

Inference of natural selection from allele frequency time series data using exact simulation techniques

Jaromir Sant*

joint work with

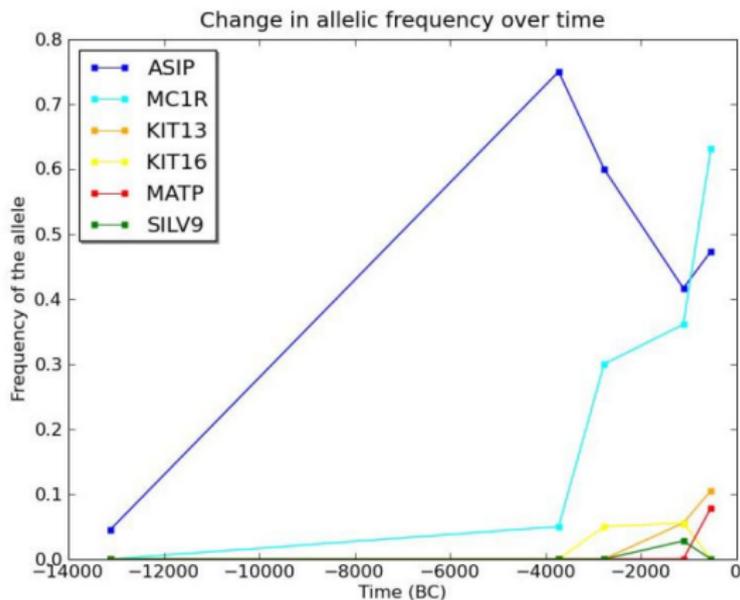
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University of Warwick

*Alan Turing Institute, London

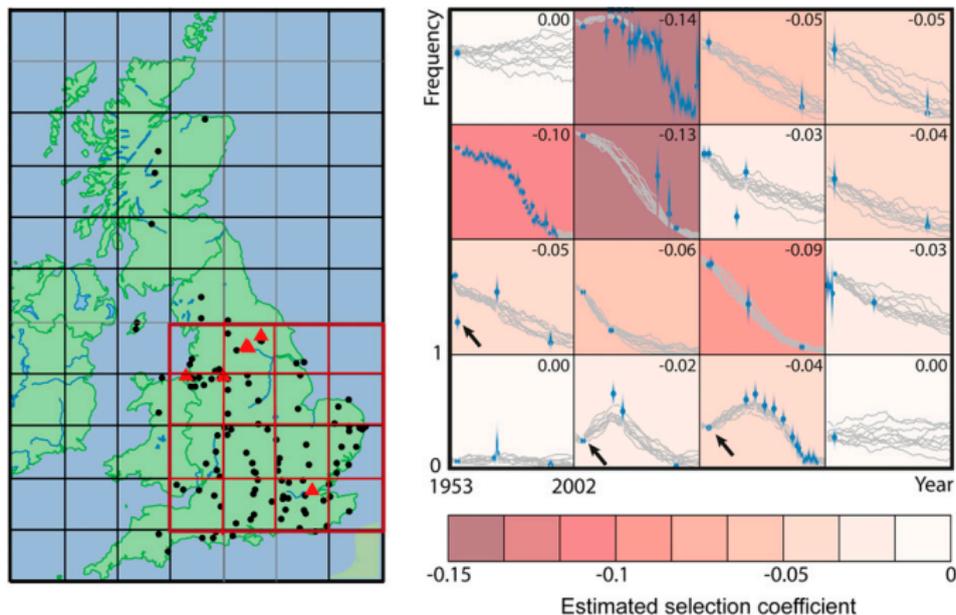
February 12, 2021

- Advances in gene sequencing + improvements in aDNA retrieval
 \implies allele frequency time series becoming more common



Ludwig et al (2009)

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Mathieson & McVean (2013)

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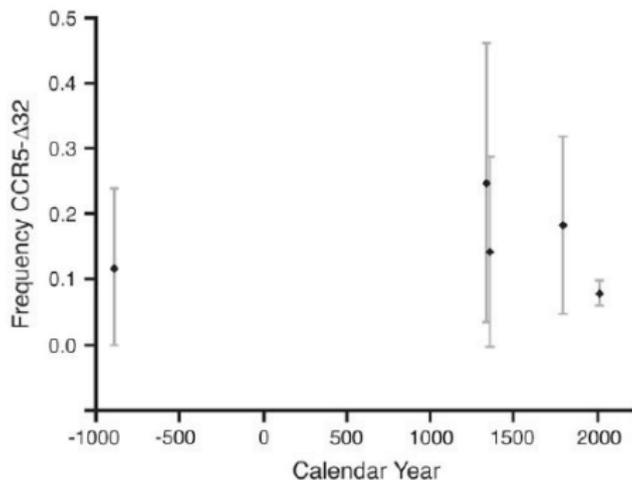


FIGURE 2.—Time-series data for the CCR5-Δ32 data (HUMMEL *et al.* 2005). Binomial confidence intervals are shown as shaded bars.

- 1 Bollback et al., 2008. "Estimation of $2N_e s$ From Temporal Allele Frequency Data."
- 2 Ludwig et al., 2009. "Coat color variation at the beginning of horse domestication."
- 3 Illingworth et al., 2012. "Quantifying Selection Acting on a Complex Trait Using Allele Frequency Time Series Data."
- 4 Malaspina et al., 2012. "Estimating Allele Age and Selection Coefficient from Time-Serial Data."
- 5 Sirén et al., 2012. "Inference on Population Histories by Approximating Infinite Alleles Diffusion."
- 6 Mathieson & McVean, 2013. "Estimating Selection Coefficients in Spatially Structured Populations from Time Series Data of Allele Frequencies."
- 7 Ferrer-Admetlla et al., 2014. "An Approximate Markov Model for the Wright-Fisher Diffusion and Its Application to Time Series Data."
- 8 Foll et al., 2014. "Influenza Virus Drug Resistance: A Time-Sampled Population Genetics Perspective."
- 9 Steinrücken et al., 2014. "A novel spectral method for inferring general diploid selection from time series genetic data."
- 10 Schraiber et al., 2016. "Bayesian Inference of Natural Selection from Allele Frequency Time Series."
- 11 Gonçalves et al., 2017. "Barker's algorithm for Bayesian inference with intractable likelihoods."
- 12 Gory et al., 2018. "Bayesian Inference of Selection in the Wright-Fisher Diffusion."
- 13 Stern et al., 2019. "An approximate full-likelihood method for inferring selection and allele frequency trajectories from DNA sequence data."
- 14 Dehasque et al., 2020. "Inference of natural selection from ancient DNA."
- 15 He et al., 2020. "Detecting and Quantifying Natural Selection at Two Linked Loci from Time Series Data of Allele Frequencies with Forward-in-Time Simulations."
- 16 He et al., 2020. "Estimation of Natural Selection and Allele Age from Time Series Allele Frequency Data Using a Novel Likelihood-Based Approach."
- 17 Kon Kam King et al., 2020. "Exact inference for a class of non-linear hidden Markov models on general state spaces."
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Allele frequencies modelled via Wright-Fisher diffusion

$$dX_t = \frac{1}{2} (\sigma X_t(1 - X_t) - \theta_2 X_t + \theta_1(1 - X_t)) dt + \sqrt{X_t(1 - X_t)} dW_t$$

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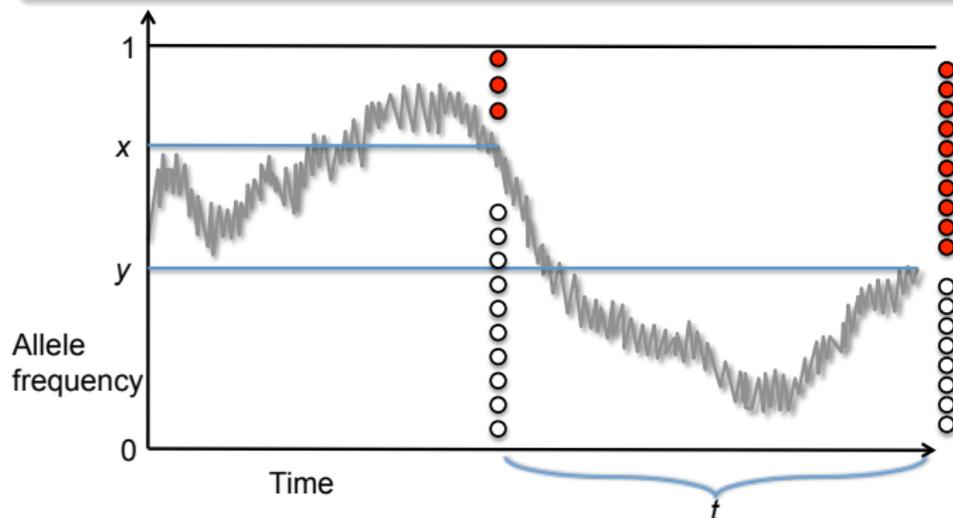
Conduct Bayesian inference on σ based on noisy observations $\{Y_{t_i}\}_{i=0}^n$ coming from WF diffusion $(X_t)_{t \geq 0}$

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Noisy observations
 $Y_{t_i} \sim \text{Bin}(N_{t_i}, X_{t_i})$

Data

Time 0: (10,3)

Time t: (8,10)

Standard Bayesian approach:

$$\begin{aligned}\mathbb{P}(\sigma|\mathbf{Y}) &\propto \mathbb{P}(\sigma)\mathbb{P}(\mathbf{Y}|\sigma) \\ &= \mathbb{P}(\sigma) \int_{[0,1]^n} \prod_{i=0}^n \text{Bin}_{N_{t_i}, x_{t_i}}(Y_{t_i}) \mathbb{P}(x_{t_0}|\sigma) p_{\sigma}^{\theta}(\Delta_i, x_{t_{i-1}}, x_{t_i}) d\mathbf{x}\end{aligned}$$

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- Euler-Maruyama not appropriate - WF has boundary behaviour!
- Should target $\mathbf{X}|\mathbf{Y}, \sigma$!

Neutral transition density

$$p_0^\theta(t, x, y) = \sum_{m=0}^{\infty} q_m(t) \sum_{\ell=0}^m \underbrace{\mathcal{B}_{m,x}(\ell)}_{\text{Binomial PMF}} \underbrace{\mathcal{D}_{\theta_1+\ell, \theta_2+m-\ell}(y)}_{\text{Beta density}},$$

where $q_m(t)$ is a known, time-dependent, mixture distribution on \mathbb{N} .

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Can simulate exactly from this distribution!

$$M \sim q_m(t),$$

$$(L \mid M = m) \sim \text{Binomial}(m, x),$$

$$(Y \mid M = m, L = \ell) \sim \text{Beta}(\theta_1 + \ell, \theta_2 + m - \ell).$$

$(q_m(t))_{m \in \mathbb{N}}$ is complicated but can be simulated from exactly.

(Jenkins & Spanò, 2017)

- $\mathbb{W}F_0$: probability measure for **neutral** paths X .
- $\mathbb{W}F_\sigma$: probability measure for **nonneutral** paths X .

Extending to non-neutral case?

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Neutral Wright-Fisher diffusion as a proposal?

- ✓ Absolute continuity: $\mathbb{W}\mathbb{F}_\sigma \ll \mathbb{W}\mathbb{F}_0$. (Dawson, 1978; Ethier & Kurtz, 1993)

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- ✓ Girsanov's formula (after some rearrangement):

$$\frac{d\mathbb{W}\mathbb{F}_\sigma}{d\mathbb{W}\mathbb{F}_0}(X) \propto \exp \left\{ A(X_T) - \int_0^T \varphi_\sigma(X_t) dt \right\} \leq 1,$$

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- ✗ **Problem:** Acceptance probability involves a complete path integral which cannot be computed.

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“Exact algorithm (EA)”

(Beskos & Roberts, 2005; Beskos et al., 2006, 2008)

- Key observation: The **RHS** is the probability of an event **that can be simulated with finite computation**.

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- Embed rejection into an MCMC scheme by augmenting the chain with the diffusion at the times of the Poisson points.

(Sermaidis et al., 2013)

Contribution to likelihood

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- Joint density of Φ, ω conditional on acceptance

$$\underbrace{e^{t(1-\lambda_\sigma)} \lambda_\sigma^\kappa}_{\text{RN of PPP}} \underbrace{\frac{1}{a(t, \vartheta, x, y)} \prod_{j=1}^{\kappa} 1_{\{\varphi_\sigma(\omega_{\psi_j}) - \varphi_\sigma^- < \gamma_j\}}}_{\text{RN of WF}}$$

wrt $\text{PP}^{(t,1)} \otimes \text{WF}_{0,\theta}^{(t,x,y)}$ with

$$a(t, \vartheta, x, y) = \mathbb{E}_{\text{WF}_{0,\theta}^{(t,x,y)}} \left[e^{-\int_0^t \varphi_\sigma(X_s) ds} \right]$$

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- **Problem!** Dominating measure depends on endpoints!

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$$\frac{d\mathbb{W}\mathbb{F}_{0,\theta}^{(x)}}{d\mathbb{W}\mathbb{F}_{0,\theta}^{(f_0,\theta)}}(X^t) = \frac{1_{\{X_0=x\}}(X^t)}{f_{0,\theta}(x)} = \frac{1}{f_{0,\theta}(x)}$$

- Setting $S(\omega) = \{(\psi_1, \omega_{\psi_1}), \dots, (\psi_\kappa, \omega_{\psi_\kappa})\}_{j=1}^\kappa$, then

$$e^{t(1-\lambda_\sigma)} \frac{\prod_{j=1}^\kappa (\varphi_\sigma^+ - \varphi_\sigma(\omega_{\psi_j}))}{a(t, \vartheta, x, y) p_0^\theta(t, x, y) f_{0, \theta}(x)}$$

is the density of $S(\omega)$ conditional on acceptance wrt the product measure $\mathbb{PP}^{(t)} \otimes \mathbb{WF}_{0, \theta}^{(t, f_0, \theta)}$

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- Dominating measure independent of latent diffusion values ✓
- But $a(t, \boldsymbol{\vartheta}, x, y)$ still untractable?
 - Cancels out with contribution from non-neutral transition density!

$$p_\sigma^\theta(t, x, y) = p_0^\theta(t, x, y) e^{\frac{\sigma}{2}(y-x)} a(t, \boldsymbol{\vartheta}, x, y)$$

Joint posterior density of σ , $\mathbf{S}(\omega)$, \mathbf{X} given observations \mathbf{Y} :

$$\begin{aligned}
 p(\sigma, \mathbf{S}(\omega), \mathbf{X} | \mathbf{Y}) &\propto p(\sigma) p(X_{t_0} | \sigma) \prod_{i=0}^n \binom{N_{t_i}}{Y_{t_i}} X_{t_i}^{Y_{t_i}} (1 - X_{t_i})^{N_{t_i} - Y_{t_i}} \\
 &\times \frac{\prod_{i=1}^n p_0^\theta(t_i - t_{i-1}, X_{t_{i-1}}, X_{t_i})}{p_0^\theta(t_n - t_0, X_{t_0}, X_{t_n})} e^{\frac{\sigma}{2}(X_{t_n} - X_{t_0}) - \lambda_\sigma(t_n - t_0)} \\
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infinite series! how to deal with endpoint updates?

Augmenting further?

Recall

$$p_0^\theta(t, x, y) = \sum_{m=0}^{\infty} q_m(t) \sum_{\ell=0}^m \underbrace{\mathcal{B}_{m,x}(\ell)}_{\text{Binomial PMF}} \underbrace{\mathcal{D}_{\theta_1+\ell, \theta_2+m-\ell}(y)}_{\text{Beta density}}$$

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Gibbs Sampler: Sequentially update

- σ conditional on $\mathbf{X}, \mathbf{S}(\omega)$ via MH step
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Proposals :

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- (informed) Beta proposals for X_{t_i} incorporating observations:

$$X_{t_i}^{n+1} \sim \text{Beta}(\theta_1 + Y_{t_i} + l_i, \theta_2 + N_{t_i} - Y_{t_i} + m_i - l_i)$$

	σ	θ_1	θ_2	Δ_i	X_{t_0}	N_{t_i}
True values	10	0.5	0.5	0.1	0.1	20

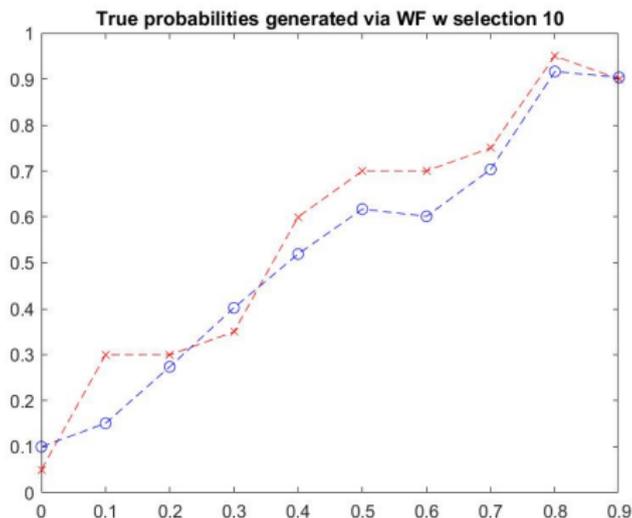
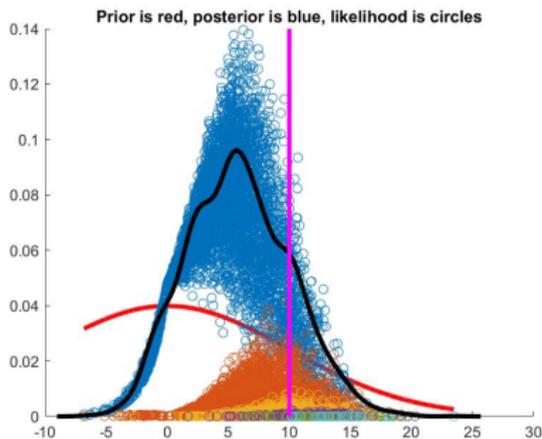
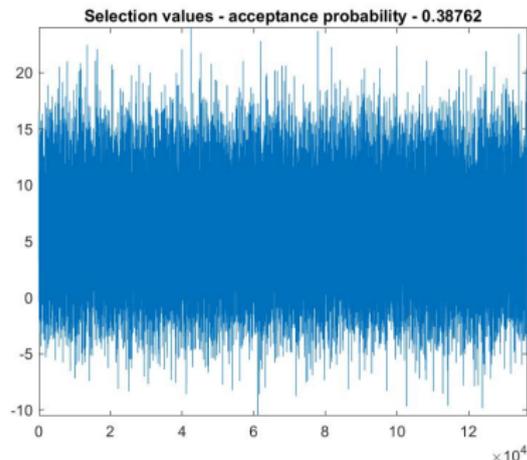


Figure: Exact draws from WF blue circle, Binomial draws red crosses

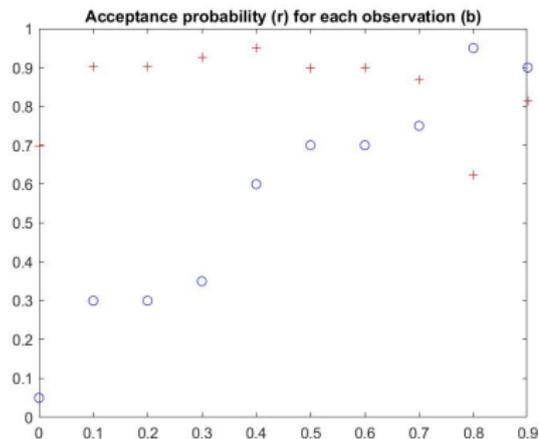


(a) Prior (red), Likelihood (circles),
(kernel smoothed) Posterior (black),
Truth (magenta)

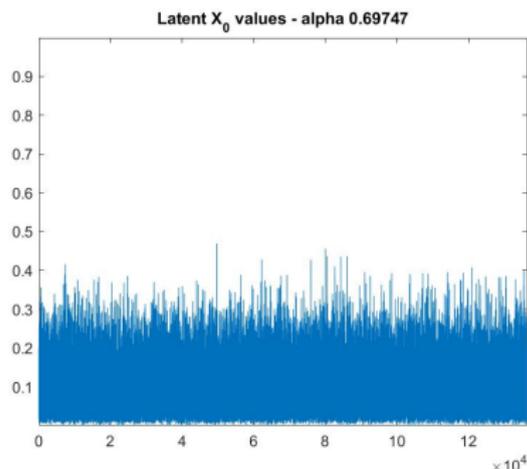


(b) Traceplot for σ

Prior : $\sigma \sim N(0, 10)$



(a) Acceptance probabilities (red crosses), Observed values (blue circles)



(b) Traceplot for X_{t_0}

Prior : $X_{t_0} \sim \text{Unif}([0, 1])$... a bit unrealistic!

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 - Aim to run on Ludwig et al (2009) horse coat colouration aDNA dataset

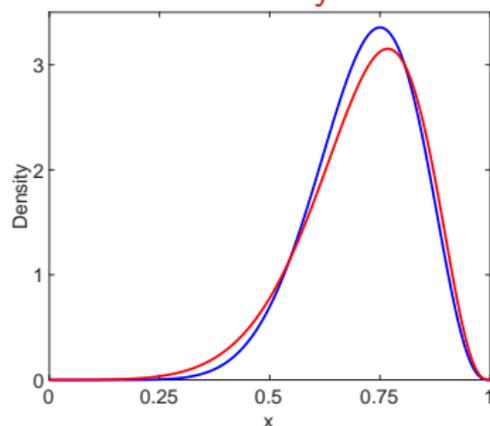
Future Work

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1. Identifiability issues



Blue: $\theta_1 = 10, \theta_2 = 4, \sigma = 0$

Red: $\theta_1 = 4, \theta_2 = 4, \sigma = 4.5$

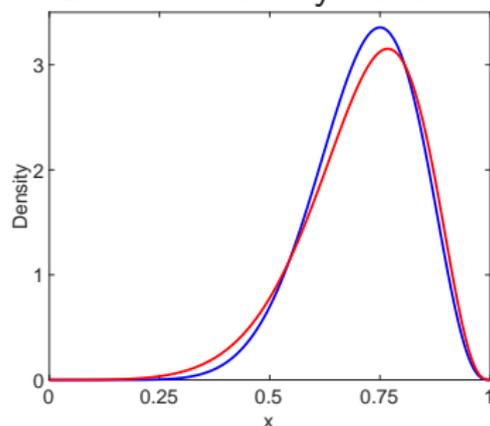
2. Absolute continuity & dominating measure

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Thanks for listening!

Ancestral process

Define $(A_n(t) : t \geq 0)$ as a **pure death process** on \mathbb{N} such that

- $A_n(0) := n$.
- If currently $A_n(t) = m$ then $m \mapsto m - 1$ at rate $\frac{m(m+\theta_1+\theta_2-1)}{2}$.

Then

$$q_m(t) = \lim_{n \rightarrow \infty} \mathbb{P}(A_n(t) = m).$$

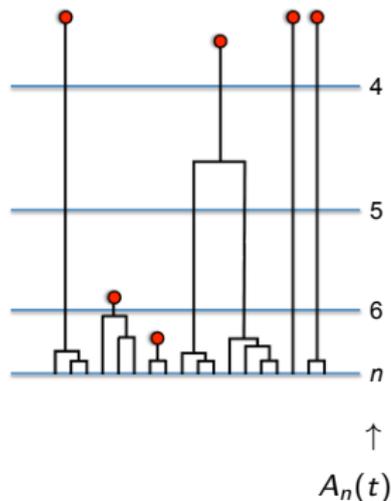
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The distribution of the **ancestral process of Kingman's coalescent with infinitely-many leaves**, when lineages are lost by both coalescence and mutation.

Mixture weights are known only as an infinite series:

$$q_m(t) = \sum_{k=m}^{\infty} (-1)^{k-m} \frac{(\theta + 2k - 1)\Gamma(\theta + m + k - 1)}{m!(k - m)!\Gamma(\theta + m)} e^{-k(k+\theta-1)t/2}.$$

(Griffiths, 1980; Tavaré, 1984)

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Proposition (Jenkins & Spanò, 2017)

It is possible to sample **exactly** from the distribution of the ancestral process of Kingman's coalescent with mutation,

$$\{q_m(t) : m = 0, 1, \dots\}.$$

Theorem

(Barbour et al., 2000)

- In the **nonneutral** case, the transition density has expansion

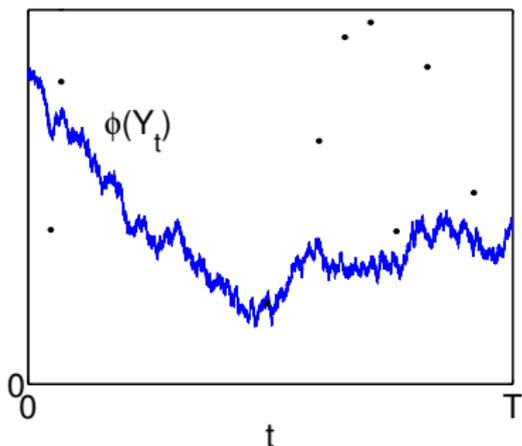
$$f(y | x; t) = \sum_{m=0}^{\infty} \sum_{l=0}^m q_{l,m}^{\circ}(x, t) \underbrace{\mathcal{D}_{\theta_1+l, \theta_2+m-l}^{\sigma, h}(y)}_{\text{'Weighted' Beta density}},$$

- But the masses of the distribution $q_{l,m}^{\circ}(x, t)$ are **intractable**.

$$\frac{d\mathbb{W}\mathbb{F}_{\sigma,h}}{d\mathbb{W}\mathbb{F}_0}(X) \propto \exp\{A(X_T)\} \exp\left\{-\int_0^T \varphi_\sigma(X_t) dt\right\} \leq 1,$$

Exact algorithm (EA) for simulating from $\mathbb{W}\mathbb{F}_{\sigma,h}$ (Jenkins & Spanò, 2017)

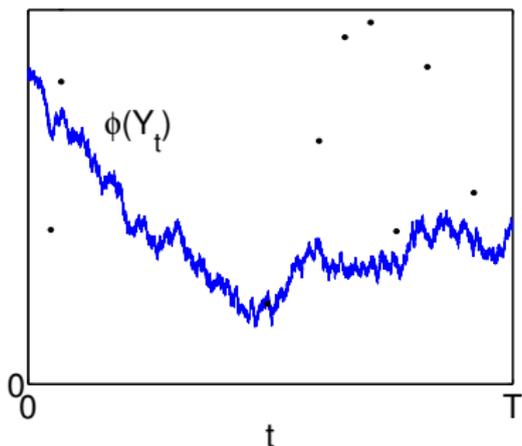
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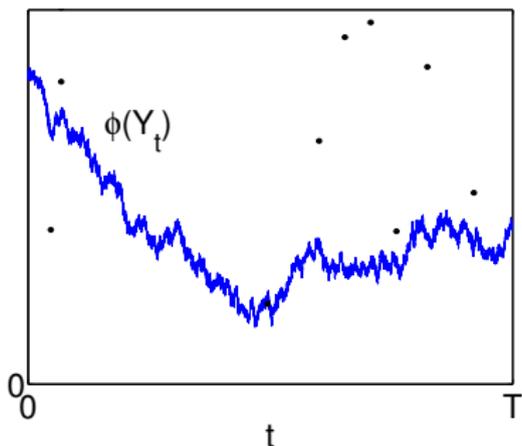
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- Accept w.p. $e^{\{A(X_T)\}}$ if all Poisson points are above the revealed points of X .



Function arising in Girsanov formula:

$$\begin{aligned}\varphi_\sigma(x) = & \frac{\sigma}{2}x(1-x) \left[\sigma \left(x + h(1-2x) \right)^2 + 1 - 2h \right] \\ & + \frac{\sigma}{2} \left(x + h(1-2x) \right) [\theta_1(1-x) - \theta_2x].\end{aligned}$$