Non-Parametric Bayesian Population Dynamics Inference

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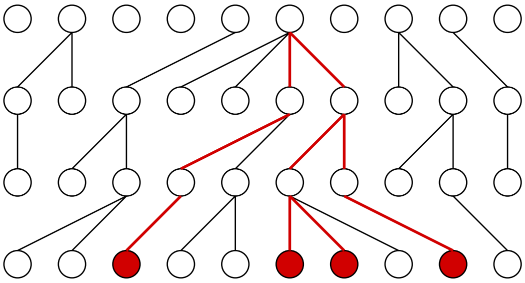
SISMID

Review: Continuous-Time Coalescent



- Time measured in N generation units
- N = const $\rightarrow u_k \sim \text{Exp}\left[\binom{k}{2}\right]$
- $N = N(t) \rightarrow$

  $$\Pr(u_k > t | t_{k+1}) = e^{-\binom{k}{2}\int_{t_{k+1}}^{t+t_{k+1}} \frac{N}{N(u)} du}$$
- u_k are not independent any more

- Constant population size
- Exponential growth

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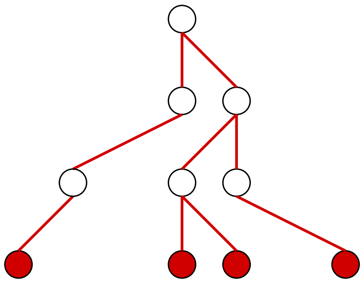

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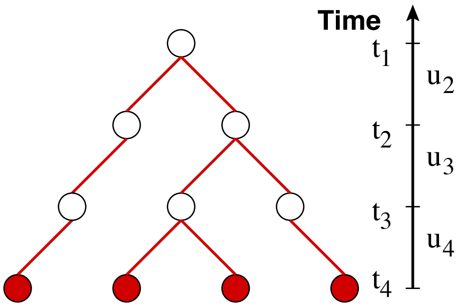

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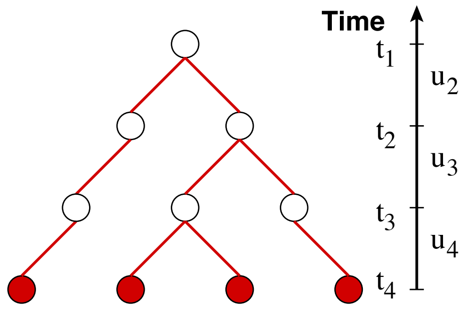

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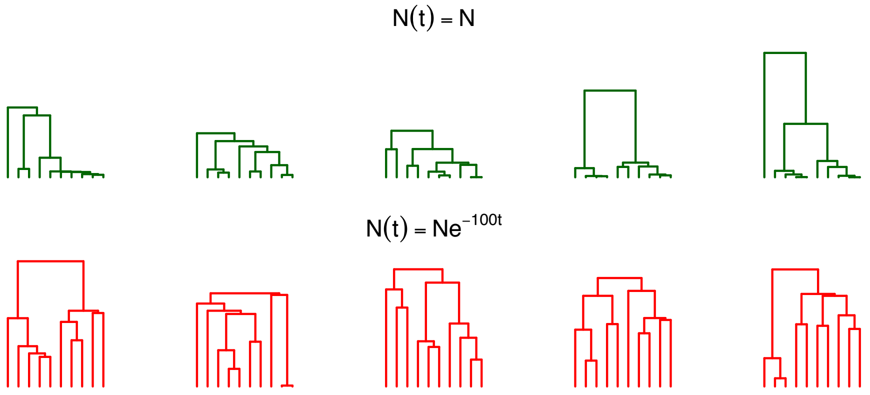
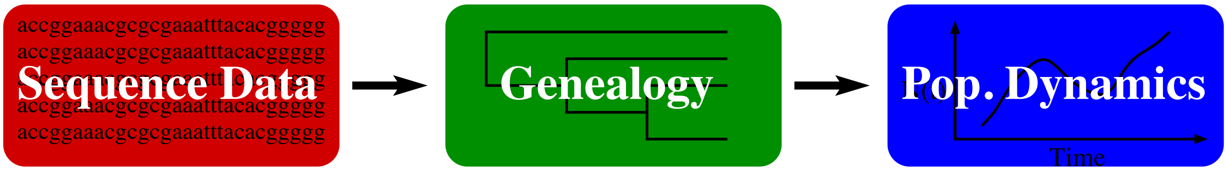


Sequence Data → Population Model Parameters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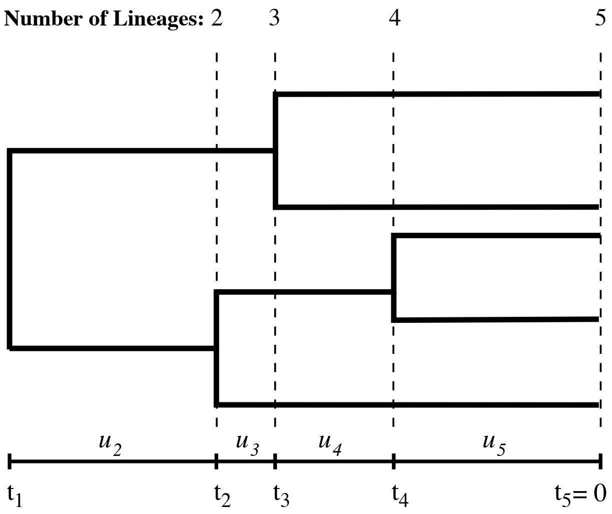
accggaaacgcgcgaaatttacacggggg
Time

Sequence Data → Genealogy → Pop. Dynamics

More Formally (Bayesian Approach):

- $\Pr(\mathbf{G}, \mathbf{Q}, \theta \mid \mathbf{D}) \propto \Pr(\mathbf{D} \mid \mathbf{G}, \mathbf{Q}) \Pr(\mathbf{Q}) \Pr(\mathbf{G} \mid \theta) \Pr(\theta)$
- **G** - genealogy with branch lengths
- **Q** - substitution matrix
- θ - population genetics parameters
- **D** - sequence data
- $\Pr(\mathbf{G} \mid \theta)$ - **Coalescent prior**

Piecewise Constant Demographic Model

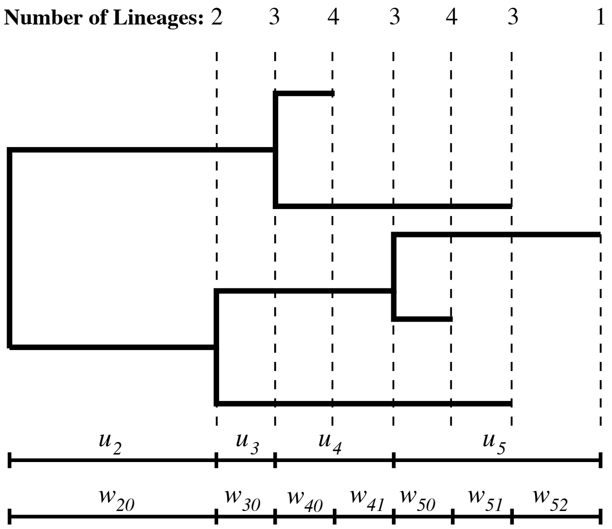


Isochronous Data

- $N_e(t) = \theta_k$ for $t_k < t \leq t_{k-1}$.
- $u_2, \ldots, u_n$ are independent
- $\Pr(u_k \mid \theta_k) = \frac{k(k-1)}{2\theta_k} e^{-\frac{k(k-1)u_k}{2\theta_k}}$
- $\Pr(\mathbf{F} \mid \boldsymbol{\theta}) \propto \prod_{k=2}^{n} \Pr(u_k \mid \theta_k)$

- Equivalent to estimating exponential mean from one observation.
- Need further restrictions to estimate θ!

Piecewise Constant Demographic Model



Heterochronous Data

- $w_{20}, \ldots, w_{nj_n}$ are independent
- $\Pr(w_{k0} \mid \theta_k) = \frac{n_{k0}(n_{k0}-1)}{2\theta_k} e^{-\frac{n_{k0}(n_{k0}-1)w_{k0}}{2\theta_k}}$
- $\Pr\left(w_{kj} \mid \theta_k\right) = e^{-\frac{n_{kj}(n_{kj}-1)w_{kj}}{2\theta_k}}, j > 0$
- $\Pr(\mathbf{F} \mid \boldsymbol{\theta}) \propto \prod_{k=2}^{n} \prod_{j=0}^{j_k} \Pr(w_{kj} \mid \theta_k)$

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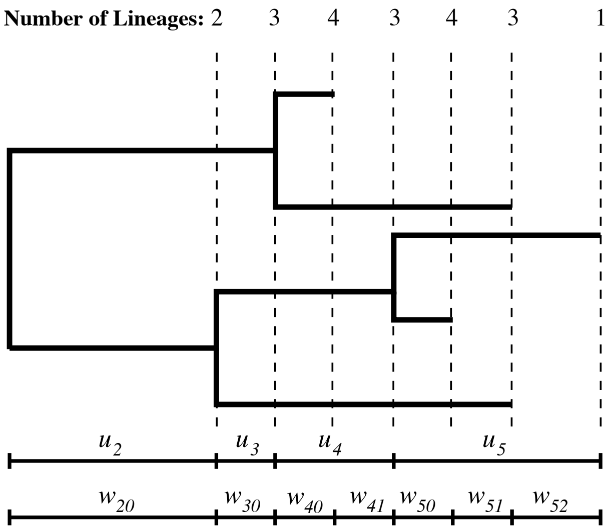

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Current Approaches

Strimmer and Pybus (2001)

- Make $N_e(t)$ constant across some inter-Coalescent times
- Group inter-Coalescent intervals with AIC

Drummond et al. (2005)

- Multiple change-point model with fixed number of change-points
- Change-points allowed only at Coalescent events
- Joint estimation of phylogenies and population dynamics

Opgen-Rhein et al. (2005)

- Multiple change-point model with random number of change-points
- Change-points allowed anywhere in interval $(0, t_1]$
- Posterior is approximated with rjMCMC

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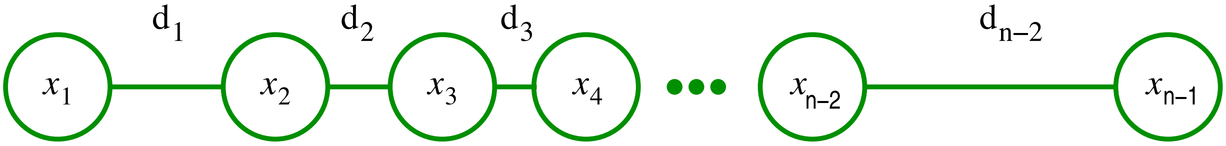
Smoothing Prior (GMRF approach)

- Go to the log scale $x_k = \log \theta_k$
- $\Pr(\mathbf{x} \mid \omega) \propto \omega^{(n-2)/2} \exp\left[-\frac{\omega}{2}\sum_{k=1}^{n-2}\frac{1}{d_k}(x_{k+1}-x_k)^2\right]$



Weighting Schemes

1. Uniform: $d_k = 1$
2. Time-Aware: $d_k = \frac{u_{k+1}+u_k}{2}$

- $\Pr(\mathbf{x}, \omega) = \Pr(\mathbf{x} \mid \omega)\Pr(\omega)$
- $\Pr(\omega) \propto \omega^{\alpha-1}e^{-\beta\omega}$, diffuse prior with $\alpha = 0.01$, $\beta = 0.01$

MCMC Algorithm

$$\Pr(\mathbf{G}, \mathbf{Q}, \mathbf{x} \mid \mathbf{D}) \propto \Pr(\mathbf{D} \mid \mathbf{G}, \mathbf{Q}) \Pr(\mathbf{Q}) \Pr(\mathbf{G} \mid \mathbf{x}) \Pr(\mathbf{x})$$

Updating Population Size Trajectory

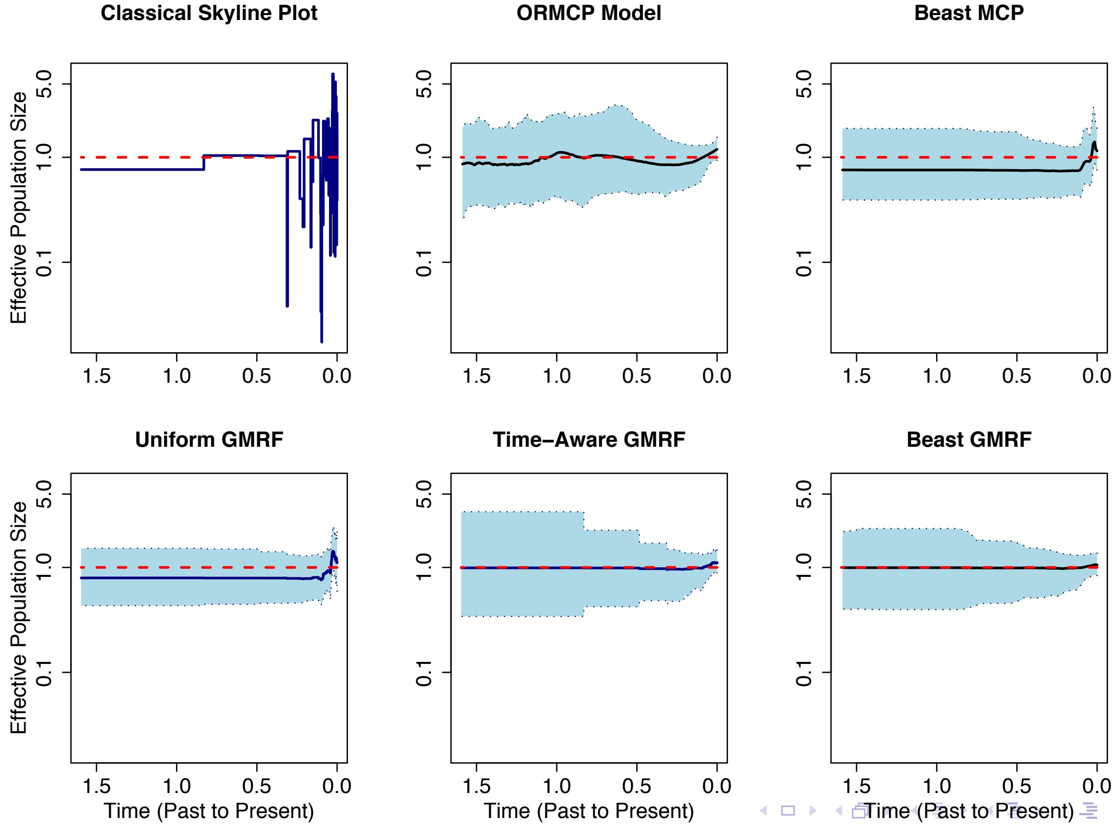
- Use fast GMRF sampling (Rue et al., 2001, 2004)
- Draw ω^* from an arbitrary univariate proposal distribution
- Use Gaussian approximation of $\Pr(\mathbf{x} \mid \omega^*, \mathbf{G})$ to propose $\mathbf{x}^*$
- Jointly accept/reject $(\omega^*, \mathbf{x}^*)$ in Metropolis-Hastings step

Object-Oriented Reality?

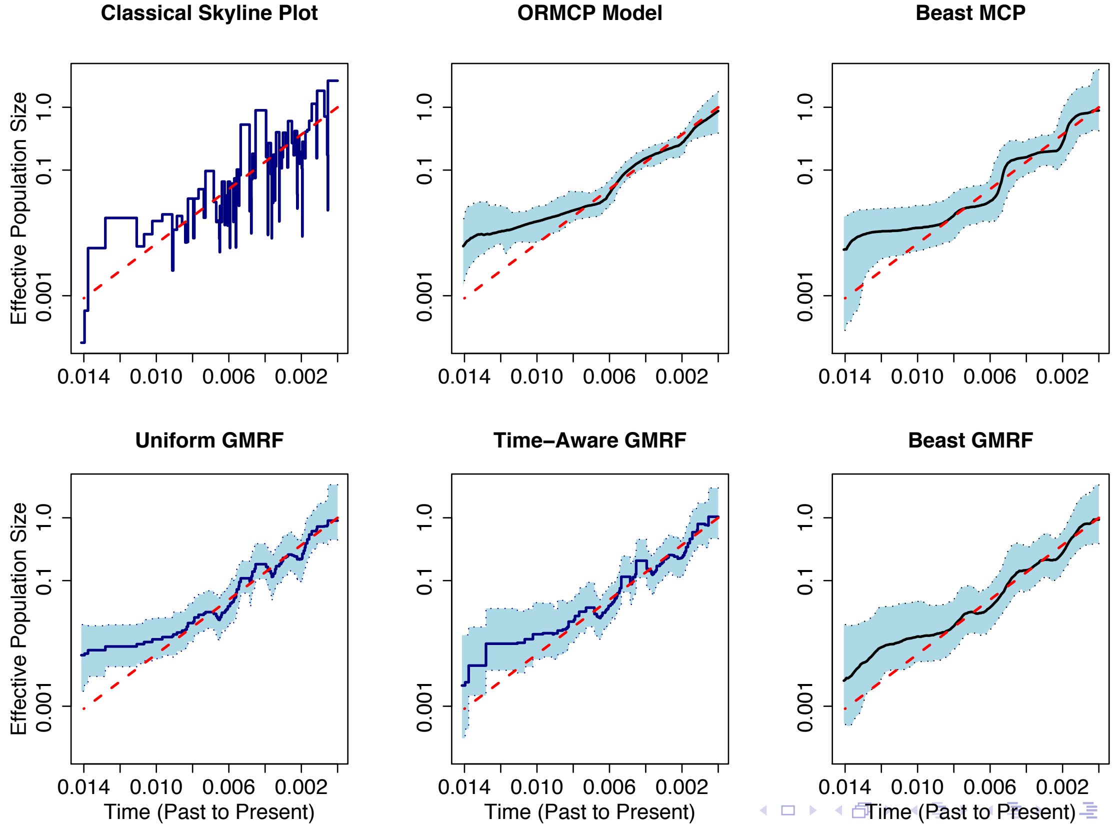
BEAST = **B**ayesian **E**volutionary **A**nalysis **S**ampling **T**rees

- $\Pr(\mathbf{G} \mid \mathbf{x}, \mathbf{D}, \mathbf{Q})$ - sampled by BEAST
- $\Pr(\mathbf{Q} \mid \mathbf{G}, \mathbf{D})$ - sampled by BEAST

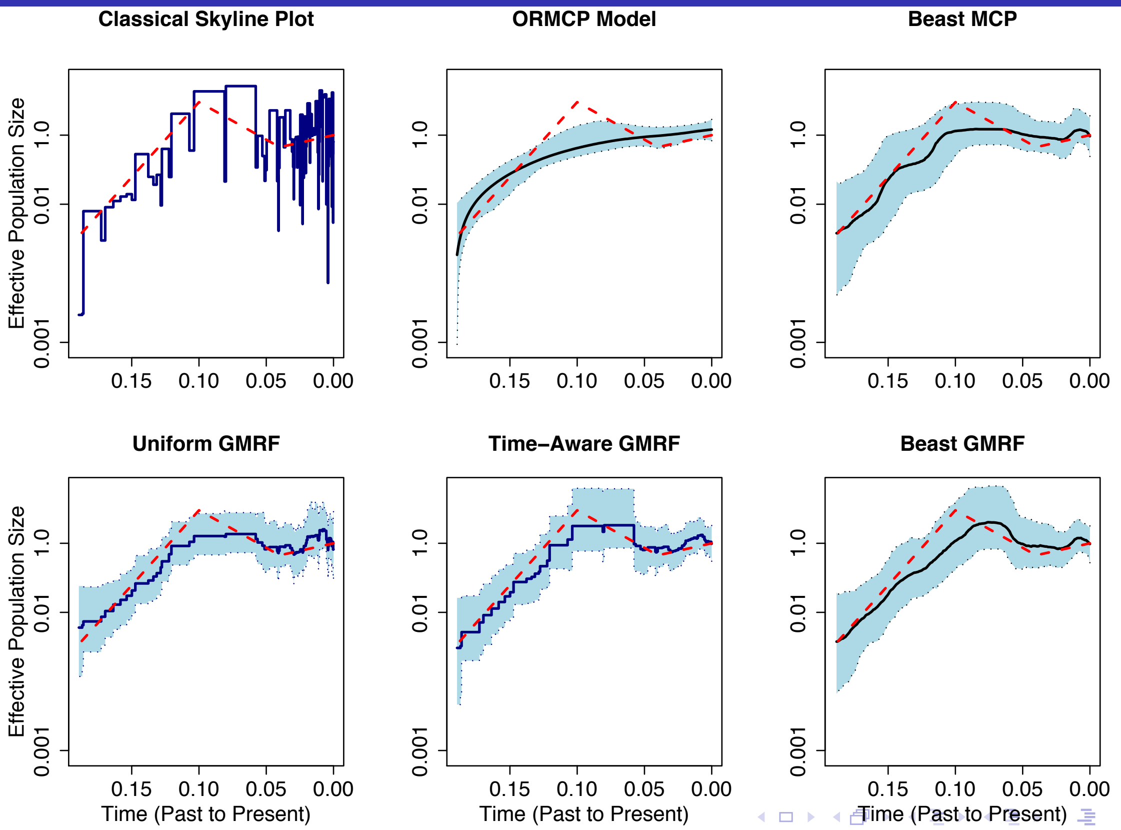
Simulation: Constant Population Size



Simulation: Exponential Growth



Simulation: Exponential Growth with Bottleneck



Accuracy in Simulations

$$\text{Percent Error} = \int_0^{\text{TMRCA}} \frac{|\widehat{N}_e(t) - N_e(t)|}{N_e(t)} dt \times 100, \qquad (1)$$

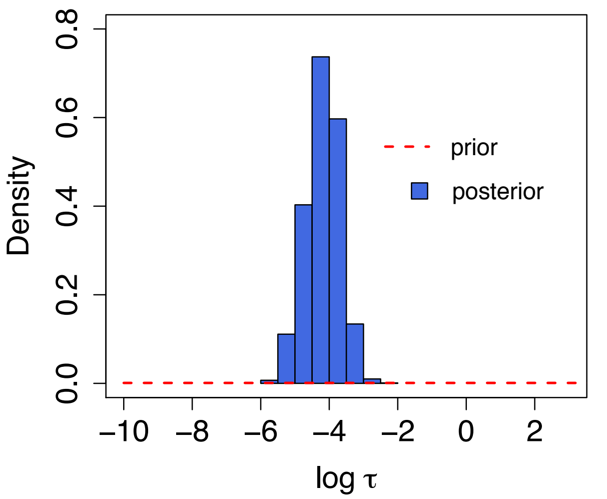
Table: Percent error in simulations. We compare percent errors, defined in equation (1), for the Opgen-Rhein multiple change-point (ORMCP), uniform and fixed-tree time-aware Gaussian Markov random field (GMRF) smoothing, BEAST multiple change-point (MCP) model, and BEAST GMRF smoothing.

Model	Constant	Exponential	Bottleneck
ORMCP	14.0	1.7	7.4
Uniform GMRF	32.8	1.5	5.9
Time-Aware GMRF	2.8	1.2	4.8
BEAST MCP	38.2	1.6	5.2
BEAST GMRF	1.7	1.0	5.4

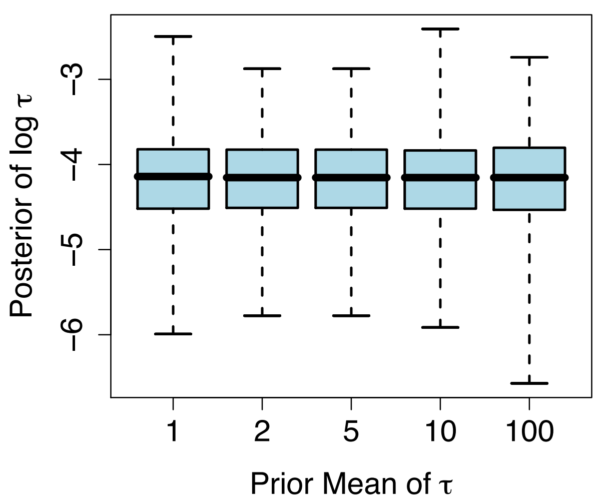
GMRF Precision Prior Sensitivity

- ω - GMRF precision, controls smoothness
- Usually $\Pr(\omega \mid \mathbf{D})$ is sensitive to perturbations of $\Pr(\omega)$
- Not in our Coalescent model!

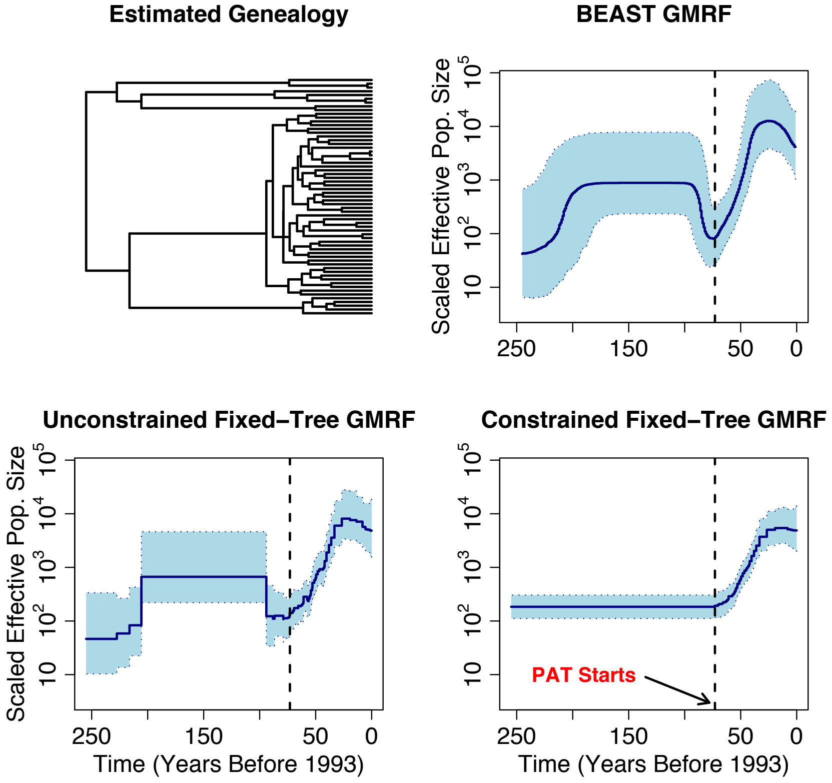
GMRF Precision Prior and Posterior



GMRF Precision Sensitiviy to Prior

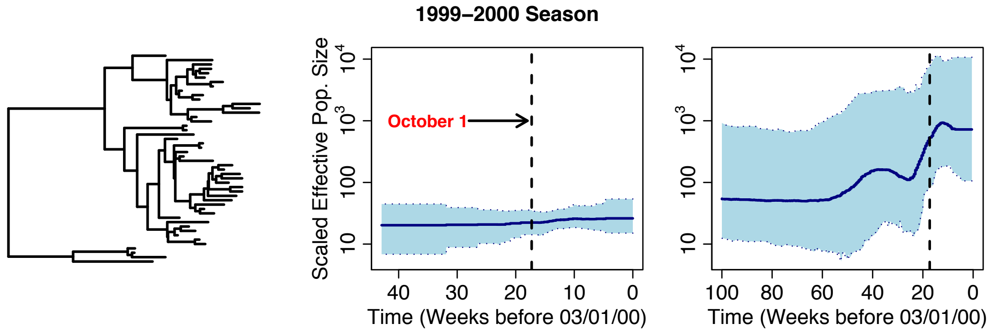


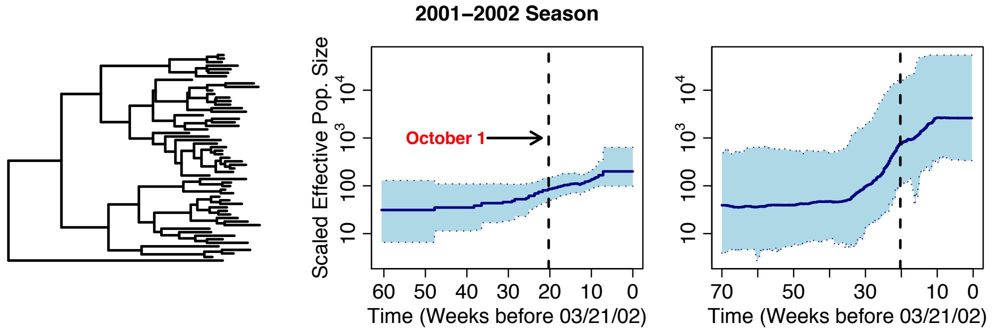
HCV Epidemics in Egypt



- Random population sample
- No sign of population sub-structure
- Parenteral antischistosomal therapy (PAT) was practiced from 1920s to 1980s
- Bayes Factor 12,880 in favor of constant population size prior to 1920

Influenza Intra-Season Population Dynamics





New York state hemagglutinin sequences serially sampled (Ghedin et al., 2005)

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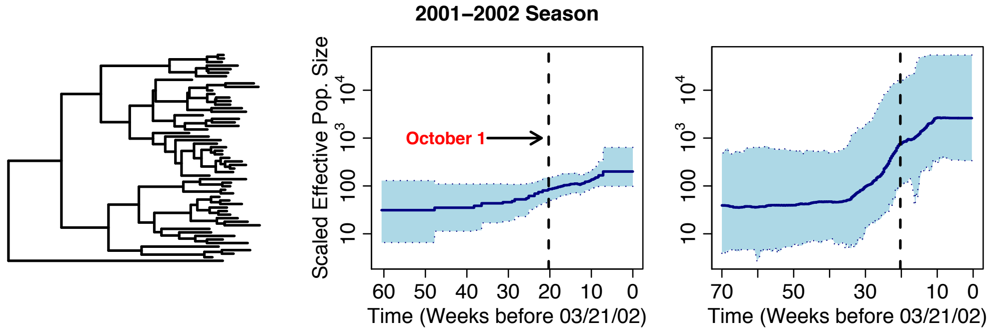

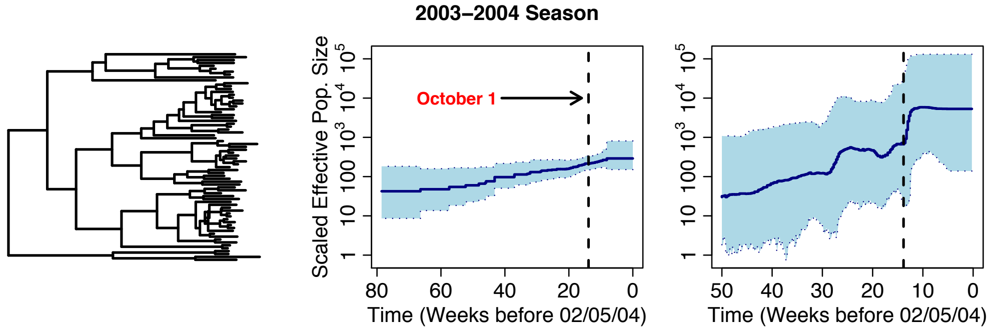

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Summary

- Genealogies inform us about population size trajectories
- Prior restrictions are necessary for non(semi)-parametric estimation of $N_e(t)$
- Smoothing can be imposed by GMRF priors

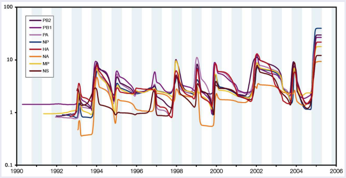
Software: The Skyride

- Implemented as a Coalescent prior in BEAST
- Exploits approximate Gibbs sampling
- Faster convergence? Better mixing?

Reference: Minin, Bloomquist and Suchard (2008) *Molecular Biology & Evolution*, 25, 1459–1471.

Active Ideas: GMRFs are Highly Generalizable

Hierarchical Modeling

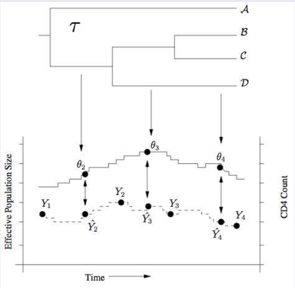


Flu genes display similar (not equal) dynamics

- Incorporate multiple loci simultaneously
- Pool information for statistical power
- No need for strict equality

Introducing Covariates

- Augment field at fixed observation times
- Formal statistical testing for:
  - External factors (environment, drug tx)
  - Population dynamics (bottle-necks, growth)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$\mathcal{A}$
$\mathcal{B}$
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θ_2
θ_3
θ_4
Y_1
Y_2
Y_3
Y_4
$\hat{Y}_2$
$\hat{Y}_3$
$\hat{Y}_4$
Effective Population Size
CD4 Count
Time