ABC for Temporally Sampled Genetic Data

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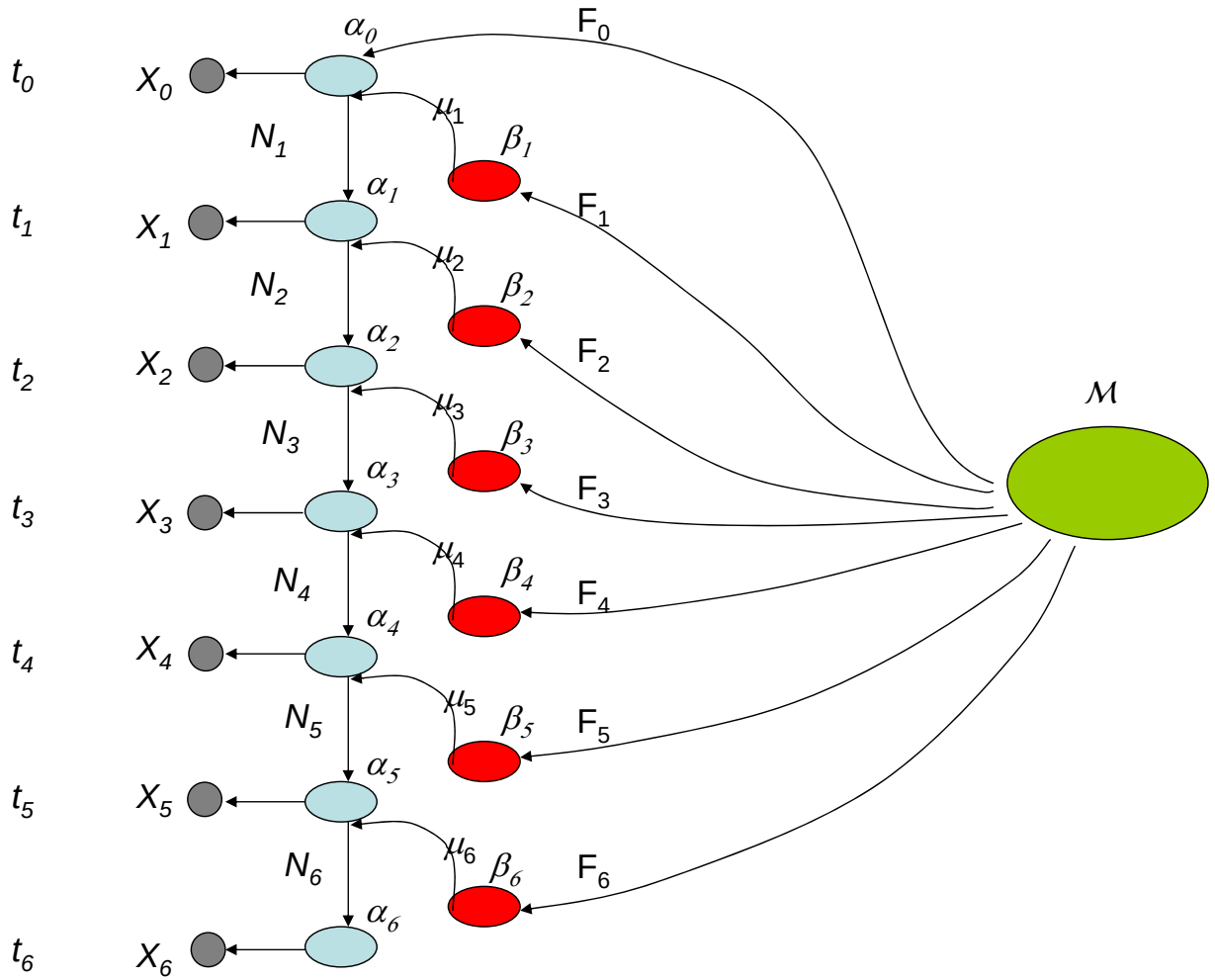
Temporal Change in Gene Frequency with Admixture

Aim is to infer parameters in a state space model of changes in gene frequency in the presence of admixture.



Temporal Change in Gene Frequency with Admixture

- Temporally sampled genetic data is quite commonly obtained.
- Changes are usually attributed to genetic drift (a function of the population size).
- However admixture and replacement of populations over time may be confounded with drift.
- This is a major issue for ancient DNA samples

Importance Sampling, Particles, and MCMC

- Beaumont (Genetics, 2003); GIMH algorithm; using noisy estimates of likelihood obtained from sequential importance sampling in MCMC.
- Becquet and Przeworski (Genome Research, 2007); application of GIMH idea to MCMC-ABC algorithm of Marjoram et al (PNAS, 2003).
- Andrieu and Roberts (Annal. Stat. 2009)Pseudo-marginal method: convergence proofs and generalization of GIMH.
- Andrieu, Doucet, and Holenstein (RSSB, 2010); Particle MCMC
- Peters and Cornebise (RSSB, discussion of A,D,&H, 2010); ABC and particle MCMC.

Framework for Temporal Model with Admixture (1)

S temporal samples are taken.

- t_i Time of ith sample ($i = 0, \ldots, S$).
- Δt_j Difference between time of jth and $(j-1)$th sample ($j = 1, \ldots, S$).
- N_j Effective population size for jth interval.
- μ_j Admixture proportion for jth interval.
- F_i F_{ST} of ith admixing population.

Framework for Temporal Model with Admixture (2)

Use a Dirichlet rather than coalescent to model variance in allele frequencies:

- Laval *et al.*, (Genetics, 2003)
- Kitakado *et al.*, (Genetics, 2006)

This does not give the same allele frequency distribution as the coalescent, but for a given F_{ST}, the variance is the same (see discussant contributions to Nicholson *et al* (RSSB, 2002)).

Framework for Temporal Model with Admixture (3)

For frequency vector α_i of length K alleles, sampled at time t_i, we model the change in frequency due to drift over the interval Δt_i with effective size N_i as

$$\alpha_i \sim D(\phi_i \alpha'_{(i-1),1}, \ldots, \phi_i \alpha'_{(i-1),K})$$

where

$$\phi_i = \frac{\exp(-\Delta t_i / N_i)}{(1 - exp(-\Delta t_i / N_i))}.$$

The observed frequencies, X_i are assumed to be multinomial samples from α_i

Framework for Temporal Model with Admixture (4)

Admixture is modelled as

$$\alpha'_{i-1} = (1 - \mu_i)\alpha_{i-1} + \mu_i \beta_i.$$

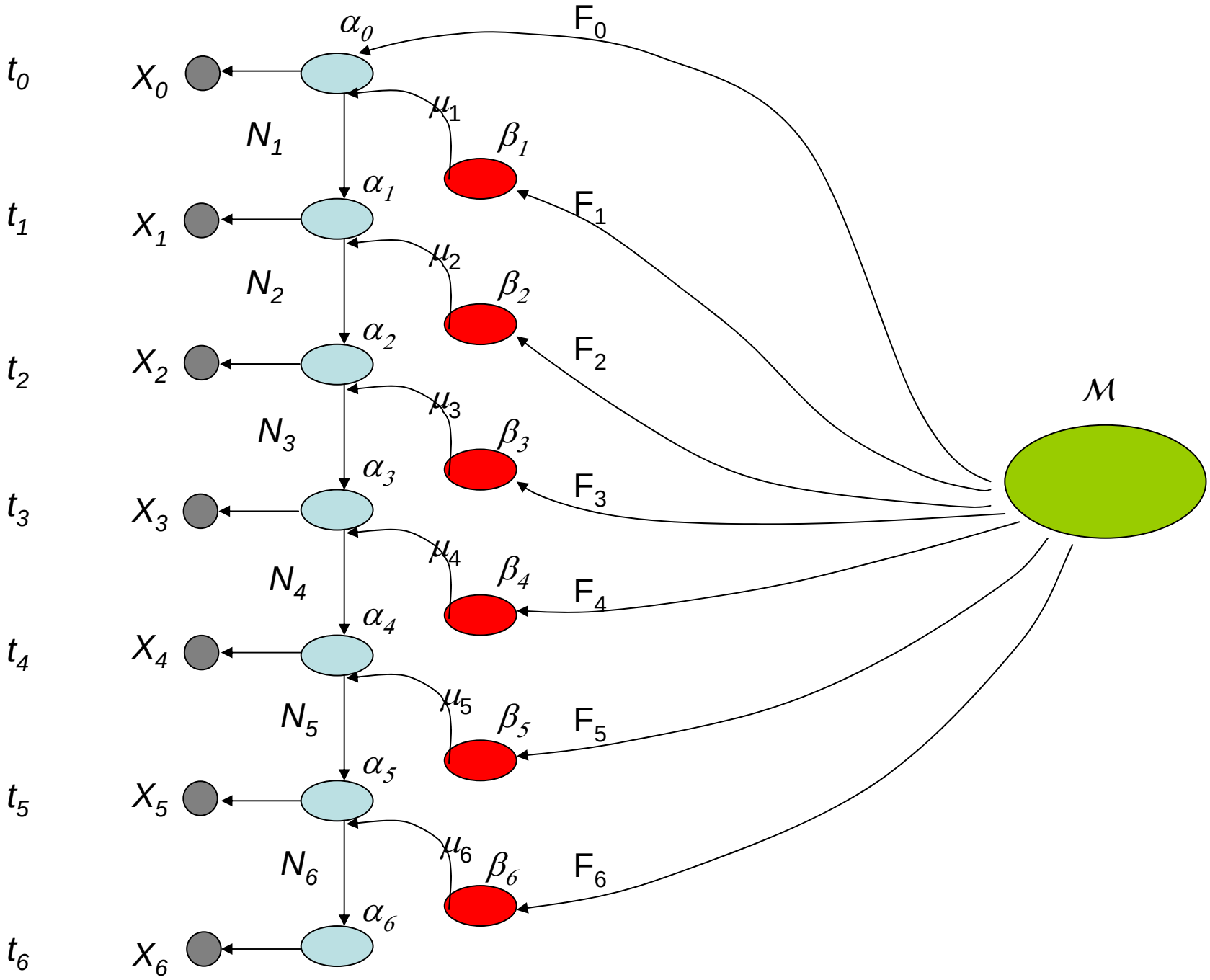
The admixing frequencies β_j, $(j = 1, \ldots, S)$, and the initial α_0, are drawn from Dirichlet distributions, parameterized by F_i $(i = 0, \ldots, S)$, and metapopulation frequency $\mathcal{M}$. *E.g*:

$$\beta_1 \sim D(\theta_1 \mathcal{M}_1, \ldots, \theta_1 \mathcal{M}_K)$$

with

$$\theta_1 = \frac{1}{F_1} - 1$$

(Sewall Wright's infinite island model)



MCMC implementation of TMA

Aim is to infer parameters in this model in a Bayesian framework.
The likelihood is:

$$P(X_0|\alpha_0)P(\alpha_0|F_0,\mathcal{M})$$
$$\times \prod_{i=1}^{S}\{P(X_i|\alpha_i)P(\alpha_i|\alpha_{i-1},N_i,\Delta t_i,\mu_i,\beta_i)P(\beta_i|F_i,\mathcal{M})\}$$

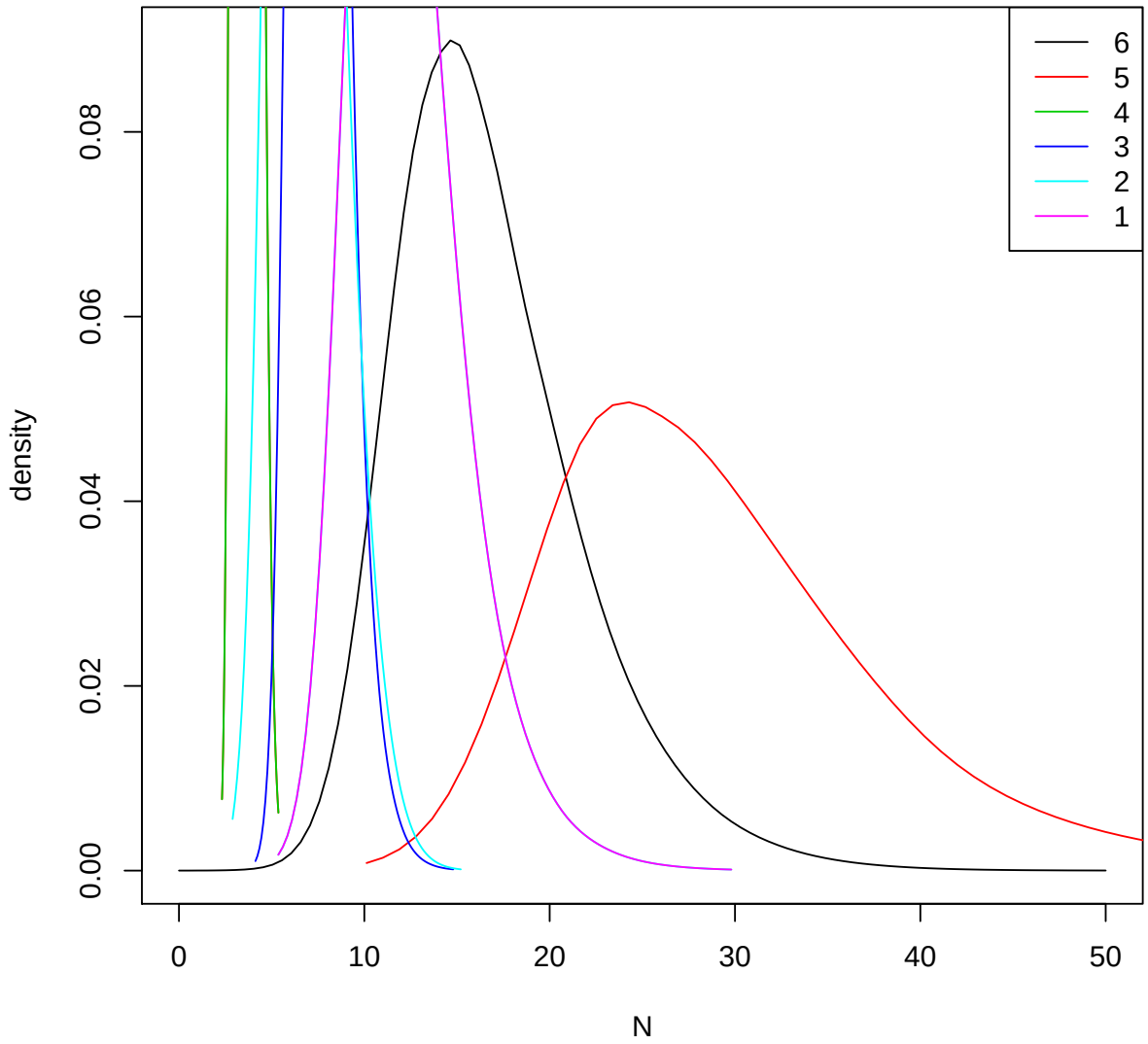
- The t_is are known.
- Assume a hierarchical prior on N_i (Gaussian on log-scale)
- Assume beta priors on μ_i and F_i
- Assume Dirichlet prior on $\mathcal{M}$

Update parameters using Metropolis-Hastings.

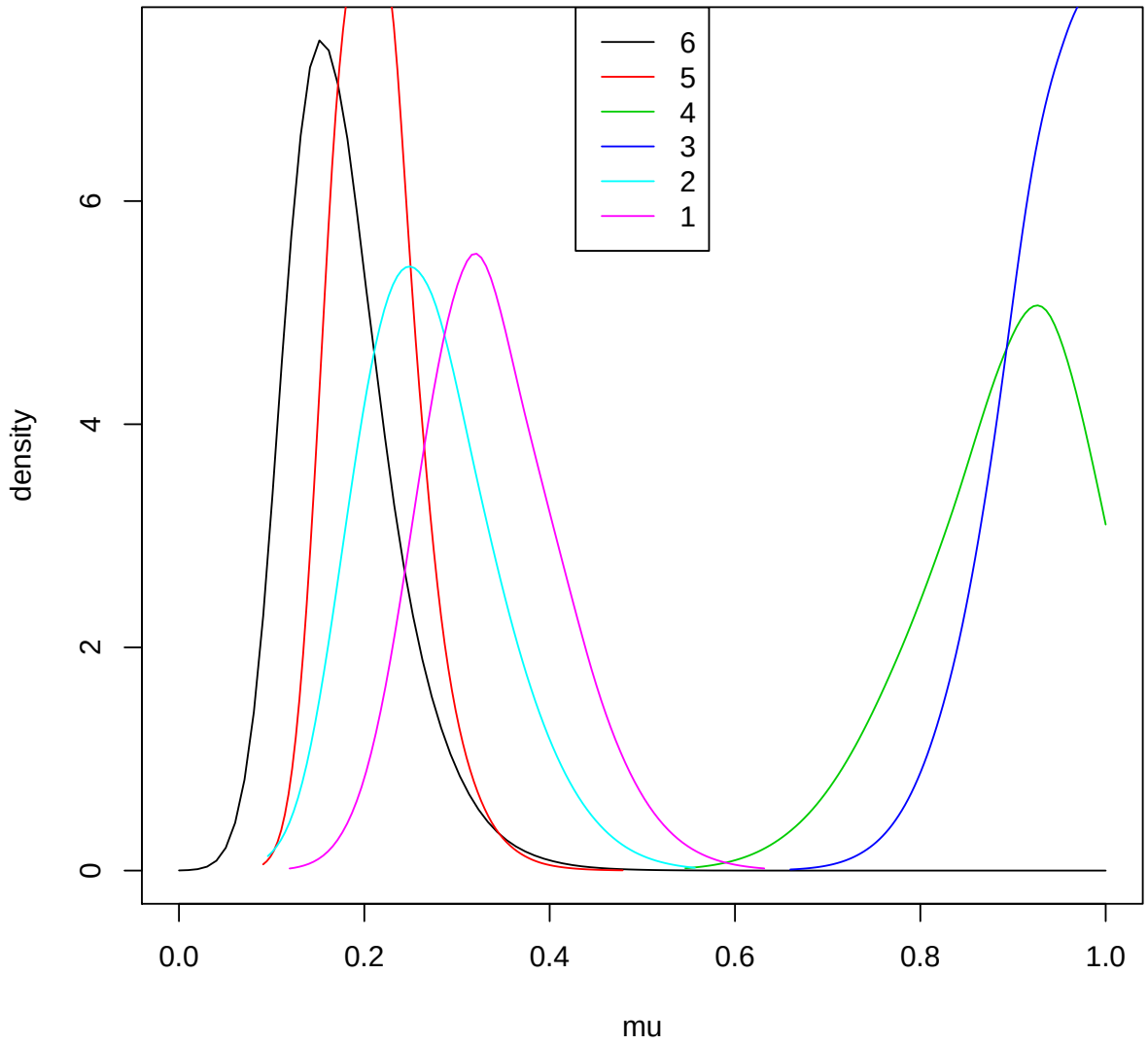
Application to Bryozoan data

1. Data from a freshwater Bryozoan, *Cristatella mucedo*, studied by Beth Okamura (NHM, London) and Sophia Ahmed (Roscoff, France).
2. 8 highly polymorphic microsatellite loci genotyped by Sophia Ahmed.
3. Sampled over 7 time periods.
4. Gene frequencies change markedly; unlikely to be due to drift.
5. Aim is to estimate effective population sizes, admixture proportions, and F_{ST} of putative admixing populations.

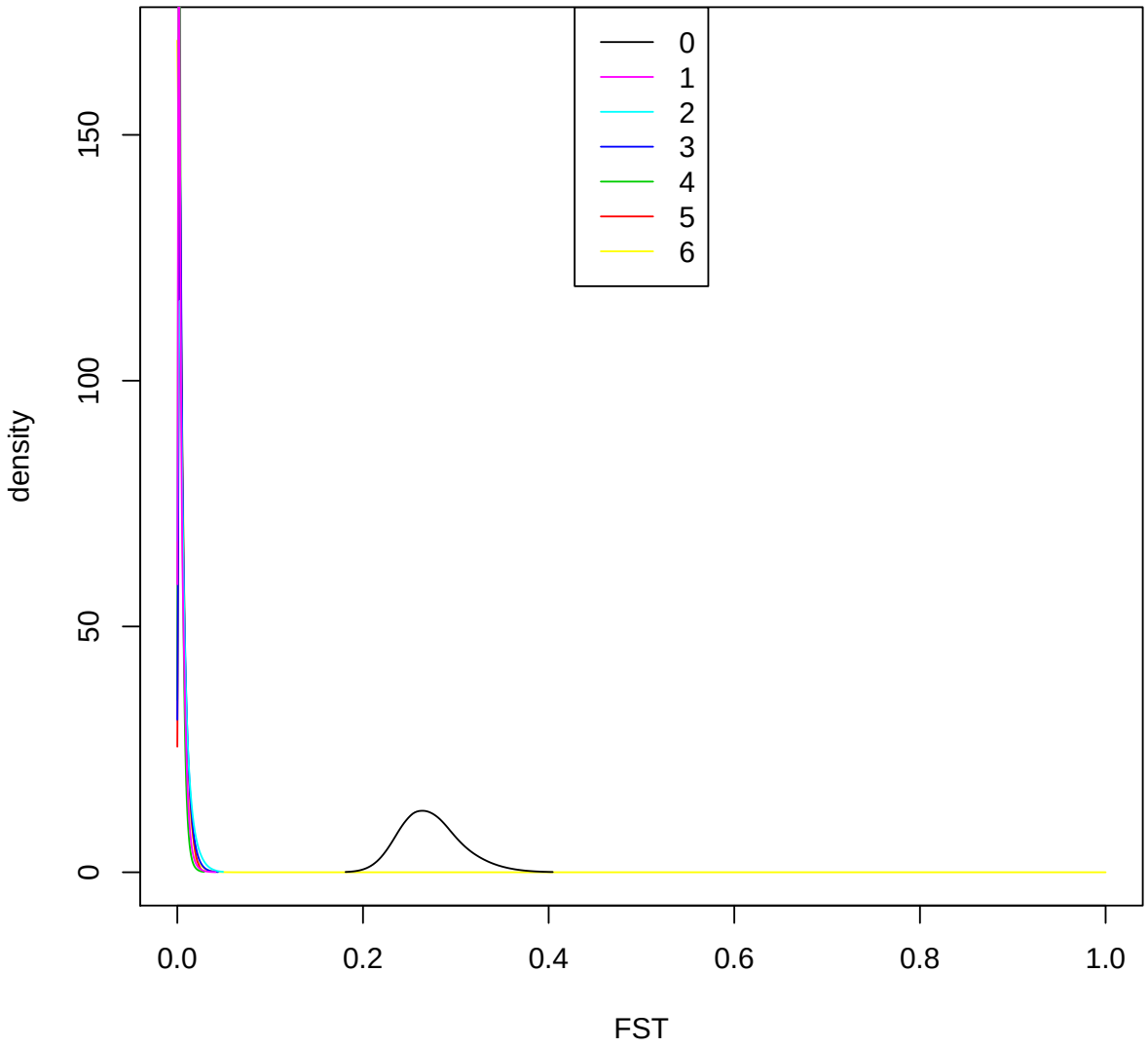
Bryozoan data: results with MCMC algorithm



Cryozoan data: results with MCMC algorithm



Bryozoan data: results with MCMC algorithm

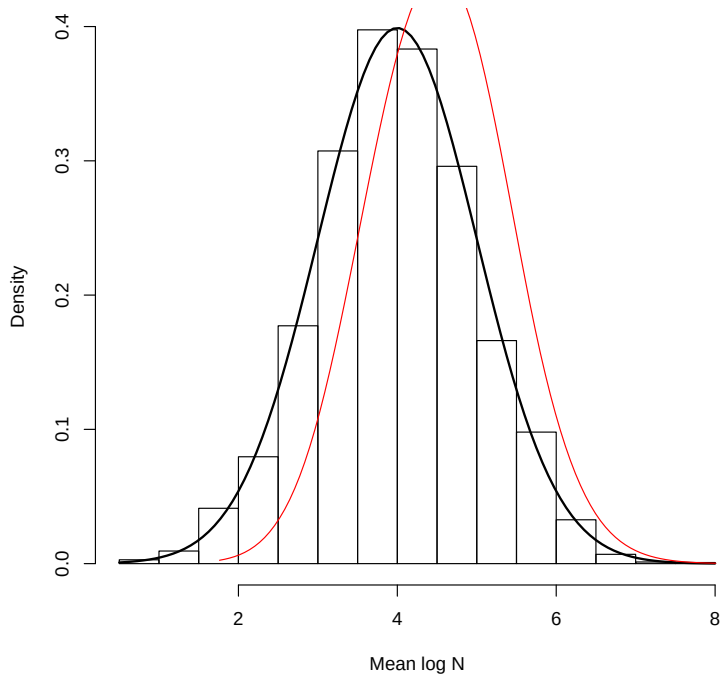


Convergence of MCMC

Comparison of runs with likelihood held constant, to check for recovery of priors.

Data sampled at 4 time points, 2 loci, 5 alleles each.

Histogram — α_i held constant Red line — α_i updated Black line — prior $\Gamma(4,1)$



Particle MCMC Implementation of TMA

Aim is to avoid MCMC updates for $\alpha_1, \ldots, \alpha_S$, but use MCMC for all other parameters (including α_0).

At each MCMC step, use importance sampling of the α_i to compute noisy likelihood estimate, conditioning on all parameter values at that stage in the MCMC.

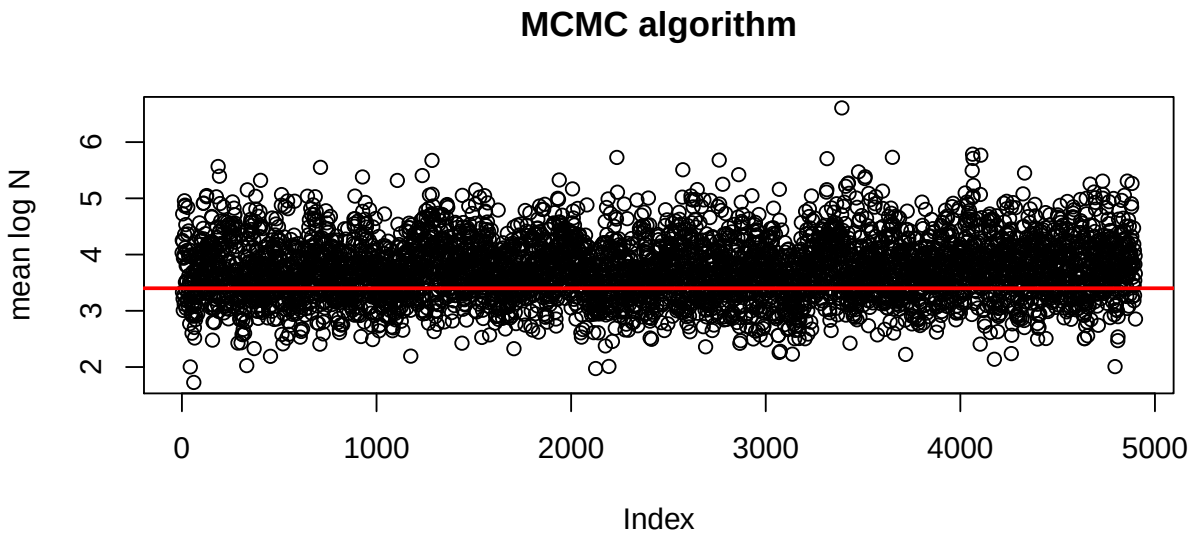
Particle MCMC Implementation of TMA

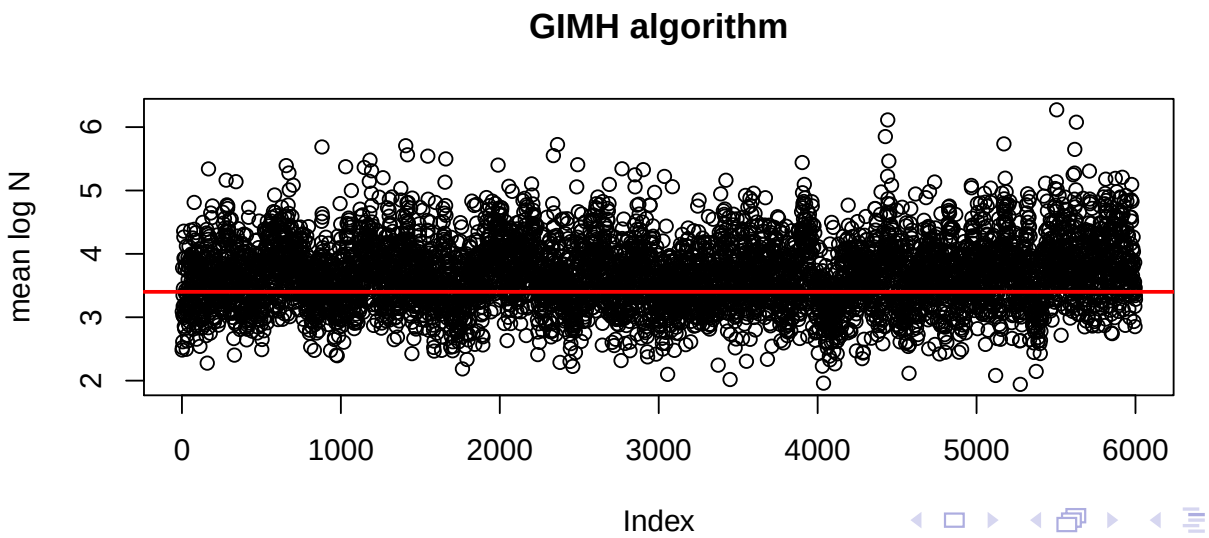
Schematic Algorithm

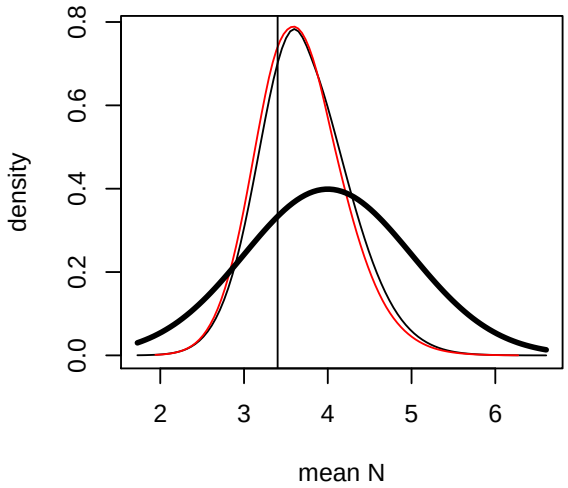
1. For sample point 1:
   1. set $\phi_1 = \frac{\exp(-\Delta t_1/N_1)}{(1-exp(-\Delta t_1/N_1))}$.
   2. Simulate M particles: $\alpha_1^{(j)} \sim q(\alpha_1^{(j)}) := D(\{\phi_1 + X_1\}\alpha_0')$.
   3. Compute importance weight $W_1^{(j)} = p(X_1|\alpha_1^{(j)})p(\alpha_1^{(j)}|\alpha_0', \phi_1)/q(\alpha_1^{(j)})$.
   4. Set $\tilde{L}_1 = 1/M \sum W_1^{(j)}$.
2. For sample points $i > 1$:
   1. Set ϕ_i.
   2. Simulate M particles: $\alpha_i^{(j)} \sim q(\alpha_i^{(j)}) := D(\{\phi_i + X_i\}\alpha_{i-1}^{\prime(j)})$, where
      $\alpha_{i-1}^{\prime(j)} = (1-\mu_i)\alpha_{i-1}^{(j)} + \mu_i\beta_i$
      where $\alpha_{i-1}^{(j)}$ is sampled from particles at step $i-1$ with weight $W_{i-1}^{(l)}$, $l = 1, \ldots, M$
   3. Compute weights *etc.* as for time step 1.
3. Set $\tilde{L} = P(X_0|\alpha_0)\prod_{i=1}^{S}\tilde{L}_i$.

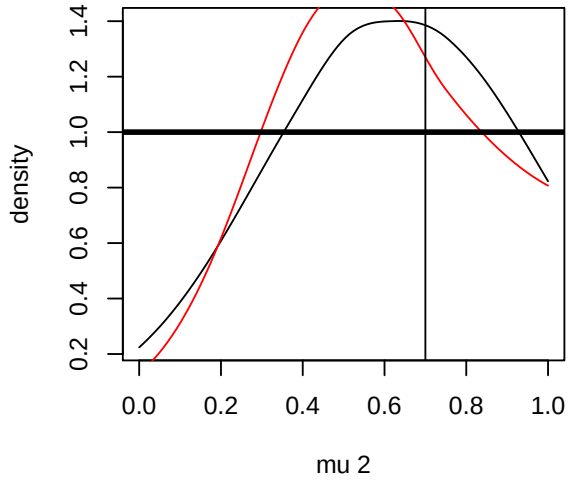
Results from Particle MCMC

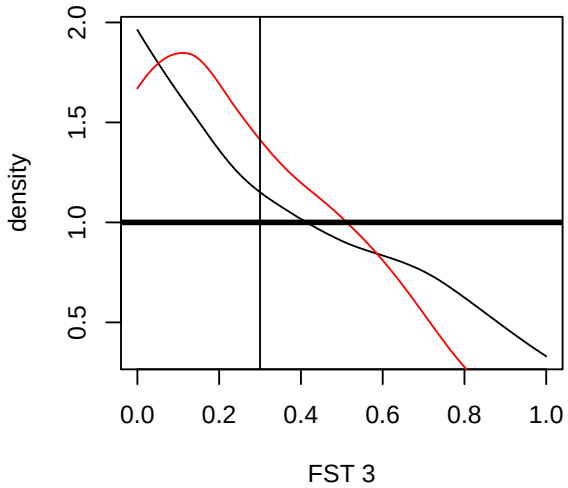
Trace of mean N











ABC and Particle MCMC

Motivation is to see whether this approach is feasible and competitive with particle MCMC.

Replace importance estimate of $\tilde{L}_i$ with proportion of simulated points that are within tolerance interval.

ABC and Particle MCMC: application to TMA

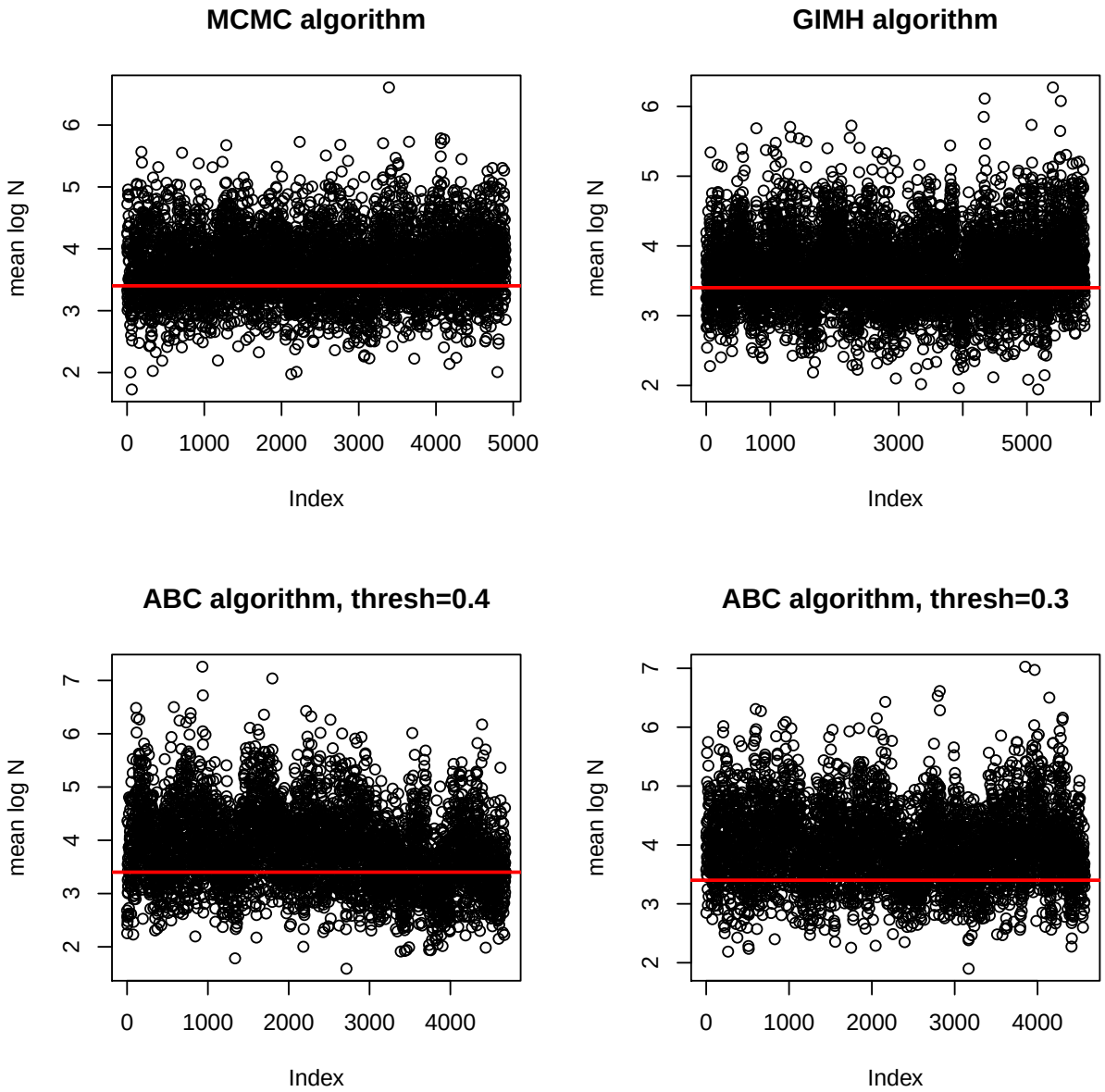
Implementation

1. For sample point 1:
   1. set $\phi_1 = \frac{\exp(-\Delta t_1/N_1)}{(1-exp(-\Delta t_1/N_1))}$.
   2. Simulate M particles: $\alpha_1^{(j)} \sim D(\phi_1 \alpha_0')$, $X_1' \sim \text{Multinom}(\alpha_1^{(j)})$.
   3. Compute (0,1) weight $W_1^{(j)} = I(|X_1' - X_1| < \delta)$.
   4. Set $\tilde{L}_1 = 1/M \sum W_1^{(j)}$.
2. For sample points $i > 1$:
   1. Set ϕ_i.
   2. Simulate M particles: $\alpha_i^{(j)} \sim D(\phi_i \alpha_{i-1}'^{(j)})$, where $\alpha_{i-1}'^{(j)} = (1-\mu_i)\alpha_{i-1}^{(j)} + \mu_i \beta_i$ where $\alpha_{i-1}^{(j)}$ is sampled from particles at step $i-1$ with weight $W_{i-1}^{(l)}$, $l = 1, \ldots, M$.
   3. Compute weights *etc.* as for time step 1.
3. Set $\tilde{L} = P(X_0|\alpha_0) \prod_{i=1}^{S} \tilde{L}_i$.

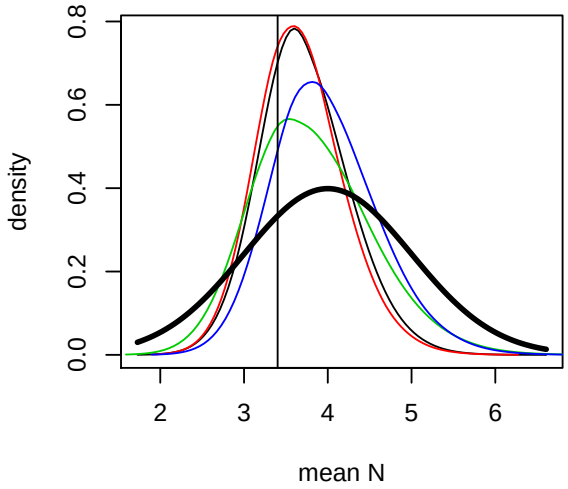
Summary Statistics

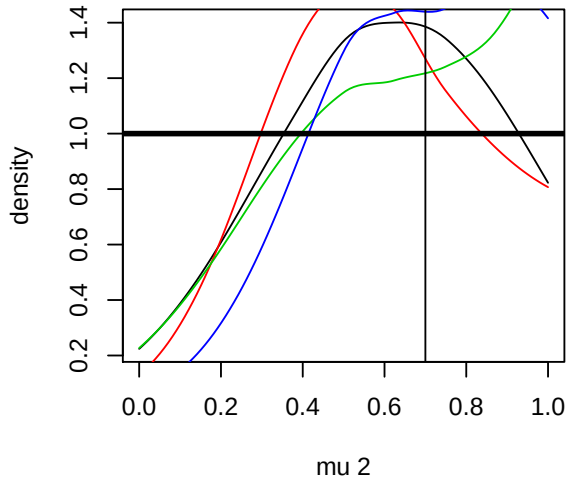
1. Allele frequency is used.
2. Compute $Q = 1/(K-1)\sum(X_i' - X_i)/(X_i + g)$ for alleles $i = 1, \ldots, K$.
3. For threshold R, accept if $Q < R$.
4. In examples, $R = 0{\cdot}3$ or $0{\cdot}4$ and $g = 1$.

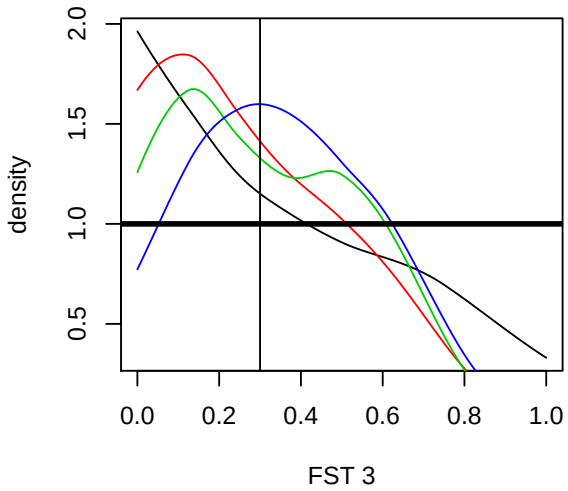
Results from Particle MCMC with ABC



Results from Particle MCMC with ABC







Acknowledgments

Beth Okamura Sophia Ahmed