Simulation and inference of phylodynamic individual level models

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Overview

Phylodynamics

Individual level models

Transmission pathway ILMs

Phylodynamic ILMs

Pathogen.jl

Phylodynamics

- The joint or conditional investigation of the dynamics of disease spread and evolution
- Appropriate when epidemiological and evolutionary processes occur at similar time scales
- Requires dense genetic sampling of a pathogen during an epidemic

Phylodynamics software I

- Typically a phylogenetic tree is inferred, and from that a transmission network generated
- MCMC; Metropolis-Hasting with specialized proposal methods for exploring phylogenetic tree space used
- Some challenges persist with low acceptance rates

Phylodynamics software II

- We leverage parameters from Individual Level Models (ILMs) (Deardon et al., 2010)
- Generate phylogenetic tree from transmission network proposals
  - "high acceptance" proposals

ILMs

- Time inhomogeneous Poisson process of disease spread through a heterogeneous population
- Inference typically conducted in Bayesian framework

Exposure in ILMs

- Individuals are in a single disease state during any period t
- Transition of i from susceptible to exposed occurs with rate

$$\lambda_{SE}(i,t) = \left[\Omega_S(i) \sum_{k \in I_{(t)}} \Omega_T(k)\kappa(i,k)\right] + \epsilon(i,t) \text{ for } i \in S_{(t)} \tag{1}$$

where,

- $I_{(t)}$ is the set of infectious individuals during time period t,
- $S_{(t)}$ is the set of susceptible individuals during time period t,
- $\Omega_S(i)$ is an susceptibility function,
- $\Omega_T(k)$ is a transmissability function,
- $\kappa(i,k)$ is an infection kernel, and,
- $\epsilon(i,t)$ is a sparks function.

ILM likelihood

$$L(D|\theta) = \prod_{t=1}^{T-1} \psi(t)\upsilon(t) \exp\left\{-\upsilon(t)\Delta_t\right\}, \tag{2}$$

where,

$$\psi(t) = \begin{cases} \frac{\lambda_{SE}(i,t)}{\upsilon(t)} & \text{if } i \in (S_{(t)} \cap E_{(t+1)}) \\ \frac{\lambda_{EI}(j,t)}{\upsilon(t)} & \text{if } j \in (E_{(t)} \cap I_{(t+1)}) \\ \frac{\lambda_{IR}(k,t)}{\upsilon(t)} & \text{if } k \in (I_{(t)} \cap R_{(t+1)}) \end{cases} \tag{3}$$

$$\upsilon(t) = \sum_{i \in S_t} \lambda_{SE}(i,t) + \sum_{j \in E_t} \lambda_{EI}(j,t) + \sum_{k \in I_t} \lambda_{IR}(k,t). \tag{4}$$

where Δ_t is the length of t^{th} inter-event period.

Transmission pathway ILM extension

- Extension allowing simulation and inference of infection sources
- Necessary for phylodynamic extension

Exposure in transmission pathway ILM

- Separate exposure rates are defined for each susceptible-infectious combination as

$$\lambda^*_{SE}(i,k,t) = \Omega_S(i)\Omega_T(j)\kappa(i,j) \text{ if } i \in S_{(t)}, k \in I_{(t)}, \tag{5}$$

and for exposures from an exogenous source as

$$\lambda^*_{SE}(i,t) = \epsilon(i,t) \text{ if } i \in S_{(t)}. \tag{6}$$

Transmission pathway ILM likelihood

$$L(D|\theta) = \prod_{t=1}^{T-1} \zeta(t)\upsilon(t) \exp\left\{-\upsilon(t)\Delta_t\right\}, \tag{7}$$

where,

$$\zeta(t) = \begin{cases} \frac{\lambda^*_{SE}(i,k,t)}{\upsilon(t)} \text{ if } i \in (S_{(t)} \cap E_{(t+1)}) \text{ by endogenous exposure by } k \\ \frac{\lambda^*_{SE}(i,t)}{\upsilon(t)} \text{ if } i \in (S_{(t)} \cap E_{(t+1)}) \text{ by exogenous exposure} \\ \frac{\lambda_{EI}(j,t)}{\upsilon(t)} \text{ if } j \in (E_{(t)} \cap I_{(t+1)}) \\ \frac{\lambda_{IR}(k,t)}{\upsilon(t)} \text{ if } k \in (I_{(t)} \cap R_{(t+1)}) \end{cases} \tag{8}$$

Phylodynamic ILM extension

- Joint model of disease spread and evolution through a heterogeneous population
- Combines transmission pathway ILM with a phylogenetic tree consistent with transmission network
- Exposure times are assumed to be pathogen divergence dates

Phylodynamic ILM simulation

- Gillespie (1977) stochastic simulation method can be utilized:
- Event time is generated from an exponential distribution based on sum of rates
- Event type is generated from discrete distribution
- Event rates are updated

Phylodynamic ILM inference: likelihood

- Full likelihood is the product of the transmission pathway ILM likelihood (Eq. 7) with corresponding phylogenetic tree likelihood
- Phylogenetic tree likelihood can be calculated using the pruning algorithm of Felsenstein (1973, 1981)

Phylodynamic ILM inference: MCMC I

- Specialized MCMC algorithms necessary for phylodynamic ILM
- Algorithm must efficiently explore full posterior distribution of:
  - Augmented data (transmission network & event timings)
  - ILM and substitution model parameters

Phylodynamic ILM inference: MCMC II

- We implement an MCMC algorithm with several different step types:
  1. Propose ILM or substitution model parameters sample
  2. Propose new set of event times
  3. Propose new set of exposure sources

MCMC III

- Proposals to transmission network are generated with a discrete probability distribution. An individual i will be proposed to have been exposed by k with probability

$$\frac{\lambda^*_{SE}(i,k,t)}{\lambda^*_{SE}(i,t) + \sum_k \lambda^*_{SE}(i,k,t)}, \tag{9}$$

  and by an exogenous source with probability

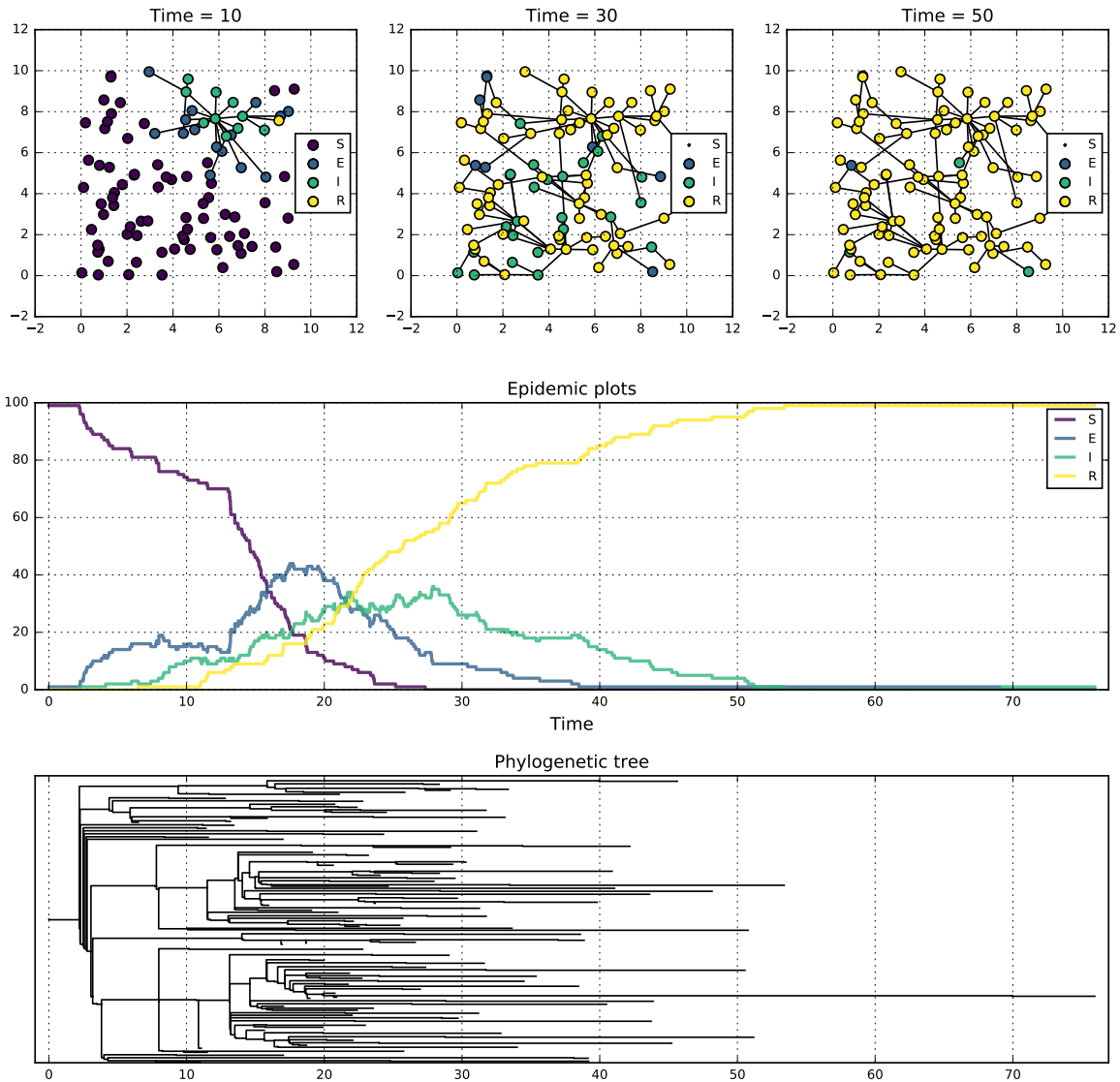
$$\frac{\lambda^*_{SE}(i,t)}{\lambda^*_{SE}(i,t) + \sum_k \lambda^*_{SE}(i,k,t)}. \tag{10}$$

- This is accounted for in Metropolis-Hastings acceptance ratio

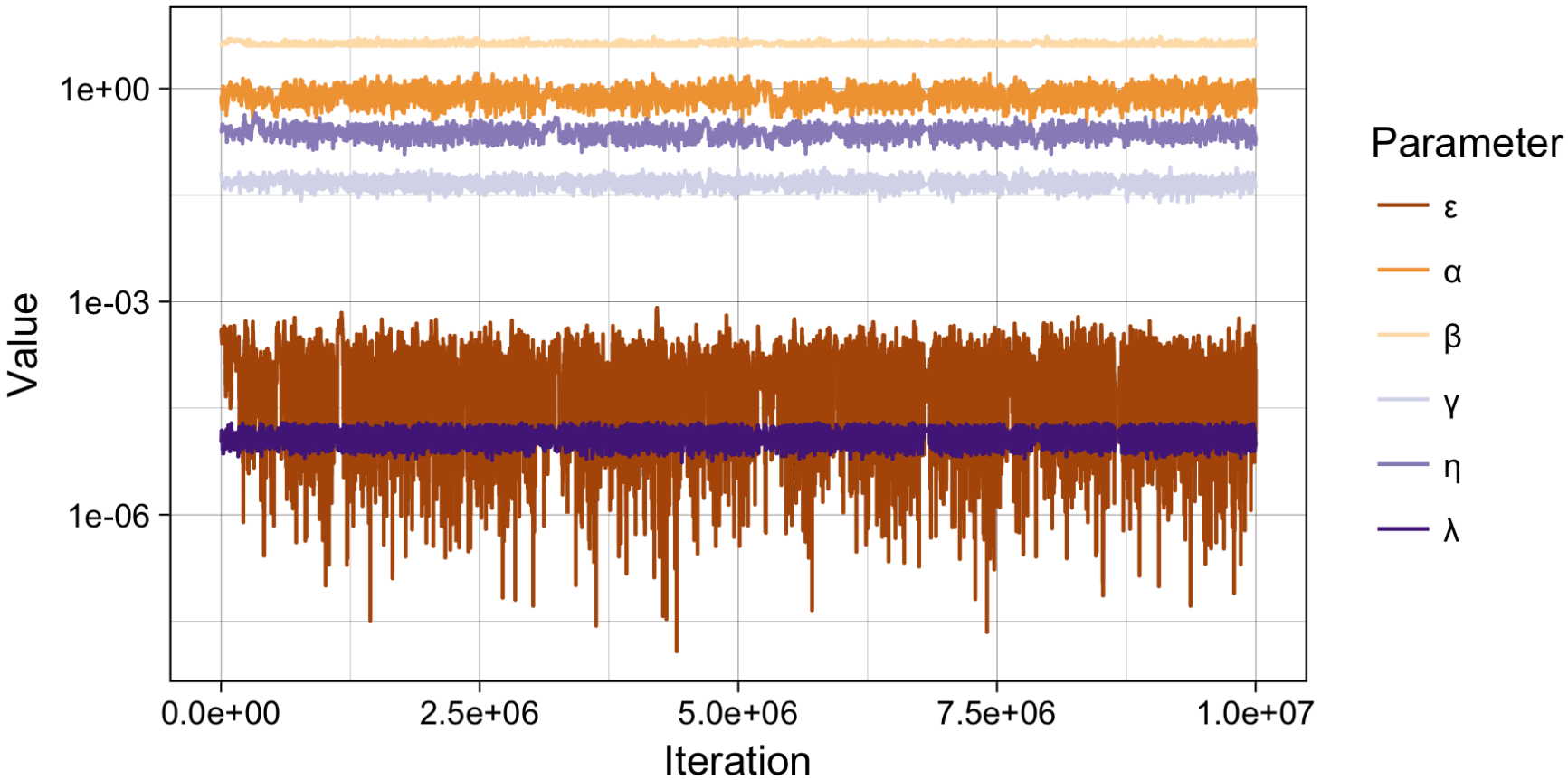
Pathogen.jl

- jangevaare/Pathogen.jl is a flexible full featured package which is in development for Phylodynamic modelling in Julia
- Julia is a fast, high level language designed for scientific computing applications that is approaching it's 1.0 release
- SEIR, SEI, SIR, and SI ILMs with fully customizable $\Omega_S, \Omega_T, \kappa, \epsilon, \Omega_L$, and Ω_R. Many substitution models.
- Initial work has included some simplifying assumptions regarding pathogen diversity.

Phylodynamic simulations in Pathogen.jl



Phylodynamic inference in Pathogen.jl



Initial findings and ongoing work

- Inference of $\lambda^*_{SE}(i, t)$, and exogenous exposures sensitive to external diversity
- Incorporation of more realistic external pathogen source diversity
- Incorporation of within host diversity
- Development of guidelines for MCMC tuning
- Further speed and usability optimizations in Pathogen.jl

References

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Thank you!

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Appendices

Latency in ILMs

- Transition of j from exposed to infectious occurs with rate

$$\lambda_{EI}(j,t) = \Omega_L(j) \text{ for } j \in E_{(t)} \tag{11}$$

where,

- $E_{(t)}$ is the set of exposed individuals during time period t, and,
- $\Omega_L(j)$ is a latency function.

Removal in ILMs

- Transition of k from infectious to removed occurs with rate

$$\lambda_{IR}(k,t) = \Omega_R(k) \text{ for } k \in I_{(t)} \tag{12}$$

where,

- $\Omega_R(k)$ is a removal function.

Phylogenetic tree likelihood I

$$
\begin{aligned}
L(D|\theta) &= \pi \times S_N, \\
S_N &= [P_{N_\mathrm{L}} \times S_{N_\mathrm{L}}] \odot [P_{N_\mathrm{R}} \times S_{N_\mathrm{R}}] \\
S_{N-1} &= [P_{N-1_\mathrm{L}} \times S_{N-1_\mathrm{L}}] \odot [P_{N-1_\mathrm{R}} \times S_{N-1_\mathrm{R}}], \\
&\dots \\
S_{\frac{N+1}{2}+1} &= \left[P_{\frac{N+1}{2}+1_\mathrm{L}} \times S_{\frac{N+1}{2}+1_\mathrm{L}}\right] \odot \left[P_{\frac{N+1}{2}+1_\mathrm{R}} \times S_{\frac{N+1}{2}+1_\mathrm{R}}\right], \\
P_j &= \exp(Q \times d_j),
\end{aligned}
$$

Phylogenetic tree likelihood II

where,

- π is a vector of nucleotide frequencies according to a nucleotide substitution model, Q
- S_j is a vector of nucleotide likelihoods at node j
- $\odot$ is the component-wise product
- N is the total number of nodes
- $S_1, \ldots, S_{\frac{N+1}{2}}$ are observed
- j_L, j_R, represent the left and right children nodes of node j, and,
- d_j is the length of the branch connecting node j to its parent node.

Felsenstein's pruning algorithm requires that the nucleotide likelihoods at internal nodes are calculated following a postorder traversal of the phylogenetic tree. As each site is assumed to be independent, the full likelihood of any phylogenetic tree is the product of site-specific likelihoods.

Alternative continuous time ILM likelihood I

$$L(D|\theta) = \prod_{t=1}^{T-1} \left[\prod_{i \in (S_{(t)} \cap E_{(t+1)})} P_{SE}(i,t) \prod_{j \in (E_{(t)} \cap I_{(t+1)})} P_{EI}(j,t) \right.$$
$$\prod_{k \in (I_{(t)} \cap R_{(t+1)})} P_{IR}(k,t) \prod_{i \in (S_{(t)} \cap S_{(t+1)})} P_{SS}(i,t)$$
$$\left. \prod_{j \in (E_{(t)} \cap E_{(t+1)})} P_{EE}(j,t) \prod_{k \in (I_{(t)} \cap I_{(t+1)})} P_{II}(k,t) \right], \quad (13)$$

where,

- D are the observed data, which includes observations of infectiousness and removal times for each individual and any risk factor information required by Ω_S, Ω_T, κ, Ω_L, and Ω_R,
- θ are the model parameters and augmented event timings for all observed individuals, and...

Alternative continuous time ILM likelihood II

$$
\begin{aligned}
P_{SE}(i,t) &= \lambda_{SE}(i,t)\exp\left\{-\lambda_{SE}(i,t)\Delta_t\right\}, && (14)\\
P_{EI}(j,t) &= \lambda_{EI}(j,t)\exp\left\{-\lambda_{EI}(j,t)\Delta_t\right\}, && (15)\\
P_{IR}(k,t) &= \lambda_{IR}(k,t)\exp\left\{-\lambda_{IR}(k,t)\Delta_t\right\}, && (16)\\
P_{SS}(i,t) &= \exp\left\{-\lambda_{SE}(i,t)\Delta_t\right\}, && (17)\\
P_{EE}(j,t) &= \exp\left\{-\lambda_{EI}(j,t)\Delta_t\right\}, && (18)\\
P_{II}(k,t) &= \exp\left\{-\lambda_{IR}(k,t)\Delta_t\right\}. && (19)
\end{aligned}
$$