The infinite alleles model revisited: a Gibbs sampling approach

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Introduction

Motivation & Goal

Data:

- A huge number of SARS-CoV-2 sequences have accumulated on GISAID since January 2020.
- The mutation rate is quite low but the sampling is excellent.
- We thus observe lots of sequences that are similar.

This motivates the development of new phylodynamic methods
better tailored to analyze big genomic data characterized by a low diversity

Goals:

- design a simpler data-generating model as compared to current phylodynamic methods,
- with quantities that we are interested in: pop size, sampling intensity, mutation rate,
- and an appropriate inference method to recover these quantities from the data.

Can we recover information on the population size and sampling intensity in the past
while working under a very simple infinite alleles model ?

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Model assumptions

Introduction

Model assumptions
- Parameters of the model
- Sampling and coalescent history
- Priors and summary

Inference method
- Gibbs sampling strategy
- Prior conjugacy properties for the parameters
- Data augmentation with past coalescent history
- Summary of the Gibbs sampler

Results
- Validation of the augmentation with the past coalescent history
- Validation of the MCMC by SBC
- Estimation of the running time
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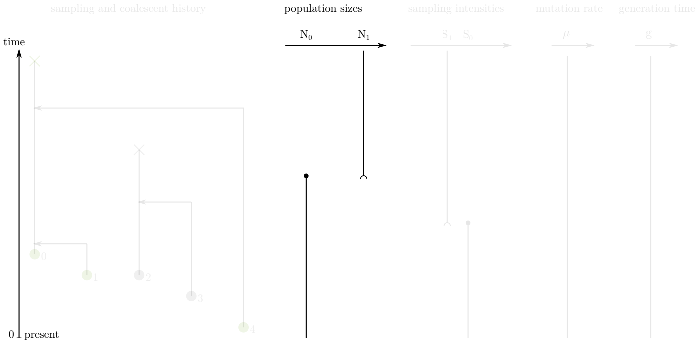
Model assumptions

Parameters of the model – Past effective population sizes N

- N is piecewise-constant on a partition $(\Delta_j^{(N)})_{j=0}^{p}$ of $(0, +\infty)$.
- a priori, $N_j \sim \mathcal{GIG}(\lambda, \chi, \psi)$.
- (GIG: Generalized Inverse Gaussian distribution, and we'll see a bit later why.)



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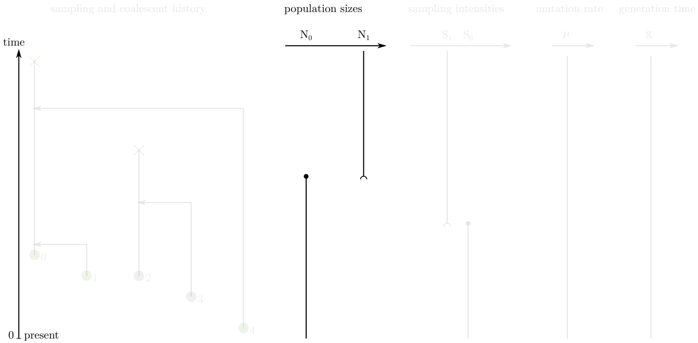

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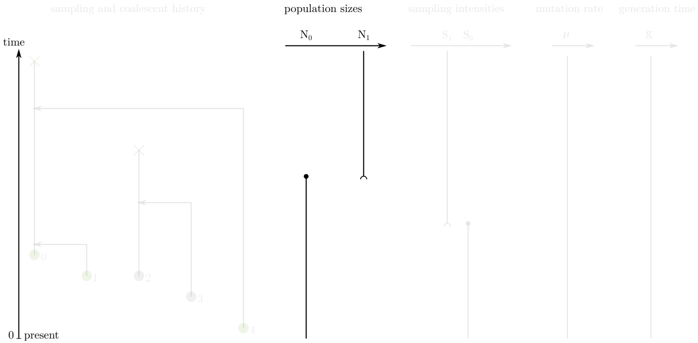

Model assumptions

Parameters of the model – Past sampling intensities S

- S is piecewise-constant through time, on a partition $(\Delta_j^{(S)})_{j=0}^{p'}$ of $(0, \infty)$.
- a priori, $S_j \sim \Gamma(\alpha_S, \beta_S)$.
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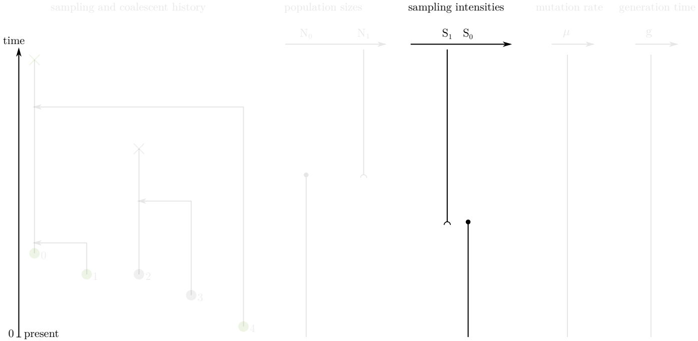

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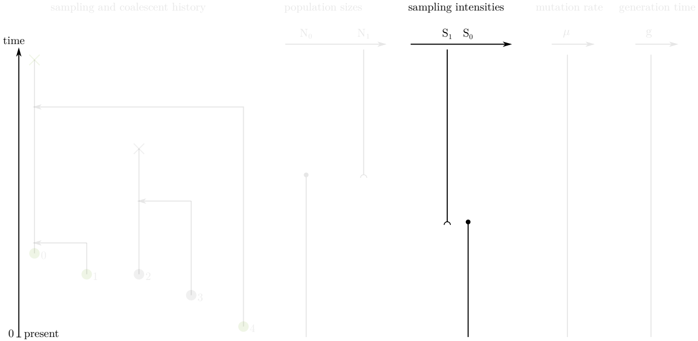

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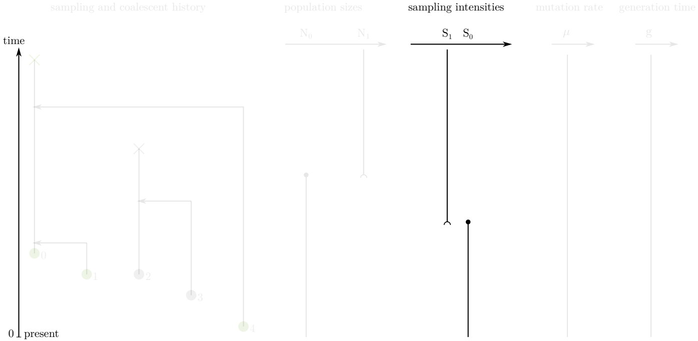

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Parameters of the model – Mutation rate μ

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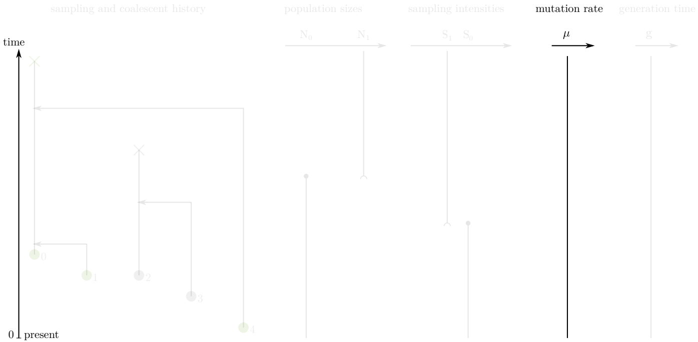

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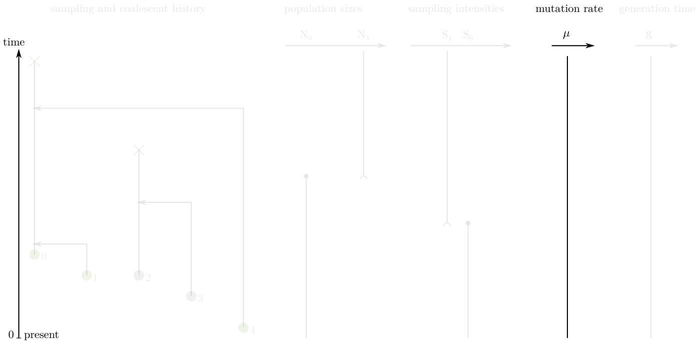

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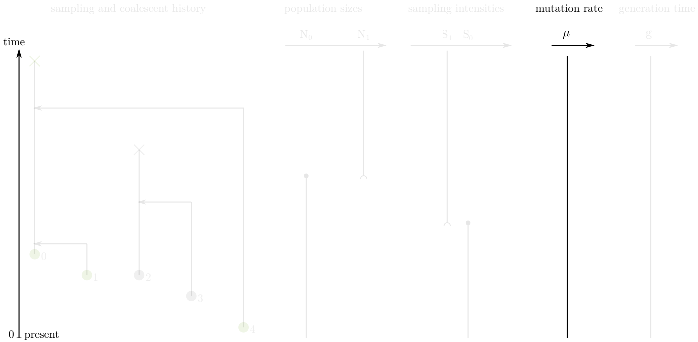

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Parameters of the model – Generation time g

- g is constant through time,
- a priori, $g \sim \Gamma^{-1}(\alpha_g, \beta_g)$.
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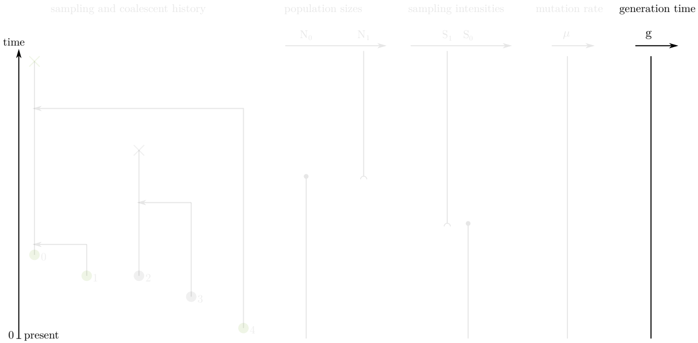

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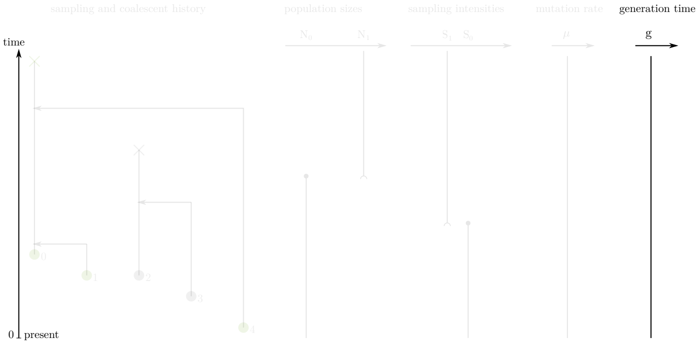

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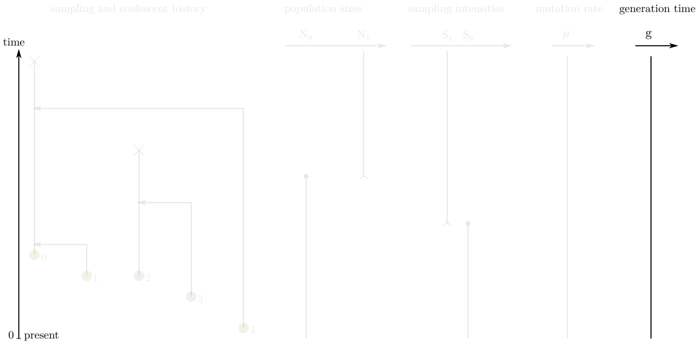


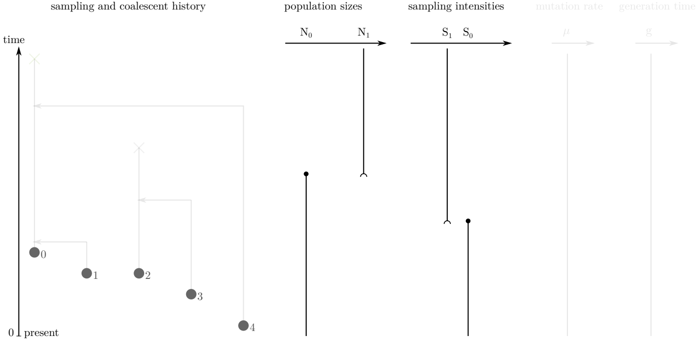
Model assumptions

Sampling and coalescent history – law of the sampling history $\mathcal{B}$

- the sampling history is given by a Poisson point process with rate

$$\lambda_t^{(b)} := S_t N_t$$

- It generates the set of ordered sampling times of our individuals $\mathcal{B} = (b_i)_{i=0}^{B-1}$.



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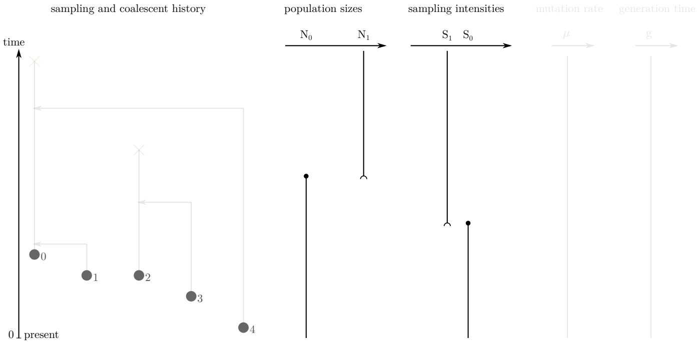


Model assumptions

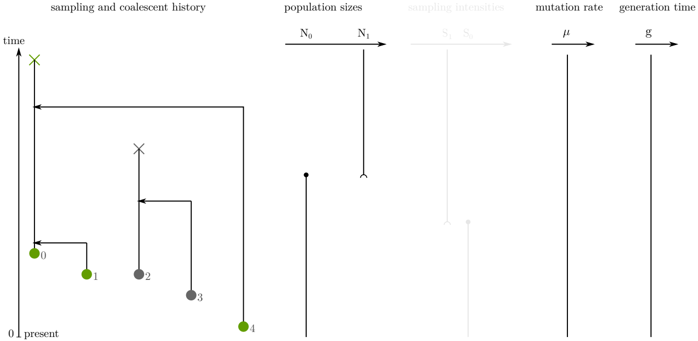
Sampling and coalescent history – law of the coalescent history $\mathcal{H}$

- While k_t lineages are alive in the process, the next coalescent/differentiation event happens with rate

$$\lambda_t^{(c)} := \binom{k_t}{2} (gN_t)^{-1}$$

$$\lambda_t^{(d)} := \mu k_t$$

- It generates a record of death events $\mathcal{H}$, and a partition of our B individuals into D alleles: $\mathcal{A}$.



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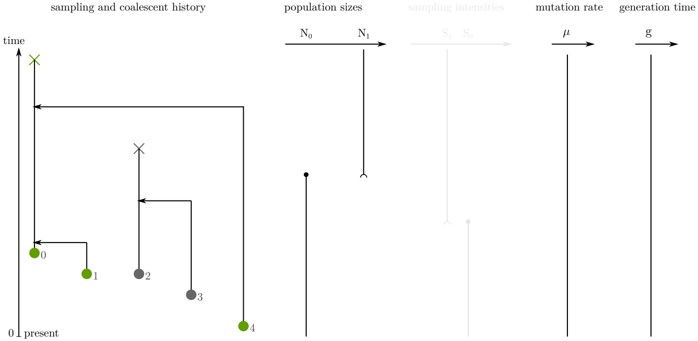
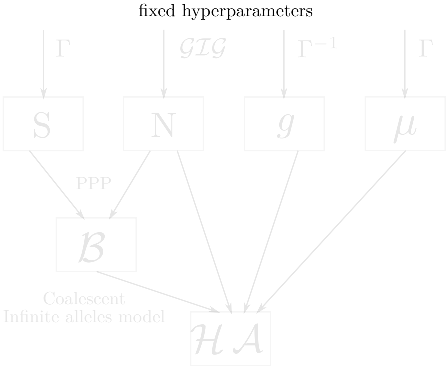


Model assumptions

Priors and summary

- The likelihood of the complete history is known and is an exponential family,

$$\mathbb{P}(\mathcal{B}, \mathcal{H} \mid N, S, \mu, g) = \left(\prod_{i=0}^{B-1} \lambda^{(b)}_{b_i} (\lambda^{(c)}_{h_i} \mathbb{1}_{o_i \neq i} + \lambda^{(d)}_{h_i} \mathbb{1}_{o_i = i}) \right) \exp \left(- \int_0^\infty (\lambda^{(b)}_t + \lambda^{(c)}_t + \lambda^{(d)}_t) dt \right)$$



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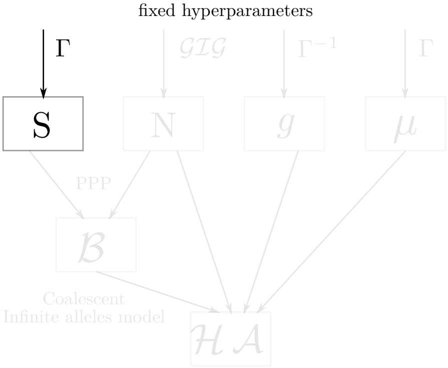

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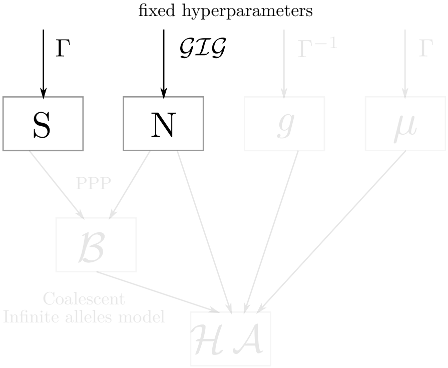

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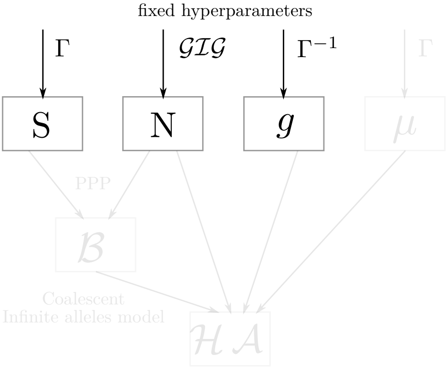

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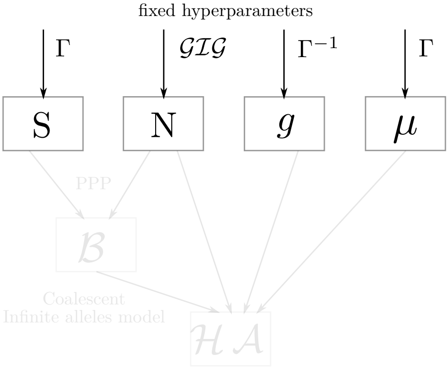

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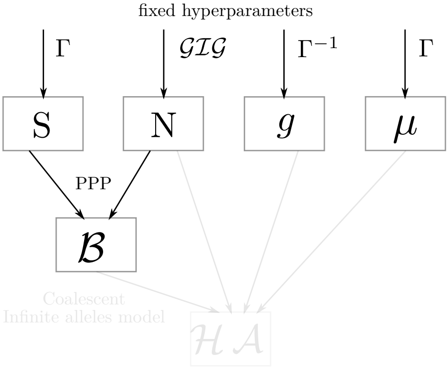

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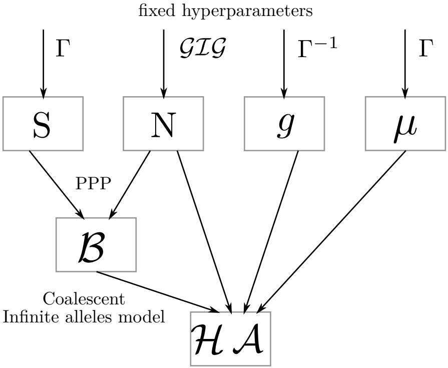

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Gibbs sampling strategy

Aim Infer the posterior distribution of N, S, μ, g,

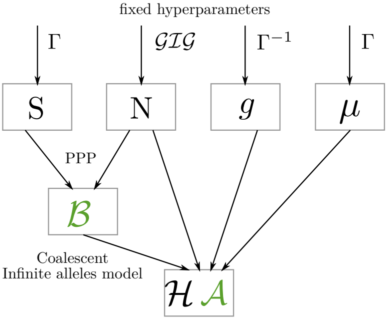
$$\mathbb{P}(N, S, \mu, g \mid \mathcal{A}, \mathcal{B}) = \int_{\mathcal{H}} \mathbb{P}(N, S, \mu, g, \mathcal{H} \mid \mathcal{A}, \mathcal{B})$$

Strategy Design a MCMC with a Gibbs sampling approach, converging to the stationary distribution of the augmented target distribution,

$$\mathbb{P}(N, S, \mu, g, \mathcal{H} \mid \mathcal{A}, \mathcal{B})$$

Subtargets Derive efficient ways to alternatively sample from,

$$\mathbb{P}(N_i | N_{-i}, S, \mu, g, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(S_i | N, S_{-i}, \mu, g, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(\mu | N, S, g, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(g | N, S, \mu, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(\mathcal{H}_i | N, S, \mu, \mathcal{A}, \mathcal{B}, \mathcal{H}_{-i})$$



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Gibbs sampling strategy

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$$\mathbb{P}\left(N, S, \mu, g \mid \mathcal{A}, \mathcal{B}\right)$$

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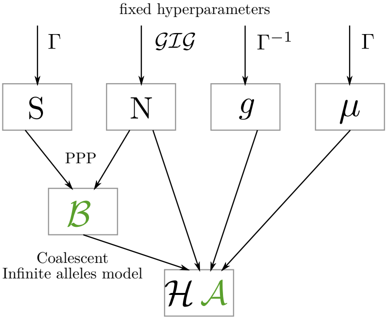

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$$\mathbb{P}(g | N, S, \mu, \mathcal{B}, \mathcal{H})$$

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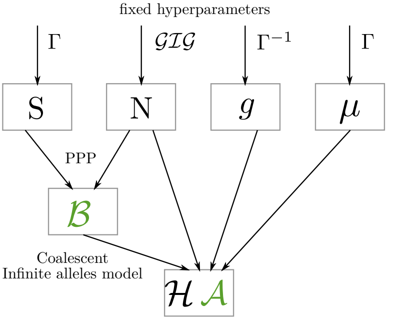

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$$\mathbb{P}(N, S, \mu, g \mid \mathcal{A}, \mathcal{B})$$

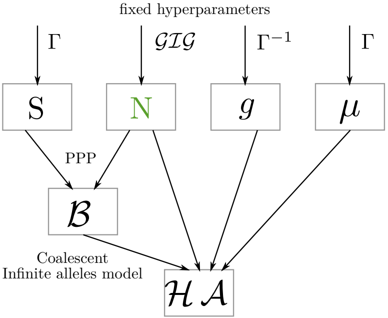
$$= \int_{\mathcal{H}} \mathbb{P}(N, S, \mu, g, \mathcal{H} \mid \mathcal{A}, \mathcal{B})$$

Strategy Design a MCMC with a Gibbs sampling approach, converging to the stationary distribution of the augmented target distribution,

$$\mathbb{P}(N, S, \mu, g, \mathcal{H} \mid \mathcal{A}, \mathcal{B})$$

Subtargets Derive efficient ways to alternatively sample from,

$$\mathbb{P}(N_i | N_{-i}, S, \mu, g, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(S_i | N, S_{-i}, \mu, g, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(\mu | N, S, g, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(g | N, S, \mu, \mathcal{B}, \mathcal{H})$$
$$\mathbb{P}(\mathcal{H}_i | N, S, \mu, \mathcal{A}, \mathcal{B}, \mathcal{H}_{-i})$$



Inference method

Gibbs sampling strategy

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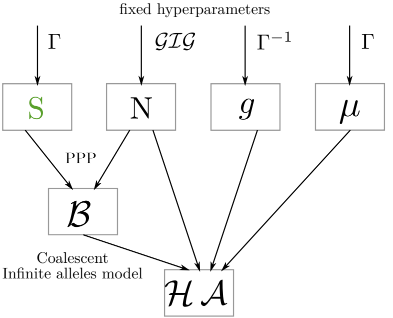

Inference method

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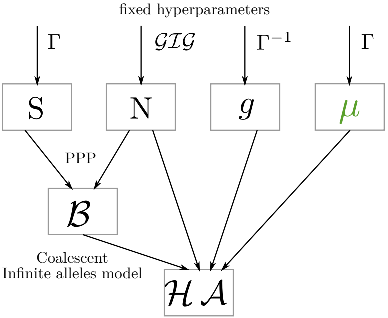

Inference method

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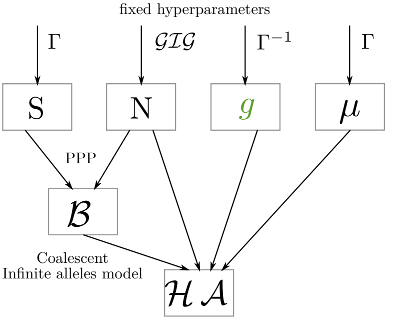

Inference method

Gibbs sampling strategy

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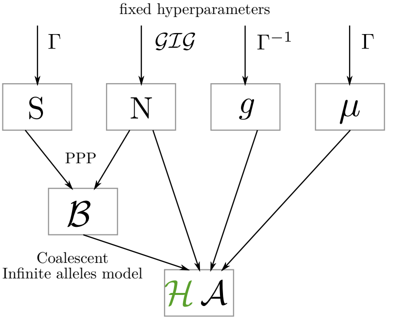

Inference method

Prior conjugacy properties for the parameters – effective population sizes N

- Assume that a priori, $N_j \sim \mathcal{GIG}(\lambda, \chi, \psi)$.
- The posterior is thus given by,

$$\begin{aligned}\mathbb{P}(N_j \mid N_{-j}, S, \mu, g, \mathcal{B}, \mathcal{H}) &\propto \mathbb{P}(N_j)\ \mathbb{P}(\mathcal{B}, \mathcal{H} \mid N, S, \mu, g) \\ &\propto N_j^{\lambda-1}\ \exp\left(-\frac{1}{2}(\chi N_j^{-1} + \psi N_j)\right) \\ &\quad N_j^{B(\Delta_j^{(N)})-C(\Delta_j^{(N)})} \\ &\quad \exp\left(-N_j^{-1} g^{-1} \sum_{l=0}^{2B} \binom{k_l}{2} |\Delta_l \cap \Delta_j^{(N)}| - N_j \sum_{k=0}^{p'-1} S_k |\Delta_k^{(S)} \cap \Delta_j^{(N)}|\right)\end{aligned}$$

Conclusion : the prior and posterior of N_j are conjugate distributions, with $N_j | N_{-j}, S, \mu, g, \mathcal{B}, \mathcal{H}\ \sim$

$$\mathcal{GIG}\left(\lambda + B(\Delta_j^{(N)}) - C(\Delta_j^{(N)})\ ,\ \chi + g^{-1} \sum_{l=0}^{2B} k_l(k_l-1)|\Delta_l \cap \Delta_j^{(N)}|\ ,\ \psi + 2\sum_{k=0}^{p'-1} S_k |\Delta_k^{(S)} \cap \Delta_j^{(N)}|\right)$$

where $C(\Delta_j^{(N)})$ and $B(\Delta_j^{(N)})$ are respectively the number of coalescent and sampling events happening over the interval $\Delta_j^{(N)}$.

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&\quad N_j^{B(\Delta_j^{(N)}) - C(\Delta_j^{(N)})} \\
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Inference method

Prior conjugacy properties for the parameters – effective population sizes N

- Assume that a priori, $N_j \sim \mathcal{GIG}(\lambda, \chi, \psi)$.
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$$\propto N_j^{\lambda-1}\ \exp\left(-\frac{1}{2}(\chi N_j^{-1} + \psi N_j)\right)$$

$$N_j^{B(\Delta_j^{(N)})-C(\Delta_j^{(N)})}$$

$$\exp\left(-N_j^{-1} g^{-1} \sum_{l=0}^{2B} \binom{k_l}{2} |\Delta_l \cap \Delta_j^{(N)}| - N_j \sum_{k=0}^{p'-1} S_k |\Delta_k^{(S)} \cap \Delta_j^{(N)}|\right)$$

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where $C(\Delta_j^{(N)})$ and $B(\Delta_j^{(N)})$ are respectively the number of coalescent and sampling events happening over the interval $\Delta_j^{(N)}$.

Inference method

Prior conjugacy properties for the parameters – sampling intensities S

- Assume that a priori, $S_j \sim \Gamma(\alpha, \beta)$.
- Its posterior is thus given by,

$$\begin{aligned}\mathbb{P}(S_j \mid N, S_{-j}, \mu, g, \mathcal{B}, \mathcal{H}) &\propto \mathbb{P}(S_j)\,\mathbb{P}(\mathcal{B}, \mathcal{H} \mid N, S, \mu, g) \\ &\propto S_j^{\alpha-1}\ \exp\left(-\beta S_j\right) \\ &\quad S_j^{B(\Delta_j^{(S)})}\ \exp\left(-S_j \sum_{k=0}^{p-1} N_k |\Delta_k^{(N)} \cap \Delta_j^{(S)}|\right)\end{aligned}$$

Conclusion : the prior and posterior of S_j are conjugate distributions, with,

$$S_j \mid N, S_{-j}, \mu, g, \mathcal{B}, \mathcal{H}\ \sim\ \Gamma\left(\alpha + B(\Delta_j^{(S)})\ ,\ \beta + \sum_{k=0}^{p-1} N_k |\Delta_k^{(N)} \cap \Delta_j^{(S)}|\right) \quad .$$

where $B(\Delta_j^{(S)})$ is the number of birth events happening over interval $\Delta_j^{(S)}$.

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Conclusion : the prior and posterior of S_j are conjugate distributions, with,

$$S_j \mid N, S_{-j}, \mu, g, \mathcal{B}, \mathcal{H} \;\sim\; \Gamma\left(\alpha + B(\Delta_j^{(S)}) \;,\; \beta + \sum_{k=0}^{p-1} N_k |\Delta_k^{(N)} \cap \Delta_j^{(S)}|\right) \quad .$$

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Conclusion : the prior and posterior of S_j are conjugate distributions, with,

$$S_j \mid N, S_{-j}, \mu, g, \mathcal{B}, \mathcal{H} \ \sim\ \Gamma\left(\alpha + B(\Delta_j^{(S)})\ ,\ \beta + \sum_{k=0}^{p-1} N_k |\Delta_k^{(N)} \cap \Delta_j^{(S)}|\right) \quad .$$

where $B(\Delta_j^{(S)})$ is the number of birth events happening over interval $\Delta_j^{(S)}$.

Inference method

Prior conjugacy properties for the parameters – mutation rate μ

- Assume that, a priori, $\mu \sim \Gamma(\alpha, \beta)$.
- Its posterior is given by,

$$\begin{aligned}\mathbb{P}(\mu \mid N, S, g, \mathcal{B}, \mathcal{H}) &\propto \mathbb{P}(\mu)\, \mathbb{P}(\mathcal{B}, \mathcal{H} \mid N, S, \mu, g) \\ &\propto \mu^{\alpha - 1} \ \exp\left(-\beta\mu\right) \\ &\quad \mu^{D} \ \exp\left(-\mu \sum_{l=0}^{2B} k_l |\Delta_l|\right)\end{aligned}$$

Conclusion : the prior and posterior of μ are conjugate distributions, with,

$$\mu \mid N, S, g, \mathcal{B}, \mathcal{H} \ \sim \ \Gamma\left(\alpha + D \ , \ \beta + \sum_{l=0}^{2B} k_l |\Delta_l|\right)$$

where D is the total number of alleles.

Inference method

Prior conjugacy properties for the parameters – mutation rate μ

- Assume that, a priori, $\mu \sim \Gamma(\alpha, \beta)$.
- Its posterior is given by,

$$\begin{aligned}\mathbb{P}(\mu \mid N, S, g, \mathcal{B}, \mathcal{H}) &\propto \mathbb{P}(\mu)\ \mathbb{P}(\mathcal{B}, \mathcal{H} \mid N, S, \mu, g) \\ &\propto \mu^{\alpha-1}\ \exp\left(-\beta\mu\right) \\ &\quad\ \mu^{D}\ \exp\left(-\mu \sum_{l=0}^{2B} k_l |\Delta_l|\right)\end{aligned}$$

Conclusion : the prior and posterior of μ are conjugate distributions, with,

$$\mu \mid N, S, g, \mathcal{B}, \mathcal{H}\ \sim\ \Gamma\left(\alpha + D\ ,\ \beta + \sum_{l=0}^{2B} k_l |\Delta_l|\right)$$

where D is the total number of alleles.

Inference method

Prior conjugacy properties for the parameters – mutation rate μ

- Assume that, a priori, $\mu \sim \Gamma(\alpha, \beta)$.
- Its posterior is given by,

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Conclusion : the prior and posterior of μ are conjugate distributions, with,

$$\mu \mid N, S, g, \mathcal{B}, \mathcal{H}\ \sim\ \Gamma\left(\alpha + D\ ,\ \beta + \sum_{l=0}^{2B} k_l |\Delta_l|\right)$$

where D is the total number of alleles.

Inference method

Prior conjugacy properties for the parameters – generation time g

- Assume that a priori, $g \sim \Gamma^{-1}(\alpha, \beta)$.
- Its posterior is given by,

$$\begin{aligned}\mathbb{P}(g \mid N, S, \mu, \mathcal{B}, \mathcal{H}) &\propto \mathbb{P}(g)\ \mathbb{P}(\mathcal{B}, \mathcal{H} \mid N, S, \mu, g)\\ &\propto g^{-(\alpha+1)}\ \exp\left(-\beta g^{-1}\right)\\ &\quad g^{-(B-D)}\ \exp\left(-g^{-1}\sum_{l=0}^{2B}\sum_{j=0}^{p-1}\binom{k_l}{2} N_j^{-1}|\Delta_l \cap \Delta_j^{(N)}|\right)\end{aligned}$$

Conclusion : the prior and posterior of g are conjugate distributions, with,

$$g \mid N, S, \mu, \mathcal{B}, \mathcal{H} \ \sim\ \Gamma^{-1}\left(\alpha + B - D\ ,\ \beta + \sum_{l=0}^{2B}\sum_{j=0}^{p-1}\binom{k_l}{2} N_j^{-1}|\Delta_l \cap \Delta_j^{(N)}|\right)$$

Inference method

Prior conjugacy properties for the parameters – generation time g

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Inference method

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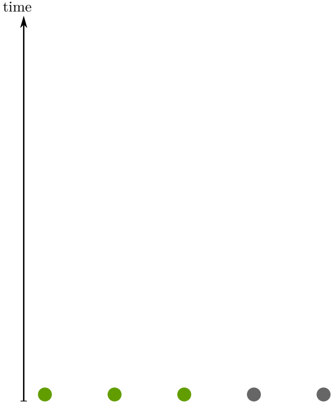
Inference method

Data augmentation with past coalescent history when all samples are taken at present

1. simulate $T_k \sim \mathcal{E}(k(\theta + k - 1)/2)$,
2. choose one of the k living lineages uniformly at random and,
   if it is a singleton in a_k, there is a mutation and this lineage is killed,
   if not, choose uniformly another lineage in the same allele and make them coalesce.



Inference method

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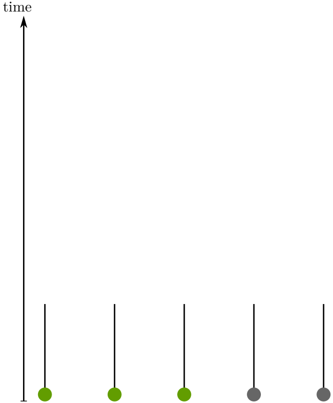

Inference method

Data augmentation with past coalescent history when all samples are taken at present

1. simulate $T_k \sim \mathcal{E}(k(\theta + k - 1)/2)$,
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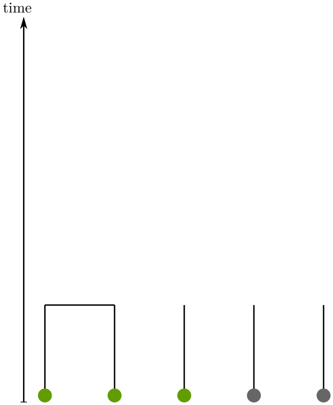

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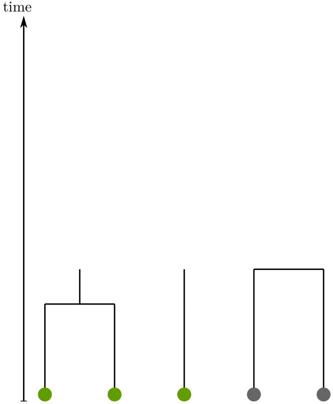

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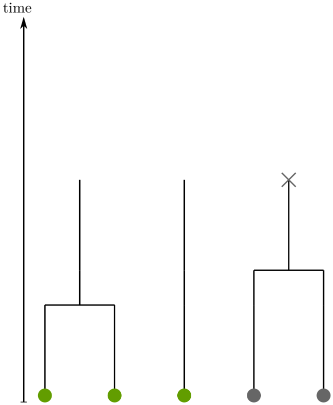

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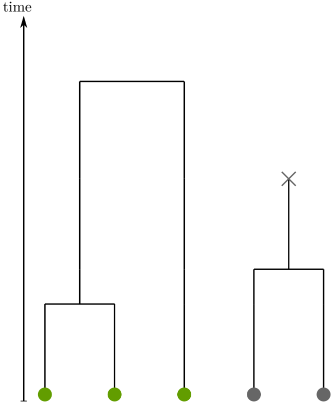

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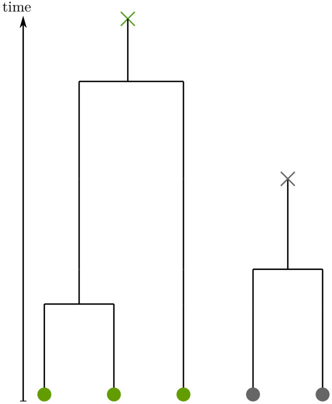

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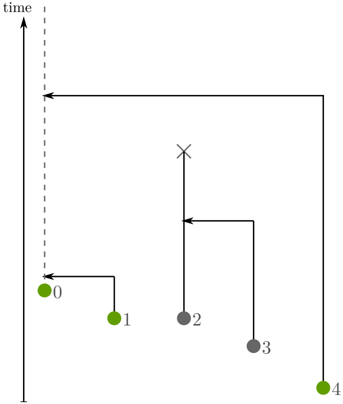

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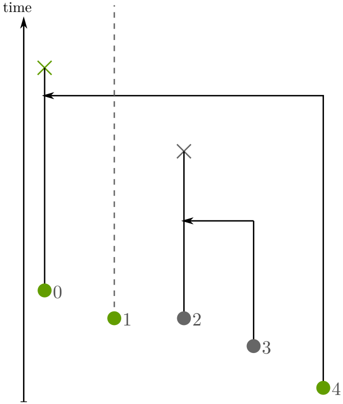

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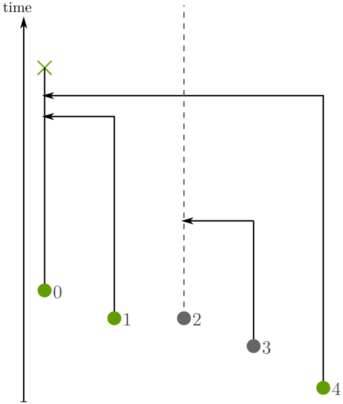

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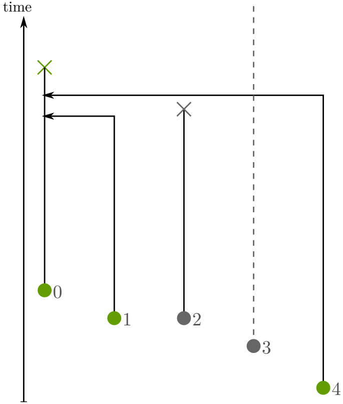

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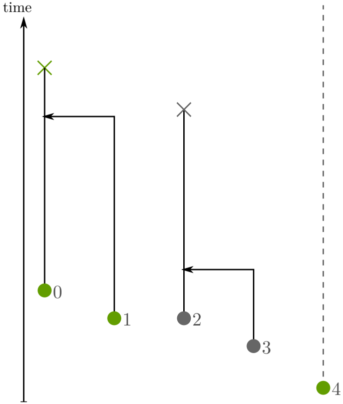

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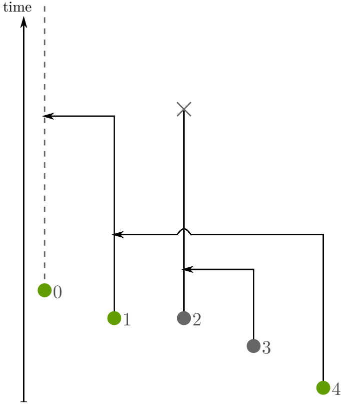

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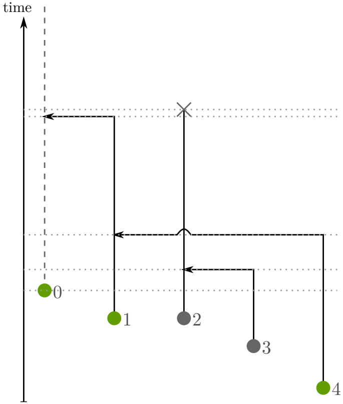

Inference method

Summary of the Gibbs sampler

Initialization:

- Fix $\forall i, H_i = b_i$ and $O_i = \min\{j \in a_i\}$.
- Draw $\forall j, N_j \sim \mathcal{GIG}(\lambda, \chi, \psi)$,
- Draw $\forall j, S_j \sim \Gamma(\alpha_S, \beta_S)$,
- Draw $\mu \sim \Gamma(\alpha_\mu, \beta_\mu)$,
- Draw $g \sim \Gamma^{-1}(\alpha_g, \beta_g)$,

One step in the chain:

- Draw each H_i, O_i in turn using $H_{-i}, O_{-i}, N, S, \mu, g$,
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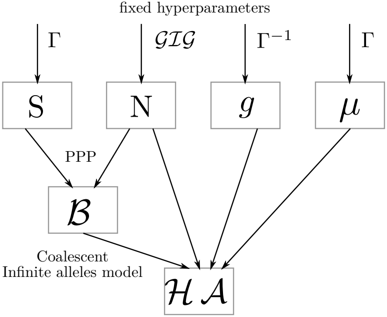

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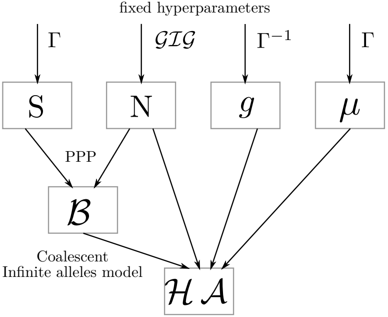

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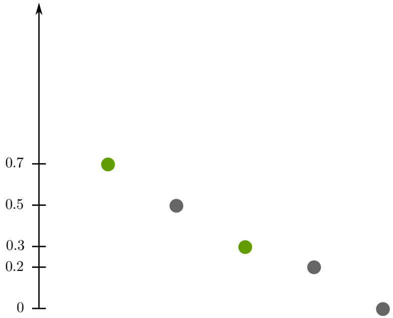
Validation of the augmentation with the past coalescent history

- Fix a very small dataset $\mathcal{A}, \mathcal{B}$ and all parameters.
- Wrap up the data augmentation in a minimalist Gibbs sampler without parameter updates.
- Compare $\mathcal{H}$ to what is obtained by naive rejection sampling on 10^4 samples.



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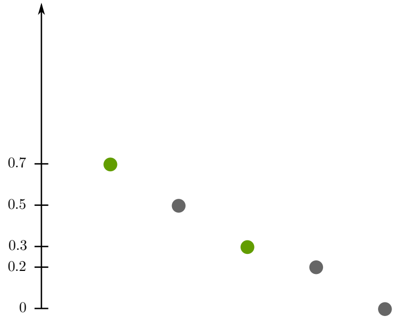

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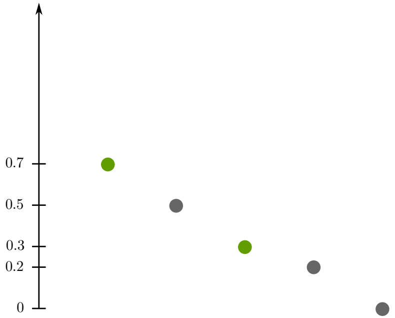

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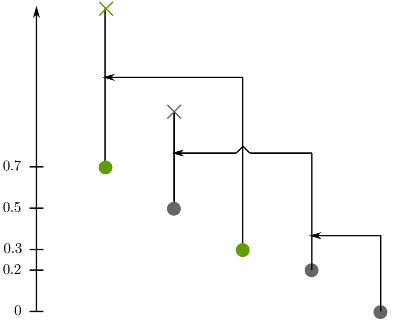

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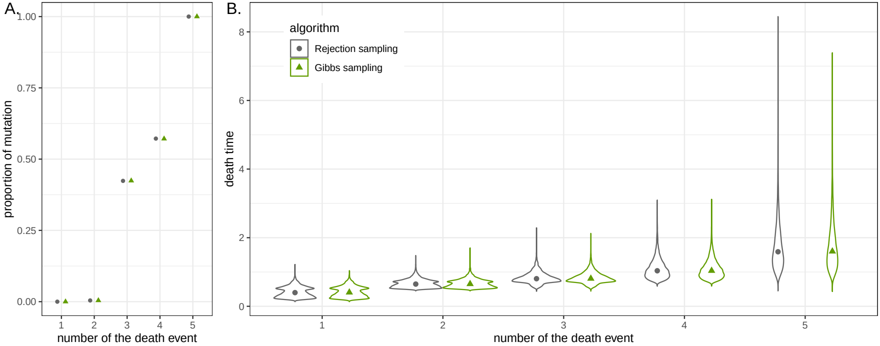

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Validation of the MCMC by SBC – following Talts et al. 2018

- Fix a set of hyperparameters.
- Sample 10^4 complete datasets $N, S, \mu, g, \mathcal{B}, \mathcal{A}$.
- On each dataset, compute the posterior of $N, S, \mu, g \mid \mathcal{A}, \mathcal{B}$.
- Check that the quantiles of the prior and posterior are the same.
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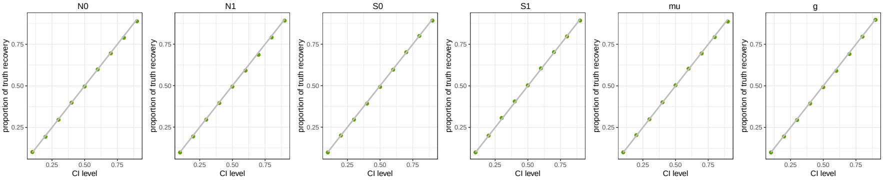

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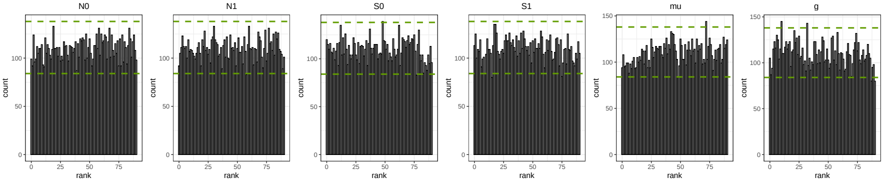
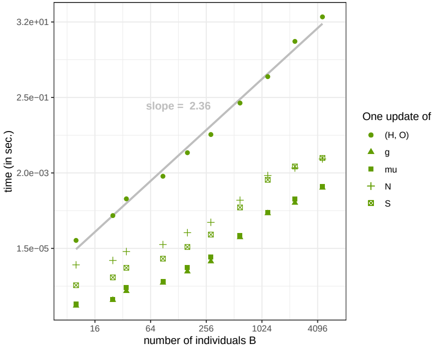
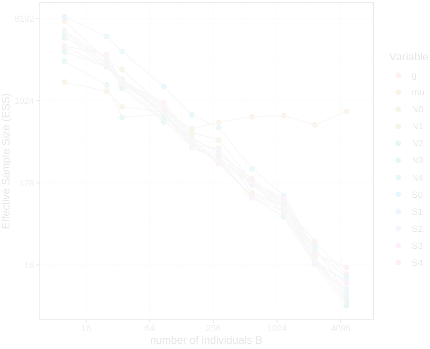


Results

Estimation of the running time

- The update of $\mathcal{H}$ runs in $O(B^2)$.
- One also needs to run the MCMC long enough to get reasonable ESS values.
- This first naive implementation seems reasonable to be used on up to $\sim 10^4$ samples.





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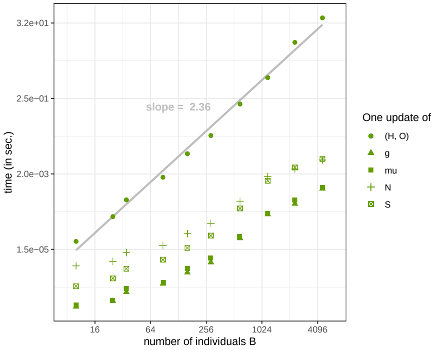

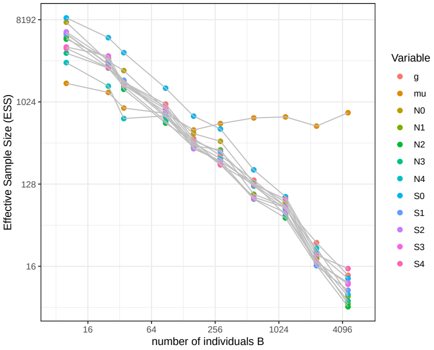

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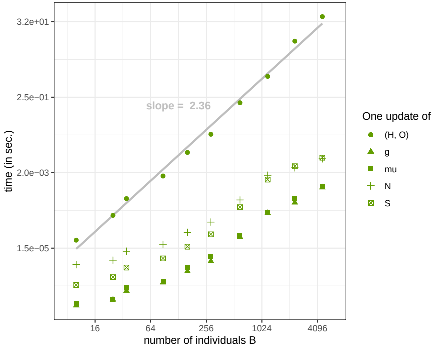

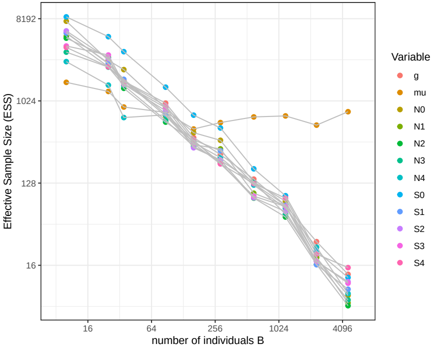

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Illustration on the SARS-CoV-2 dataset

- Sequences from GISAID until 1st of June 2020.

  CH 1284 genomes in 627 alleles,
  DE 1673 genomes in 886 alleles,
  FR 1919 genomes in 1166 alleles,
  IT 1314 genomes in 750 alleles.

- Fixed $\mu = 0.065$ mutations per genome per d, $g = 5$ d and timeline with 5 periods of 4 weeks each.
- To fix hyperparameters, imagine a period with few data,
  Make a guess on the order of magnitude of $N \sim 10^4$ and $S \sim 4 \times 10^{-5}$.
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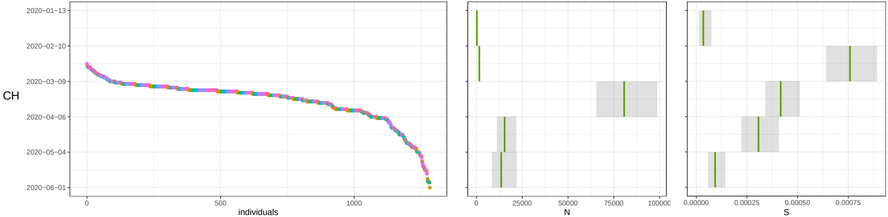

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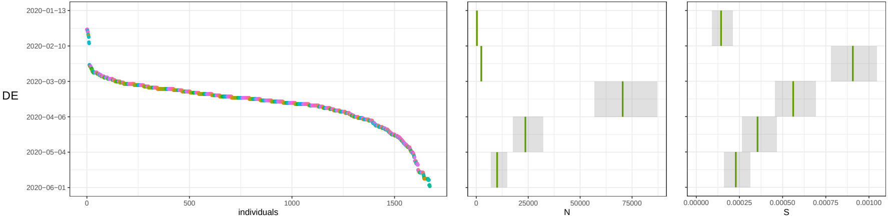

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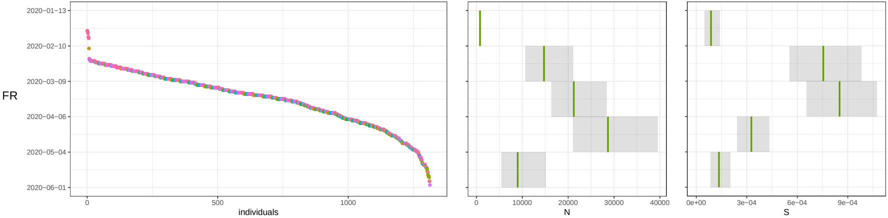

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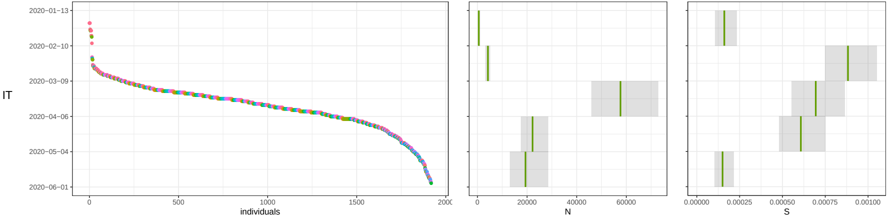

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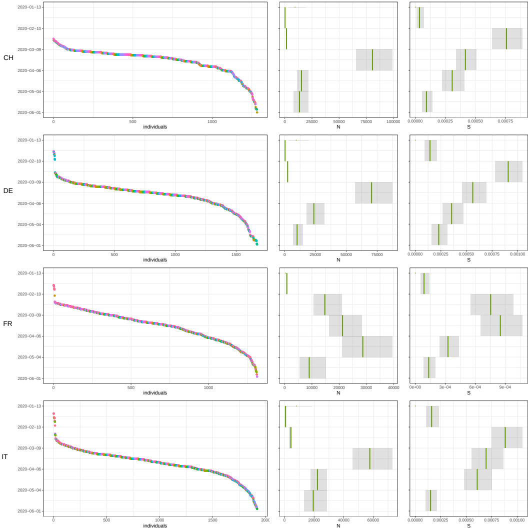

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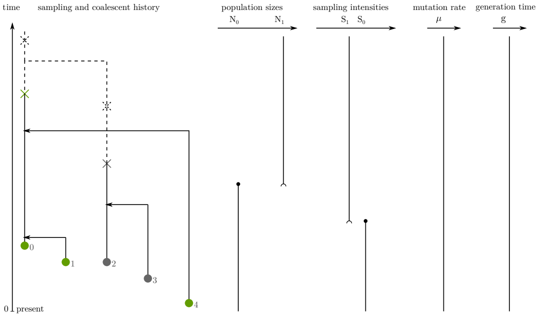
Opportunities for future developments – simulation study

How does it compare in terms of statistical power with a finite sites model ?
What signal do we loose by forgetting about the coalescent history above the first mutation ?
When does the trade-off between computation time and precision turn in favor of an infinite alleles model ?

- This could be assessed based on inferences on simulations.



- We can imagine some datasets with large allele families AND very different alleles.

Can we combine in a clever way an infinite alleles model near the tips
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Discussion

Opportunities for future developments – simulation study

How does it compare in terms of statistical power with a finite sites model ?
What signal do we loose by forgetting about the coalescent history above the first mutation ?
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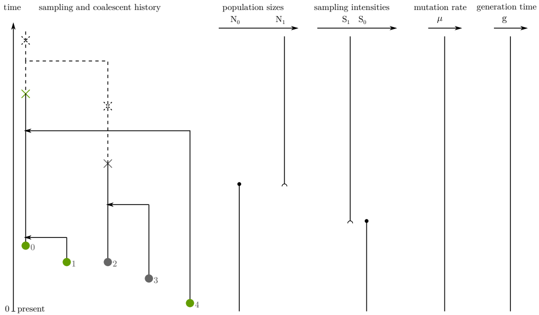

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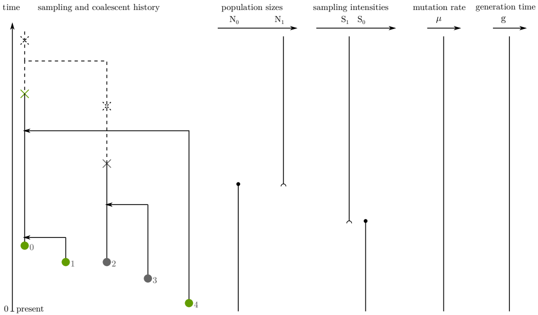

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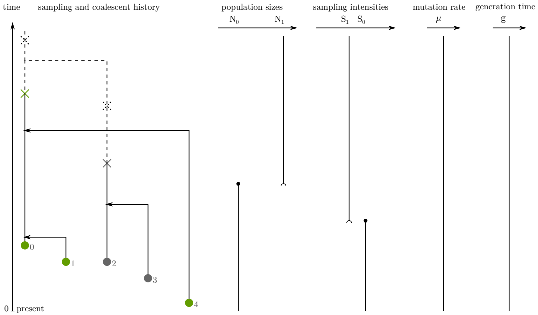

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Opportunities for future developments – Focus on running time

- It is still way too slow to apply to large (SARS-CoV-2 like) datasets.

Can we improve the running time and hope to take into account much larger datasets ?

1. Work on basic numerical optimization / parallelize chains.
2. Find a more optimized update of $\mathcal{H}$, possibly using approximations.
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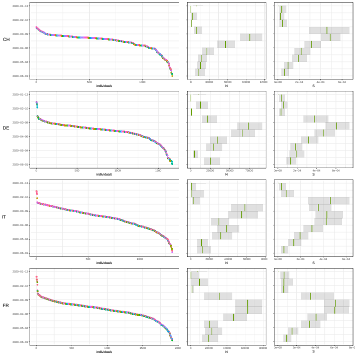
- We don't want to believe in huge steps from a time period to another.



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1. They could be agnostic about the process, chosen because they satisfy nice conjugacy properties.
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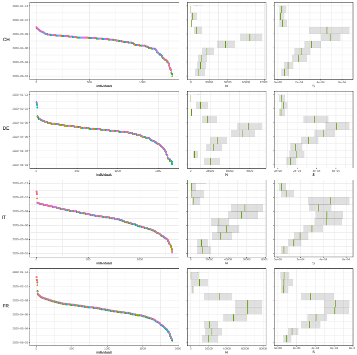

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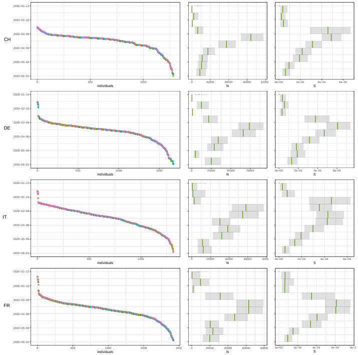

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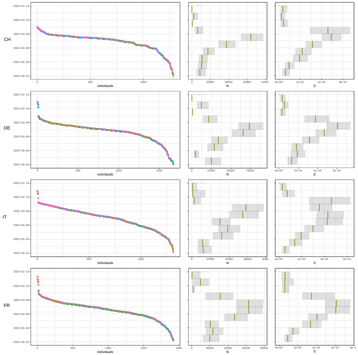

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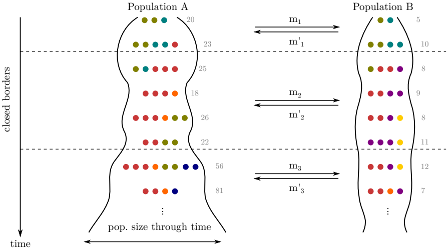
Opportunities for future developments – Demes and migrations

- The patterns of alleles across borders, with sampling through time, could inform on migration patterns.



How can we extend this work to a coalescent with demes and migrations between demes ?

1. The same augmentation strategy (one genome at a time) is likely to work as well.
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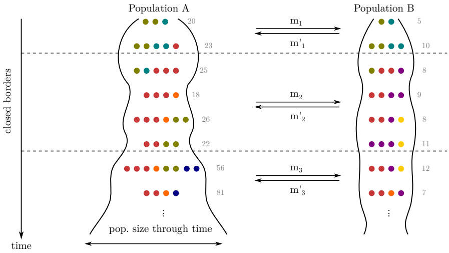

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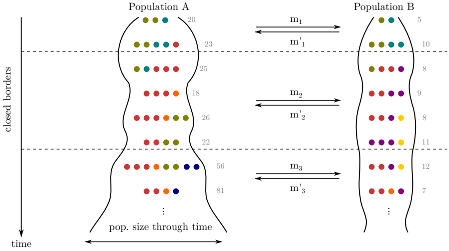

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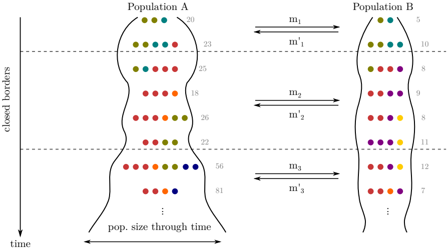

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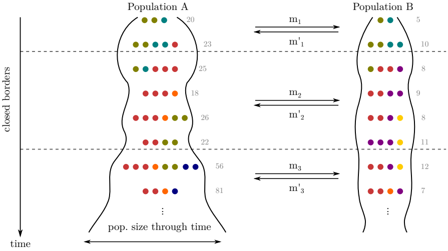

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1. Input data: an allele partition of sequences sampled through time,
2. Output inference: N, S, μ, g,
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