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Phylodynamic inference - accounting for the interaction of evolutionary and ecological processes

Phylogenetics Meeting, INI Cambridge
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Phylodynamics ?

- Genomes of rapidly evolving viruses can track past ecological and evolutionary events.
- Thus, joint reconstruction of those events while reconstructing evolutionary history is possible.

The interaction of evolutionary and ecological processes requires the joint analysis of both.



Epidemiological models - deterministic SIR

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Under which circumstances does the introduction of a virus or pathogen into a population cause an outbreak of the disease? When to expect an epidemic?

How efficient are measures to contain disease outbreak, such as vaccination or isolation?

Compartmental models: SI, SIR, SIS, SEIS, MSIR, ...



Transmission term βSI ,
birth and death rate μ ,
recovery rate γ .

$$\frac{dS}{dt} = \mu - \beta SI - \mu S$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I$$

$$\frac{dR}{dt} = \gamma I - \mu R$$



Four "identical" simulations

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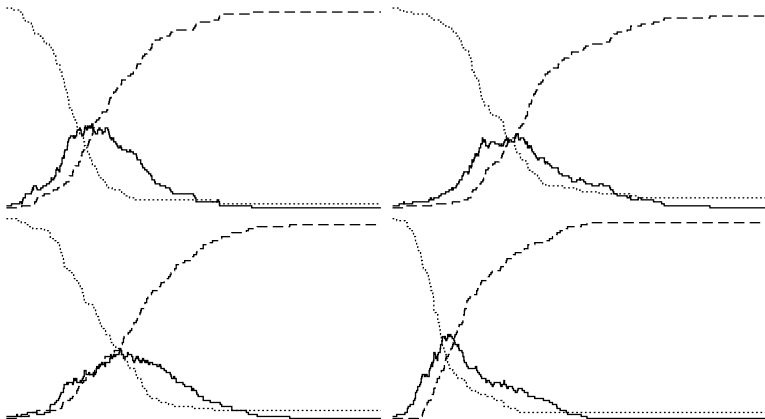
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Four realizations of a stochastic SIR model in a panmictic population with identical parameters ($R_0 \approx 3.5$).



Stochastic SIR models

Closed SIR master equation (Kermack, McKendrick, 1927) for the numbers of individuals in S, I, R (n_S, n_I, n_R):

$$\begin{aligned}\dot{P}_{n_S, n_I, n_R}(t) &= \beta(n_S + 1)(n_I - 1)P_{n_S+1, n_I-1, n_R}(t) \\ &+ \gamma(n_I + 1)P_{n_S, n_I+1, n_R-1}(t) \\ &- (\beta n_S n_I + \gamma n_I)P_{n_S, n_I, n_R}(t)\end{aligned}$$

- A single realization is described by a sequence of timed transition events (individual infection or recovery events)
- Waiting time between a pair of sequential events is exponentially distributed
(\Rightarrow continuous-time Markov process)

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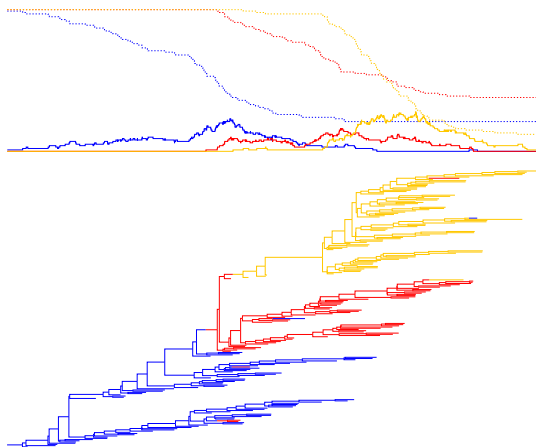
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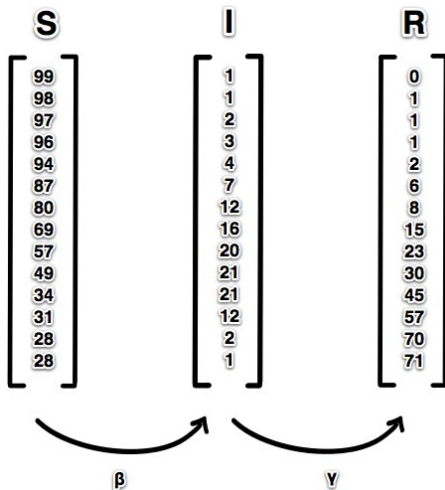
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SIR history contains precious information about the process but as opposed to the tree it cannot grasp migration.



A sampled SIR history / trajectory



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Inference Approach

- Sample phylogeny by MCMC in BEAST2 framework
- Sample hidden S,I,R components and evaluate sample tree likelihood
- **Sample dynamical parameters: infection rates, recovery rates**

Options for simulation of SIR components:

- sample entire history and compute likelihood trivially – massive state space, slow convergence
- sample partial history and approximate its likelihood
- Likelihood-free approaches
 - Reversible SSA (Vaughan, Drummond, Drummond 2010)
 - Forward simulation rejection algorithm

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Simulation of SIR components

Sample SIR trajectories

- Use tau-leaping approximation - combine few infection / recovery events in 1 step
- $\mathbf{S} = [S_i]_i$ (decreasing) and $\mathbf{R} = [R_i]_i$ (increasing) are approximately Poisson-distributed with rates β_i and γ_i :

$$\beta_i = \beta(S_i + \Delta S_i/2)(I_i + \Delta I_i/2)$$

$$\gamma_i = \gamma(I_i + \Delta I_i/2)$$

\Rightarrow approximate likelihood for a sampled SIR history

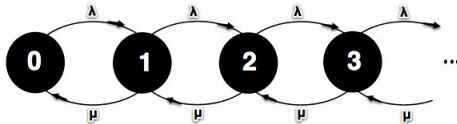
$H = \{S, I, R\}$ with m tau-leaping intervals of size τ_i :

$$f_{\tau}(H|\beta, \gamma) = \prod_{i=0}^{m-1} \frac{\beta_i \tau_i^{\Delta S_i} e^{-\beta_i \tau_i}}{\Delta S_i!} \frac{\delta_i \tau_i^{\Delta R_i} e^{-\delta_i \tau_i}}{\Delta R_i!}$$



Birth death processes in phylogenetics

The basic birth-death process

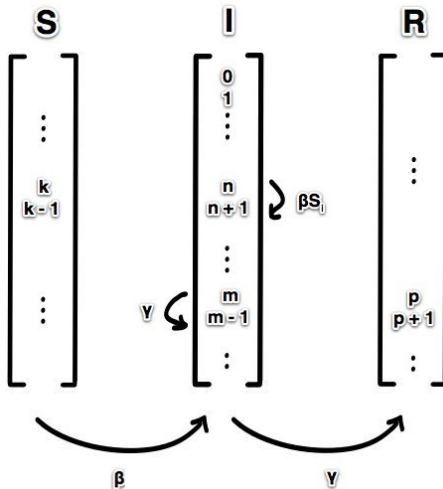


- Continuous time Markov process with state population size
- transition events: birth with rate λ and death with rate μ

Birth death serial sampling model implemented in BEAST:
Sampling-through-time in birth-death trees. Stadler 2010 J
Theor Biol



Concatenate SIR with birth death process





Concatenate an SIR model with the birth death process III

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Combine birth-death-skyline-model with SIR prior

- Sample SIR history $\{S_i, I_i, R_i\}_{i=0..m}$ at interval times $t_0 = 0 < t_1 < \dots < t_m$
- Extend the serial sampling birth-death model to allow for rate changes, such that birth in interval i occurs with rate βS_i



Putting it all together..

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Genealogy \mathcal{G} ,
SIR history H ,
birth and death rate β, γ ,
Data D

Bayesian posterior distribution:

$$f(\mathcal{G}, H, \beta, \gamma | D) \propto \frac{1}{Z} \mathbb{P}(D | \mathcal{G}) f(\mathcal{G} | H, \beta, \gamma) f(H | \beta, \gamma) f(\beta, \gamma)$$



Testing SIR prior

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Estimate birth and death rate for 100 simulated trajectories

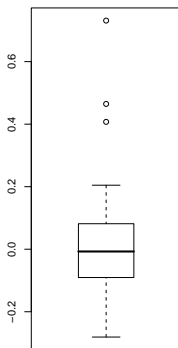
- Fix infection rate and recovery rate and simulate 100 trajectories
- Estimate infection and recovery rates in BEAST2 for each trajectory (everything else fixed)



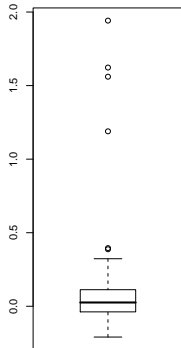
Testing SIR prior - bias

- Infection rate estimates: 96/100 in 95% HPD
- Recovery rate estimates: 95/100 in 95% HPD
- Bias = $\frac{\theta_{med} - \theta}{\theta}$

Median relative bias
infection rate



Median relative bias
recovery rate



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- Further test models individually - SIR prior and BDSkyModel
- Test combined model on sequences obtained from simulated infection processes
- Apply to real data.



Thank you for your attention

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Median error plot - SIR test

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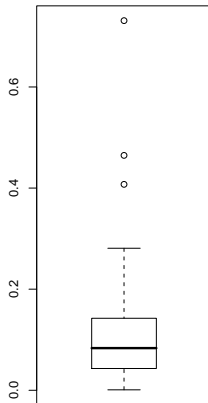
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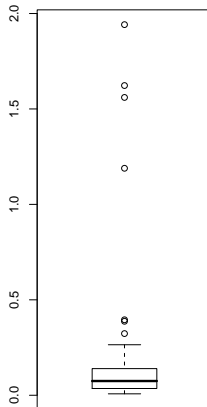
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Median relative error
birth rate



96/100 in 95%HPD

Median relative error
death rate



95/100 in 95%HPD



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- Beauti 2: GUI to **read** and write specification so no need for XML hacking
- Other GUIs; graphical model builder, ...
- Resume chains when not converged yet. Can report ESS during run
- Fast computation by using GPU through Beagle (if available)
- Easy to extend with new models, including documentation and integration in Beauti.
- Developed with documentation in mind, book in the works (for early 2012)
- Release June or July, but already available from <http://code.google.com/p/beast2/>

