ (.96)	1.075/1.35
Argentinia 96-'09	248	497	$\mathbb{BETA}$ (.998)	1.1/1.3
subset '01-'05	137	312	$\mathbb{BETA}$ (.95)	1.125/1.35
subsubset '01-'03	91	205	$\mathbb{BETA}$ (.98)	1.075/1.375
Ethiopia '06-'10	21	1334	$\mathbb{BETA}$ (.78)	1.3/1.725
East Europe/Russia	176	1164	$\mathbb{KM} + exp$ (0.98)	(1535, 3629)

data from [LRP+15],[RDK+13],[EMR+15],[CHK+15],[SKM+17] ([SBJ+16], Uganda: not completely analysed, but subsets fit better to $\mathbb{KM} + exp$)

Different sampling times, but we assume an ultrametric tree

ABC with random forest results w. F. Menardo, in prep.

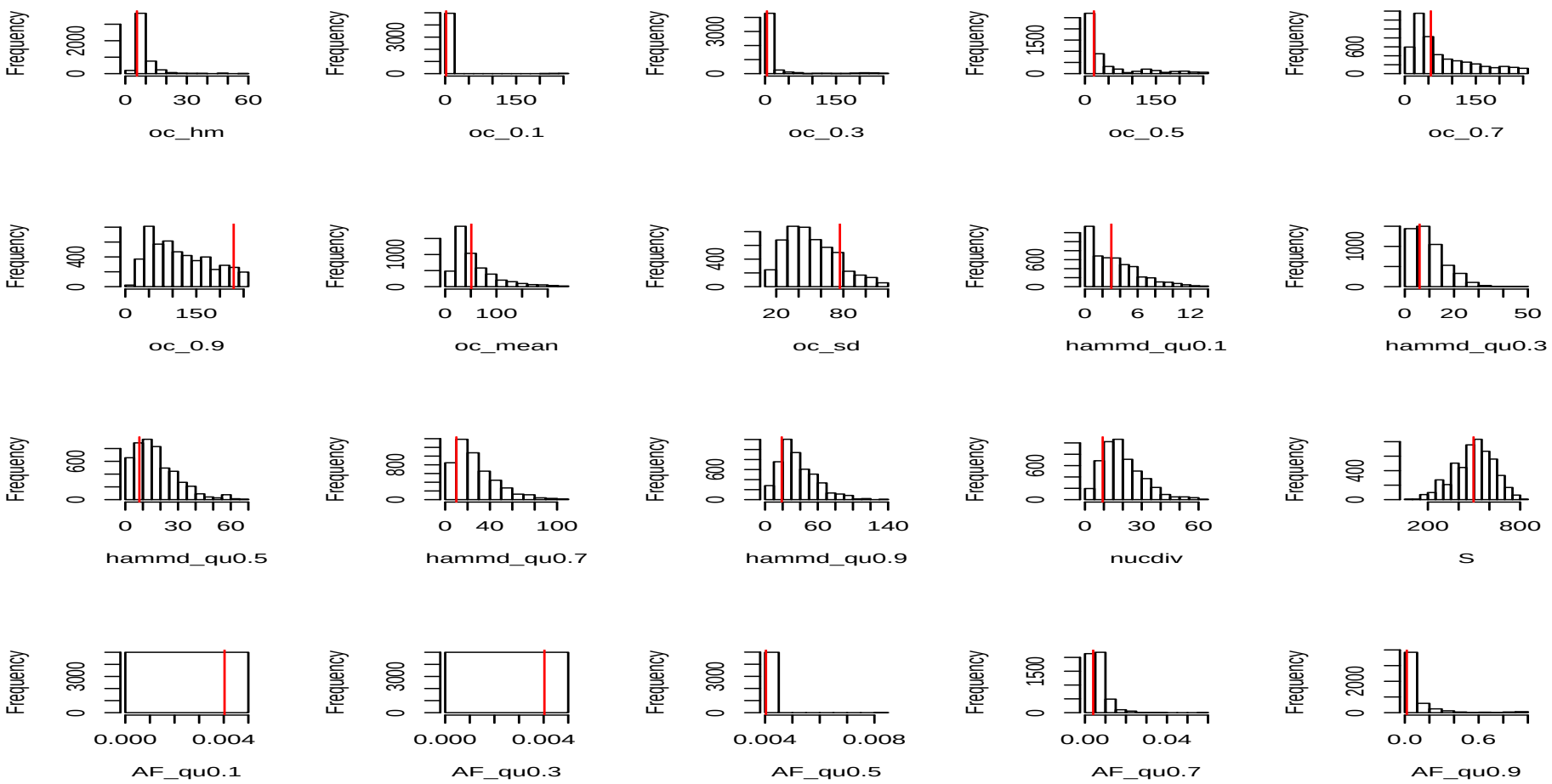
sample	n	S_{obs}	best model (post. prob.)	.1/.9 quant. posterior g, α
(Inuit, '11,'13	147	454	$\mathbb{BETA}$ (1)	1.025/1.25)
Hamburg, 99-'10	61	74	$\mathbb{BETA}$ (.98)	1/1.4
Argentinia 96-'09	248	497	$\mathbb{BETA}$ (.95)	1/1.225
subset '01-'05	137	312	$\mathbb{BETA}$ (.9)	1.025/1.3
subsubset '01-'03	91	205	$\mathbb{BETA}$ (.95)	1.025/1.3
Ethiopia '06-'10	21	1334	$\mathbb{BETA}$ (.77)	1.175/1.8
East Europe/Russia	176	1164	$\mathbb{KM} + exp$ (1)	(2536, 4867)

data from [LRP+15],[RDK+13],[EMR+15],[CHK+15],[SKM+17] ([SBJ+16], Uganda: not completely analysed, but subsets fit better to $\mathbb{KM} + exp$)

Different sampling times, but we assume an ultrametric tree

Method is rather robust $\Rightarrow$ Leave out all private mutations: $\leq 6\%$ misclassification, same results for classification

Posterior predictive checks



Multiple mergers vs. *Mycobacterium tuberculosis*

Still many questions!

- Magnitude of bias on non-singleton mutations by assuming equal sampling times?
- Account for different sampling times by modifying the coalescent trees as suggested in [HP18]?
- Better fitting model: $\mathbb{BETA}$+growth? Others?

Multiple mergers vs. *Mycobacterium tuberculosis*

Still many questions!

- Magnitude of bias on non-singleton mutations by assuming equal sampling times?
- Account for different sampling times by modifying the coalescent trees as suggested in [HP18]?
- Better fitting model: $\mathbb{BETA}$+growth? Others?
- For the majority (2/3) of data sets analysed, $\mathbb{BETA}$ reasonable alternative null model. What is a reasonable reproduction model underlying it?
- $\mathbb{BSZ}$: Some doubt (or noise), signal has to be clarified (more simulations, adjusted $\mathbb{BSZ}$?)
- Nearly all sets fit clearly to conceptually very different models: biological reasons?

Thanks for the attention!

Any questions?

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