Epidemiology meets phylogenetics

Inferring epidemiological dynamics based on genetic sequence data

Gabriel Leventhal, Sebastian Bonhoeffer

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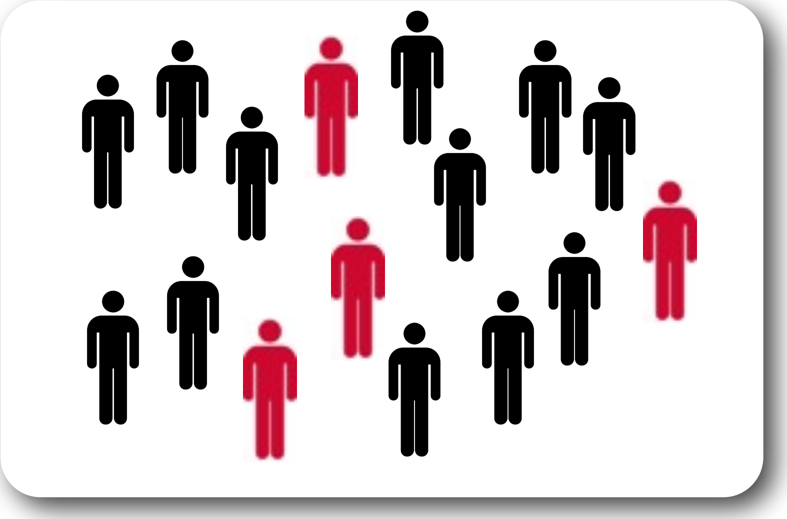

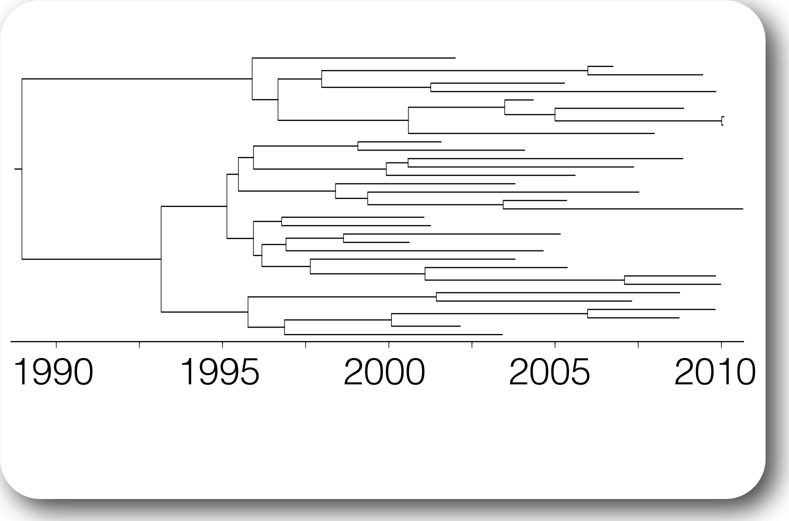

Tanja Stadler
Theoretical Biology group — Department of Environmental Systems Science
tanja.stadler@env.ethz.ch

ETH
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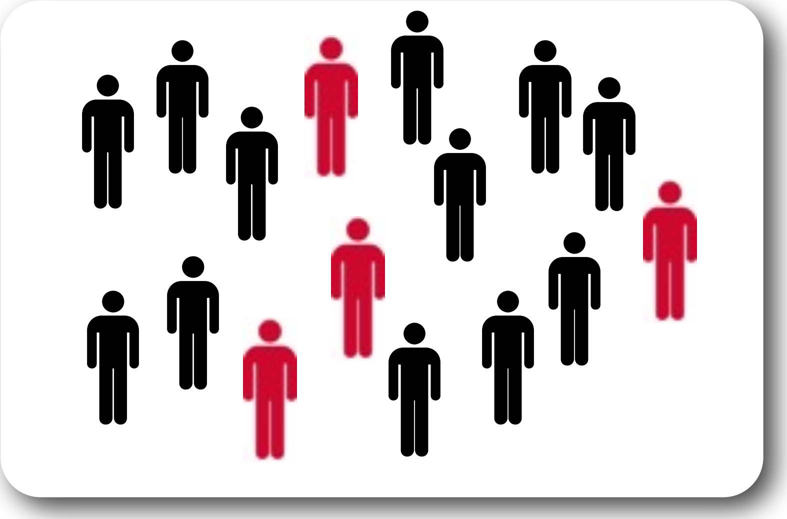

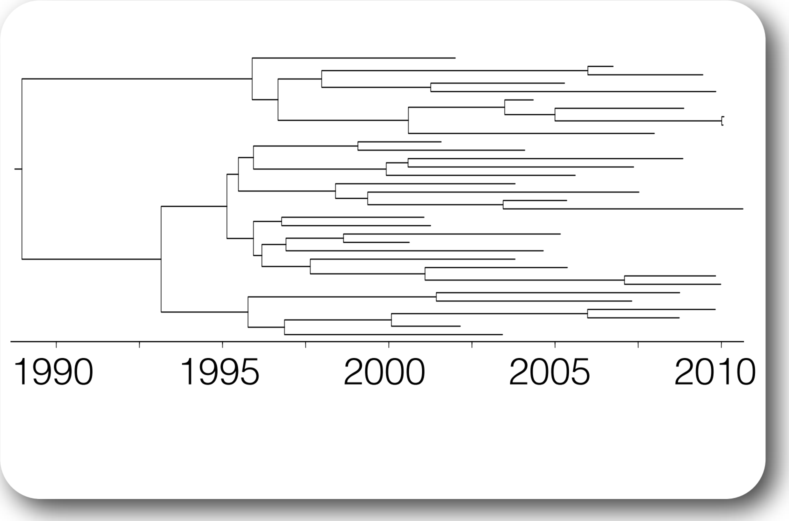

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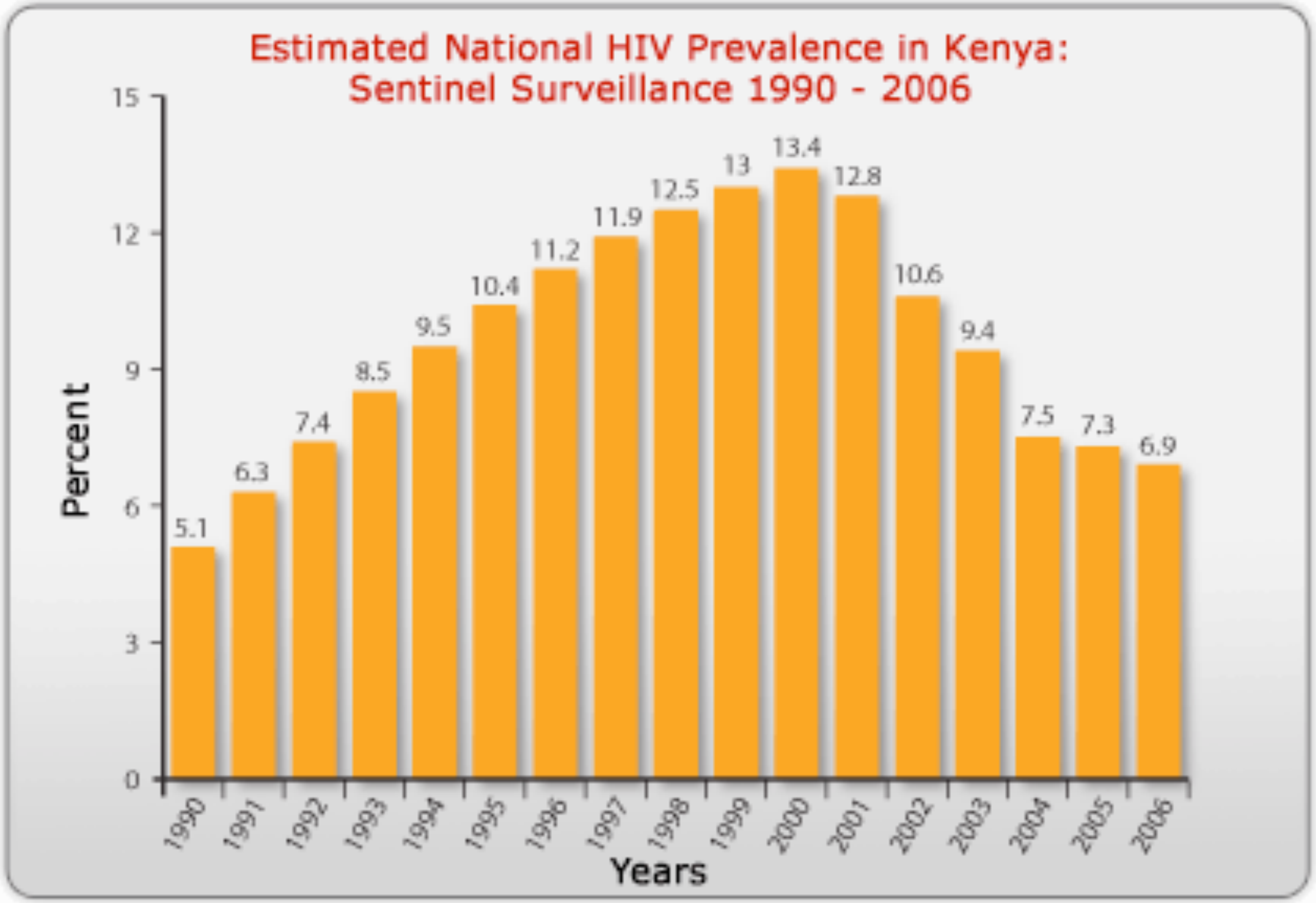
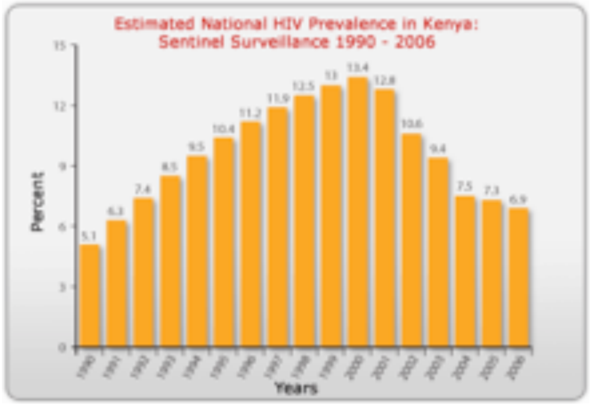
Epidemiology



Epidemiology

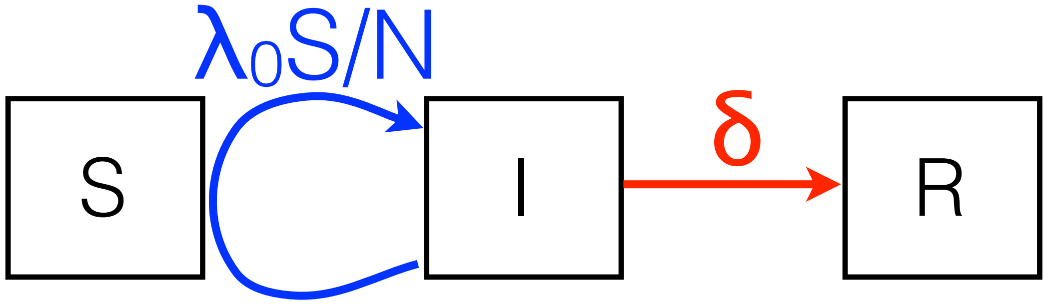
Data

# of infected individuals through time



Models

Population dynamics described by SIR models:



$$
\begin{aligned}
\frac{dS}{dt} &= -\lambda_0 IS/N \\
\frac{dI}{dt} &= \lambda_0 IS/N - \delta I \\
\frac{dR}{dt} &= \delta I
\end{aligned}
$$

Epidemiology

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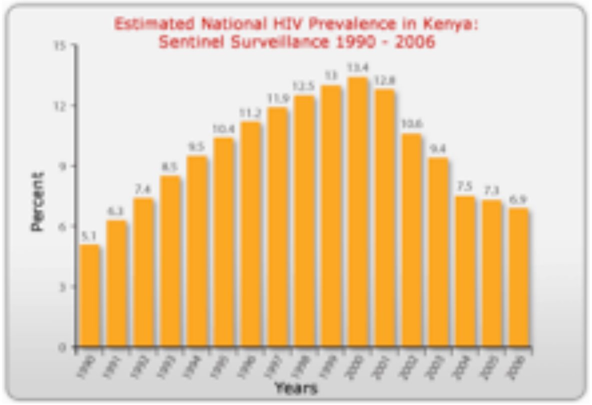

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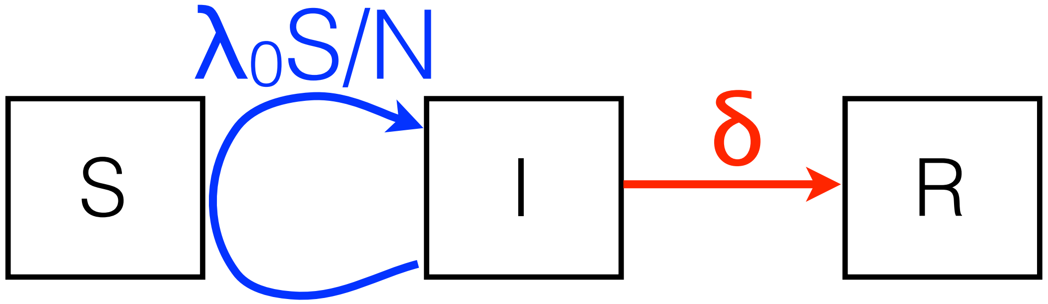

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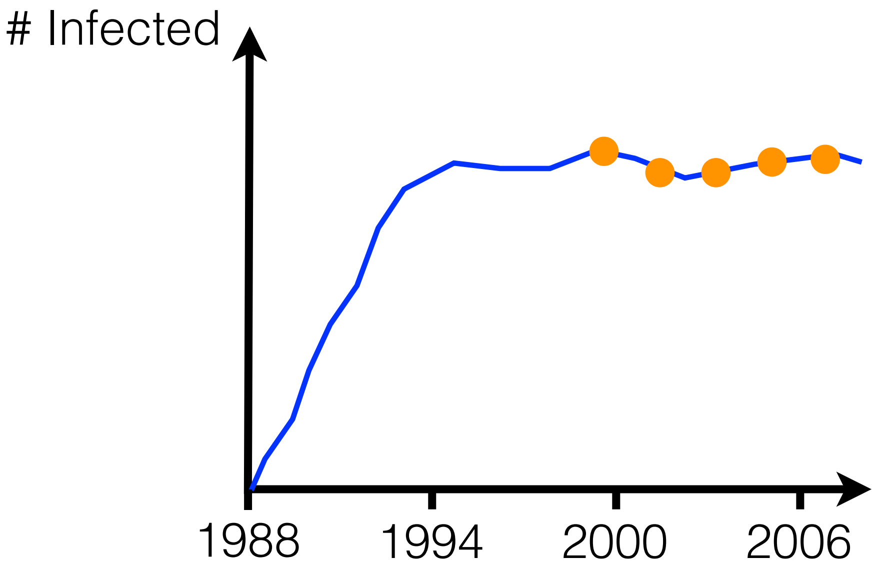
If sampling in early epidemic was missed:



Epidemiology

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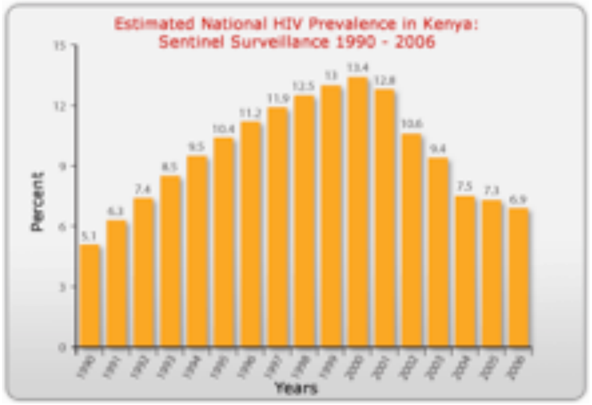

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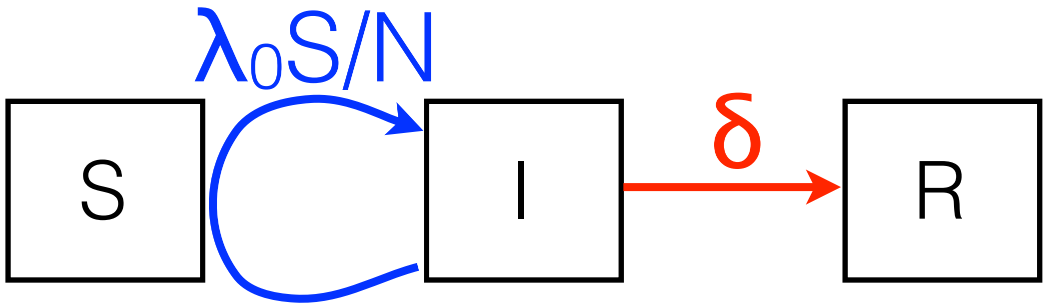

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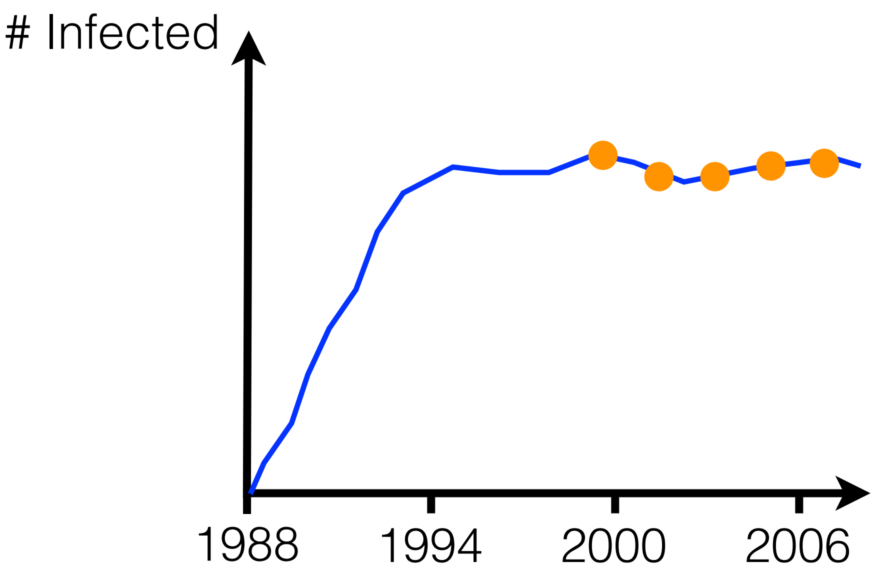
If sampling in early epidemic was missed:

- **Time of epidemic outbreak?**
- **Basic reproductive number R_0?**



Epidemiology

Data

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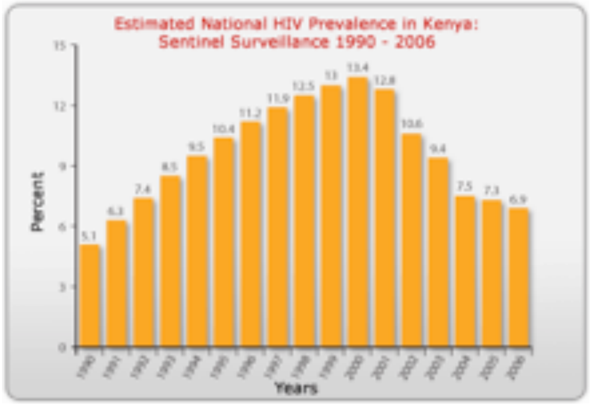

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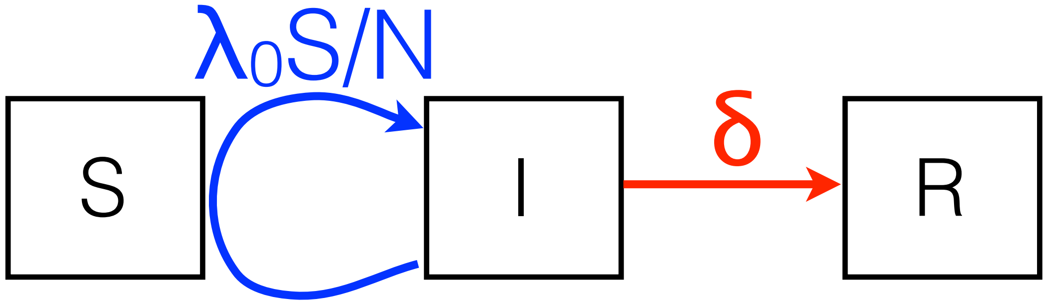

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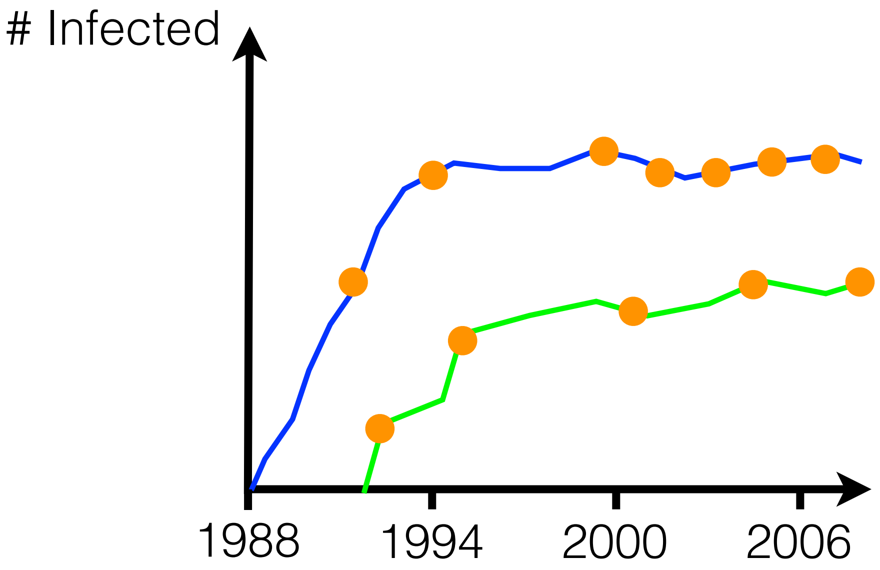
Limitations

If sampling in early epidemic was missed:

- **Time of epidemic outbreak?**
- **Basic reproductive number R_0?**

Data does not tell who infected whom:

- **Population structure?**



Genetic data entering epidemiology

Phylo-
genetics

Inf1	`ACACACCC`
Inf2	`TCACACCT`
Inf3	`AAAGACTT`
Inf4	`ACAGACTT`

Genetic data entering epidemiology

Phylo-genetics

Input:

Pathogen genetic data from different hosts

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Genetic data entering epidemiology

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Input:

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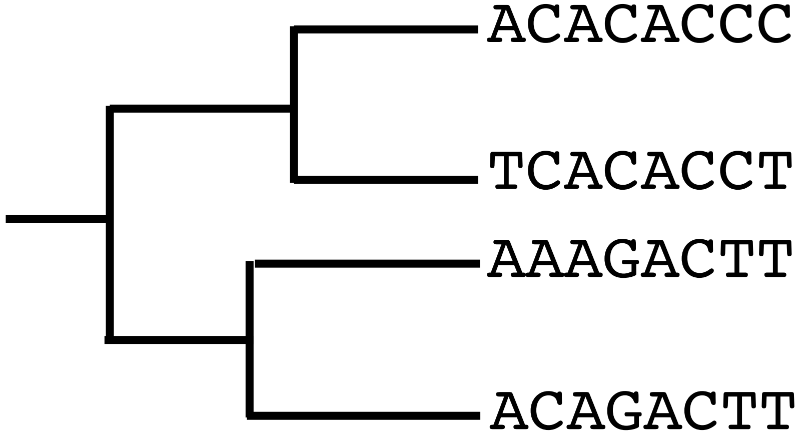
Output:

Transmission chain (who infected whom)



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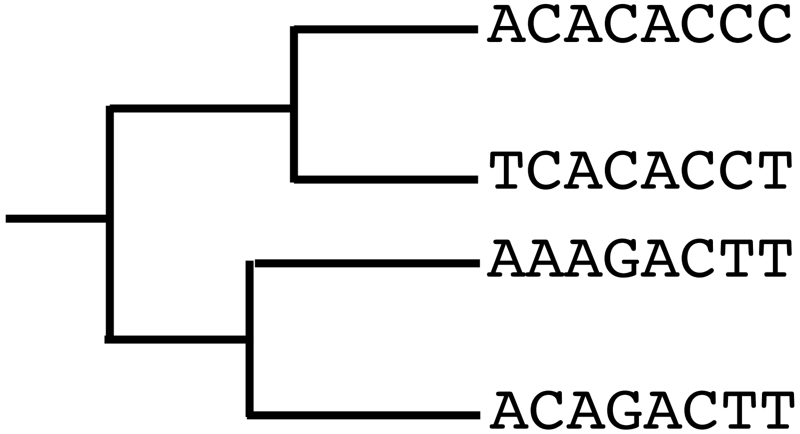

Example
key result

Emergence of HIV

Epidemic identified in 1980s

Genetic data entering epidemiology

Phylo-genetics

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Pathogen genetic data from different hosts

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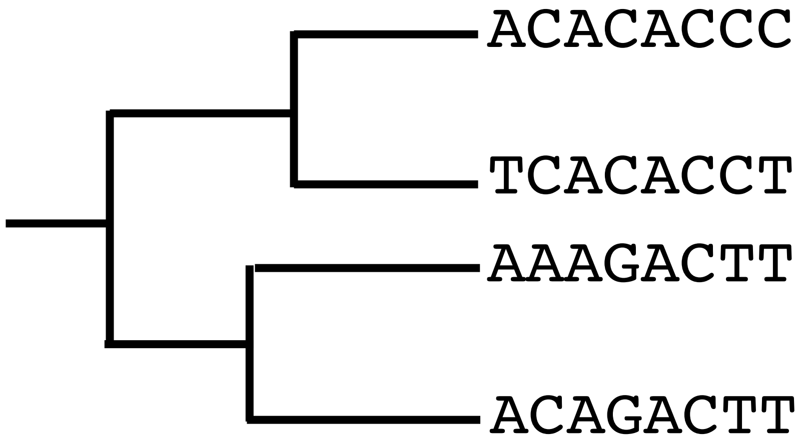
Transmission chain (who infected whom)



Example key result

Emergence of HIV

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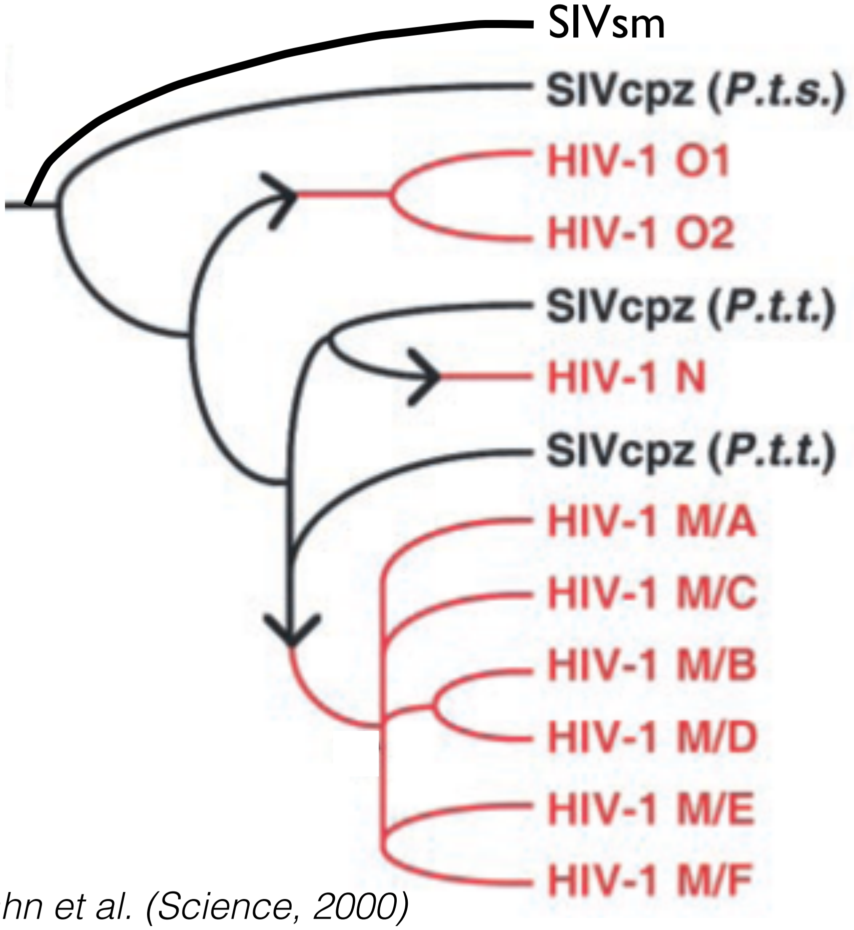
Sequence data tells us about pre-1980



adopted from Hahn et al. (Science, 2000)

Genetic data entering epidemiology

Phylo-genetics

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Pathogen genetic data from different hosts

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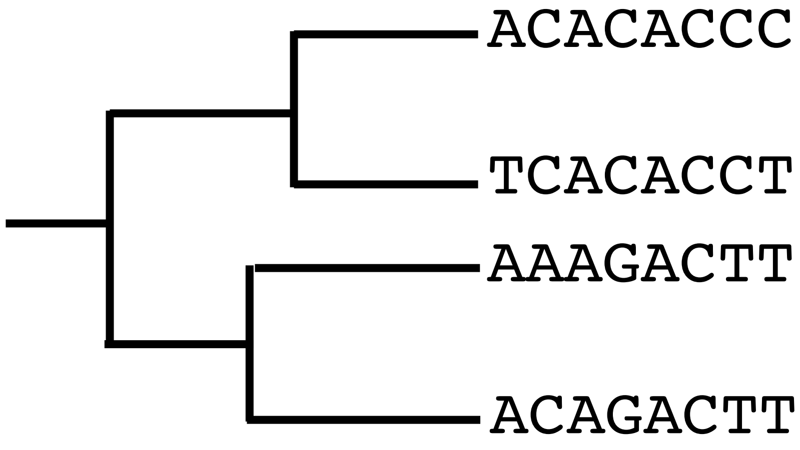
Transmission chain (who infected whom)



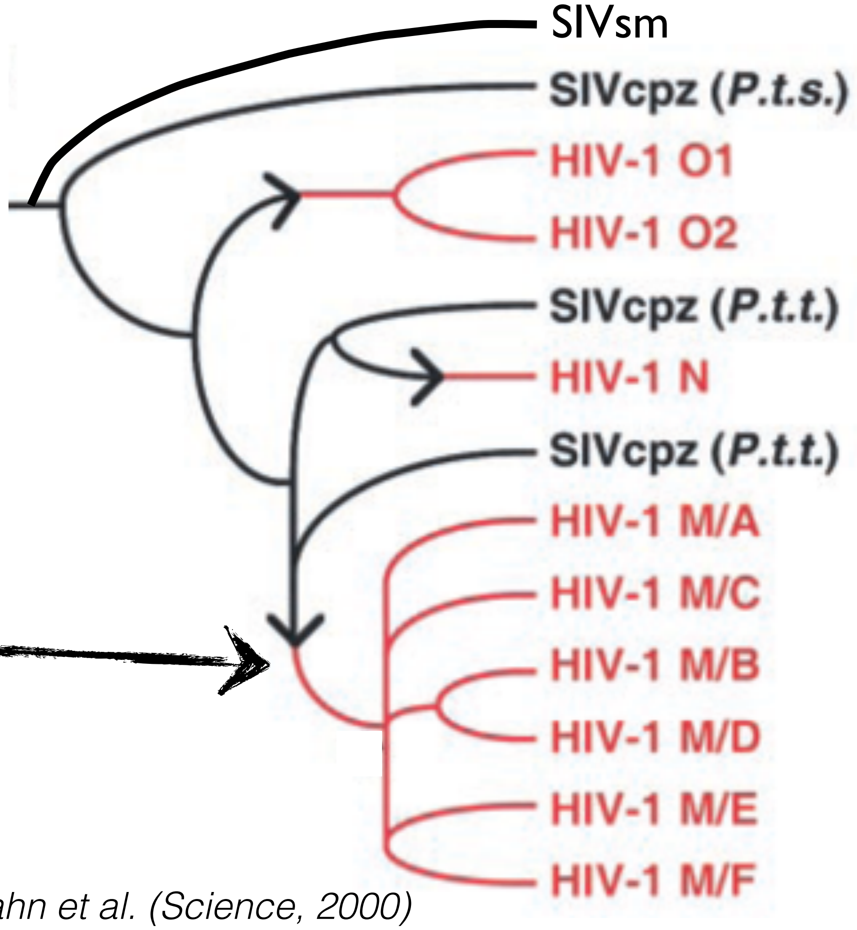
Example key result

Emergence of HIV

Epidemic identified in 1980s

Sequence data tells us about pre-1980

- Zoonosis from chimps
- In Africa
- Early 20th century



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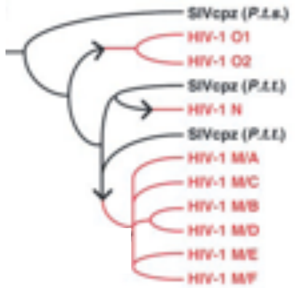
Genetic data contains information about the epidemiological dynamics

Phylo-
genetics

State of process

- Time and geographic location of outbreak



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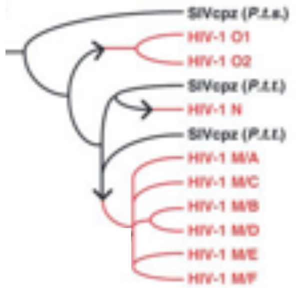

Emergence of a pathogen (here HIV)

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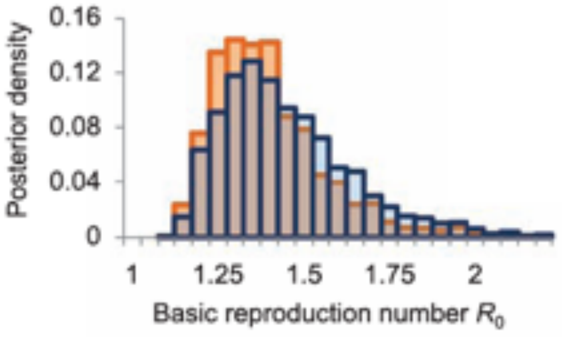
Phylo-dynamics

Dynamics of process

- Transmission process



Basic reproductive number of an emerging pathogen (here H1N1)

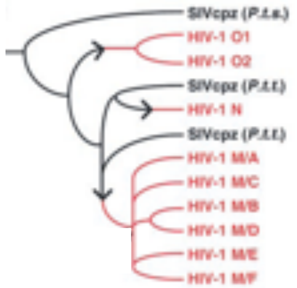
Fraser et al. (Science, 2009)

Genetic data contains information about the epidemiological dynamics

Phylo-genetics

State of process

- Time and geographic location of outbreak



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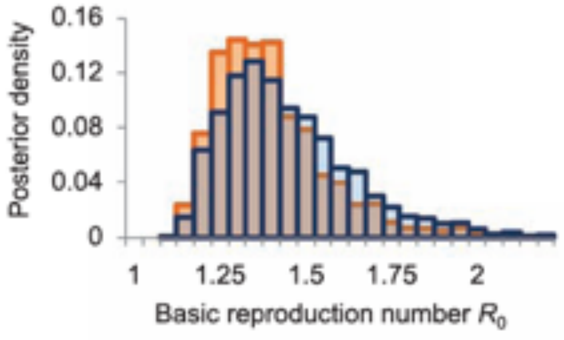
Hahn et al. (Science, 2000)

Phylo-dynamics

Dynamics of process

- Transmission process



Basic reproductive number of an emerging pathogen (here H1N1)

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Epidemio-logical models

Ideally: assume epidemiological model in phylogenetics (birth-death model)

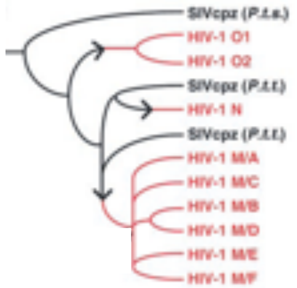
- Quantification of all model parameters!

Genetic data contains information about the epidemiological dynamics

Phylogenetics

State of process

- Time and geographic location of outbreak



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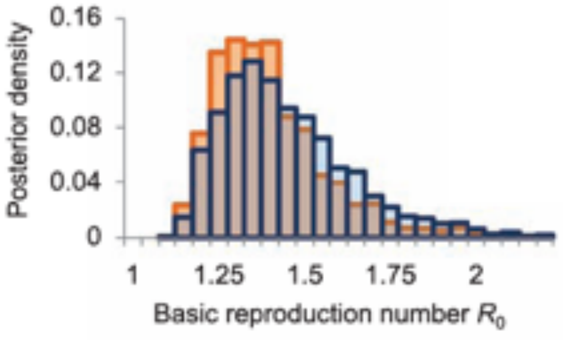
Phylodynamics

Dynamics of process

- Transmission process



Basic reproductive number of an emerging pathogen (here H1N1)
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Epidemiological models

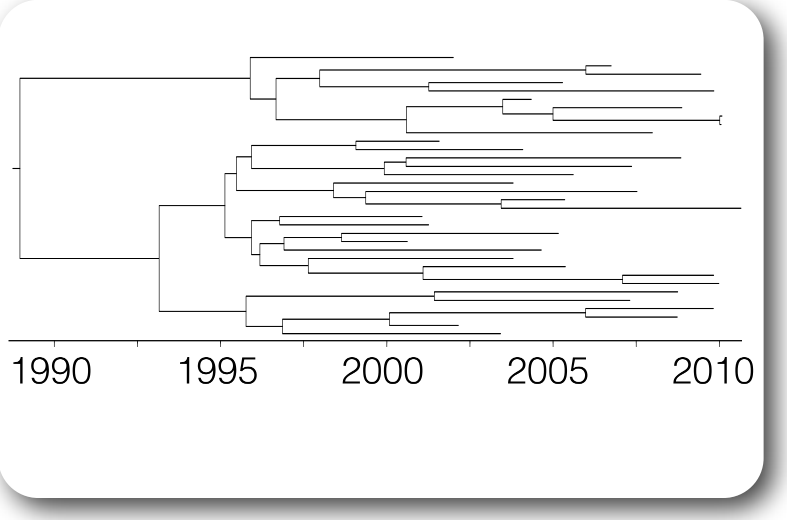
<u>Ideally:</u> assume epidemiological model in phylogenetics (birth-death model)

- Quantification of all model parameters!

<u>Approximate:</u> by population genetic model (coalescent)

- Only deterministic population size is parameterized!

Merge epidemiology and phylogenetics

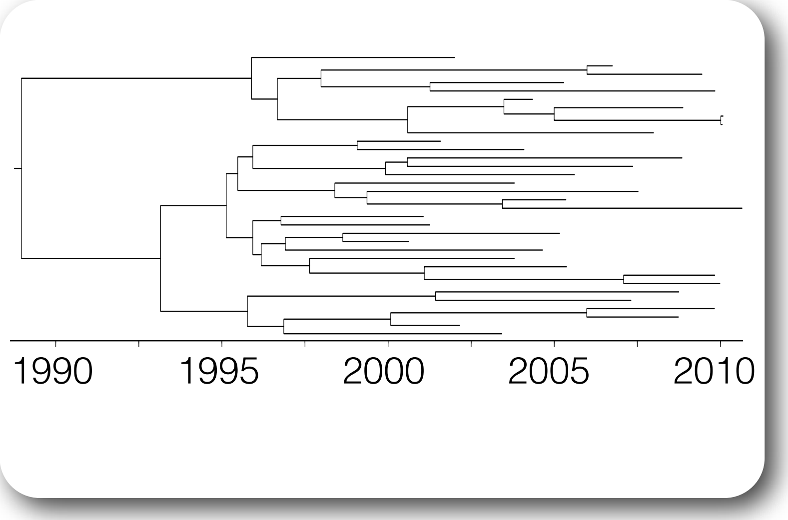


Methodology to:

1) Reconstruct phylogenetic trees

2) Fit epidemiological models to phylogenetic trees

Merge epidemiology and phylogenetics



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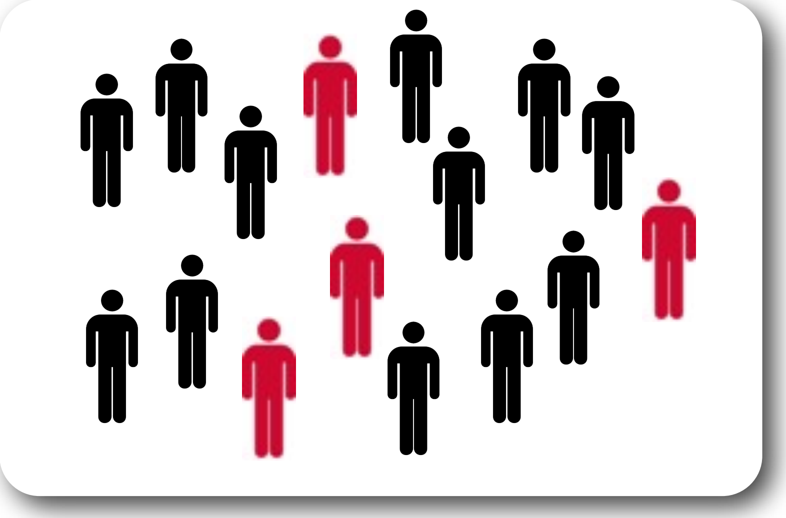


Quantification of spread of infectious diseases?

Factors governing transmission dynamics?
(e.g. population structure, environment, vaccines)

General modeling framework

Epidemiological model

Growth of tree

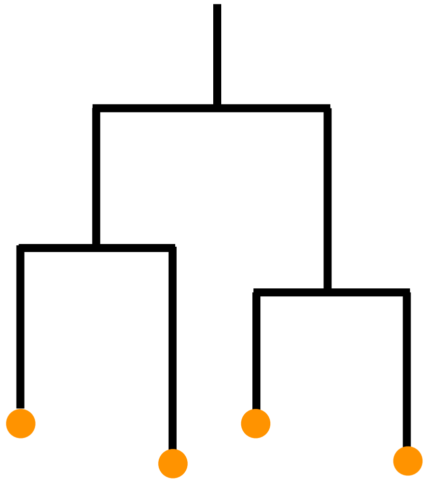
- parameters **η**

General modeling framework

Epidemiological model

Growth of tree

- parameters η



General modeling framework

Epidemiological model

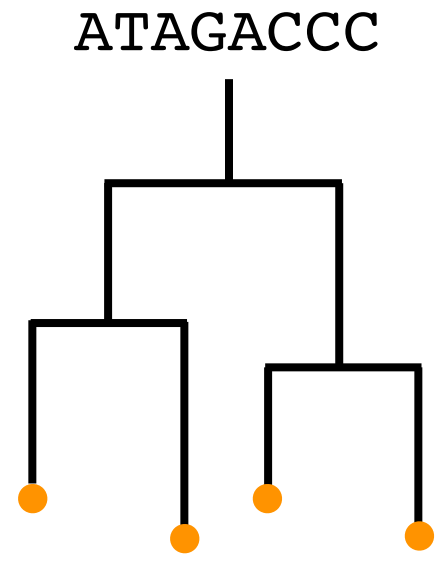
Growth of tree

- parameters η

Evolution-ary model

Evolution of sequences along tree

- parameters θ



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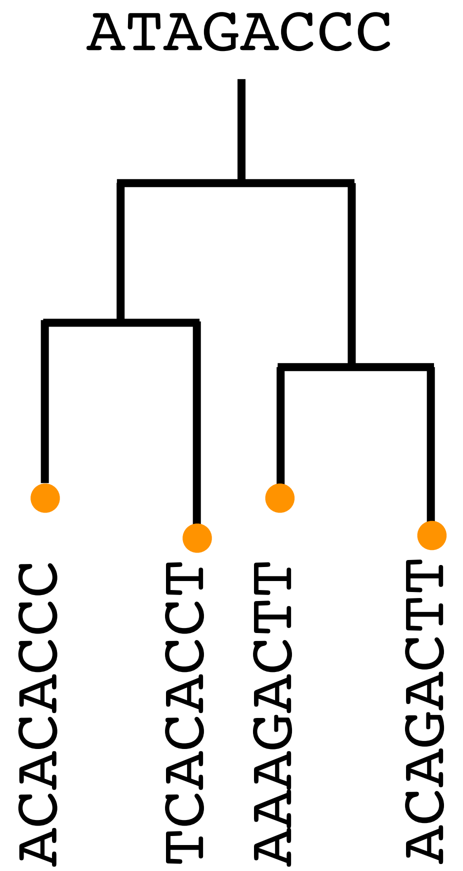
Tree distribution

Defined through η and θ



General modeling framework

Epidemiological model

Growth of tree

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Evolutionary model

Evolution of sequences along tree

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Tree distribution

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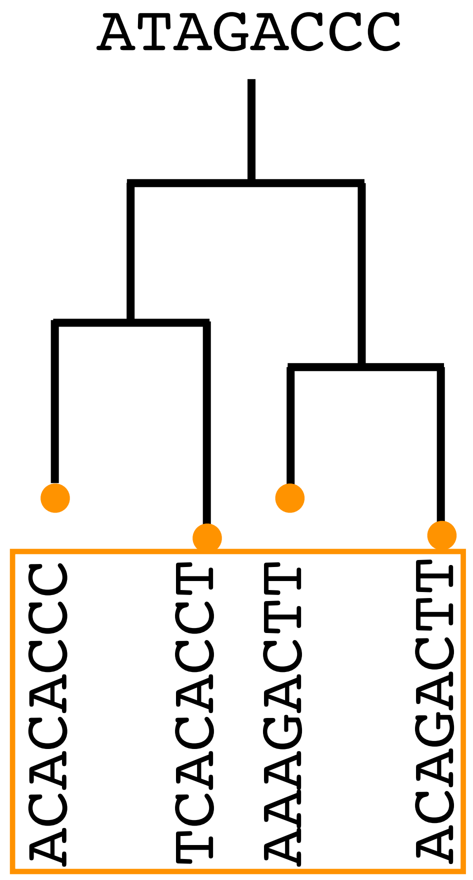
Data

Sequence alignment



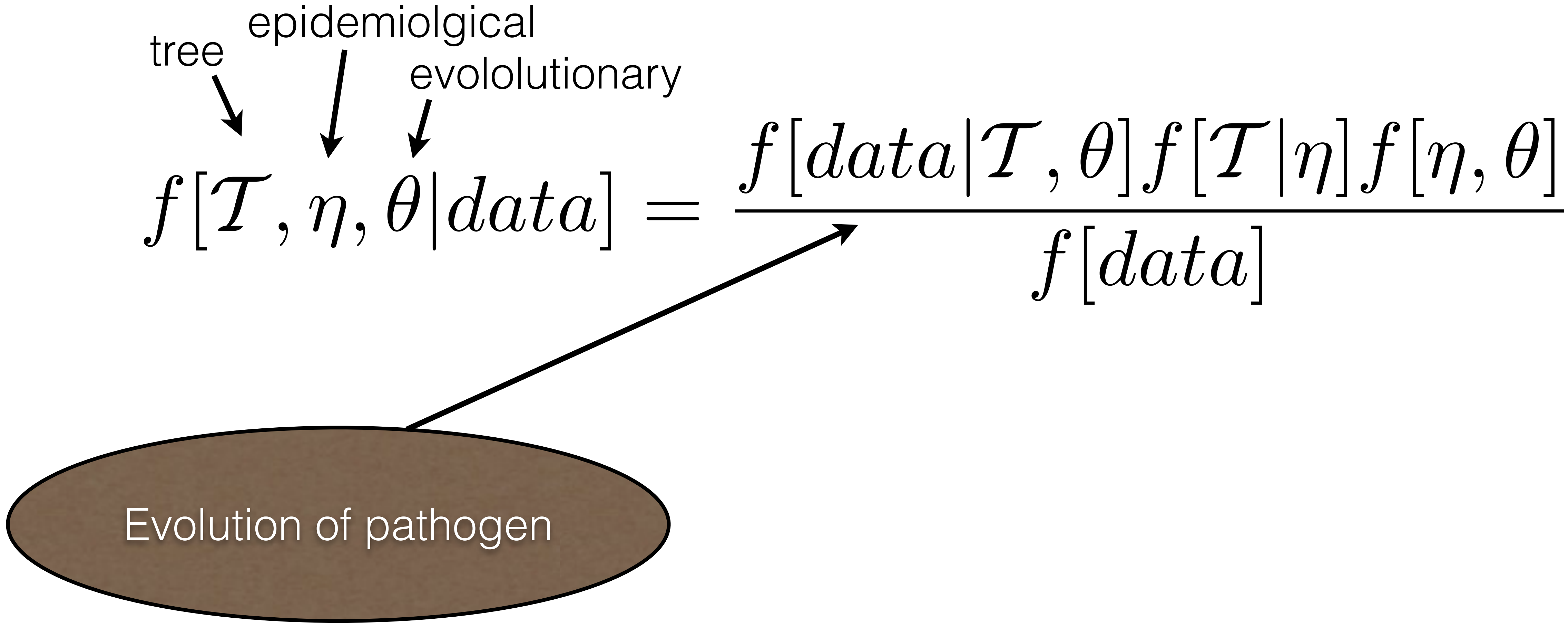
Bayesian approach for estimating epidemiological parameters

$$f[\overset{\text{tree}}{\overset{\searrow}{\mathcal{T}}}, \overset{\text{epidemiolgical}}{\overset{\downarrow}{\eta}}, \overset{\text{evololutionary}}{\overset{\downarrow}{\theta}}|data]$$

Bayesian approach for estimating epidemiological parameters

$$f[\overset{\substack{\text{tree}\\ \searrow}}{\mathcal{T}}, \overset{\substack{\text{epidemiolgical}\\ \downarrow}}{\eta}, \overset{\substack{\text{evolololutionary}\\ \swarrow}}{\theta}|data] = \frac{f[data|\mathcal{T}, \theta]f[\mathcal{T}|\eta]f[\eta, \theta]}{f[data]}$$

Bayesian approach for estimating epidemiological parameters



tree

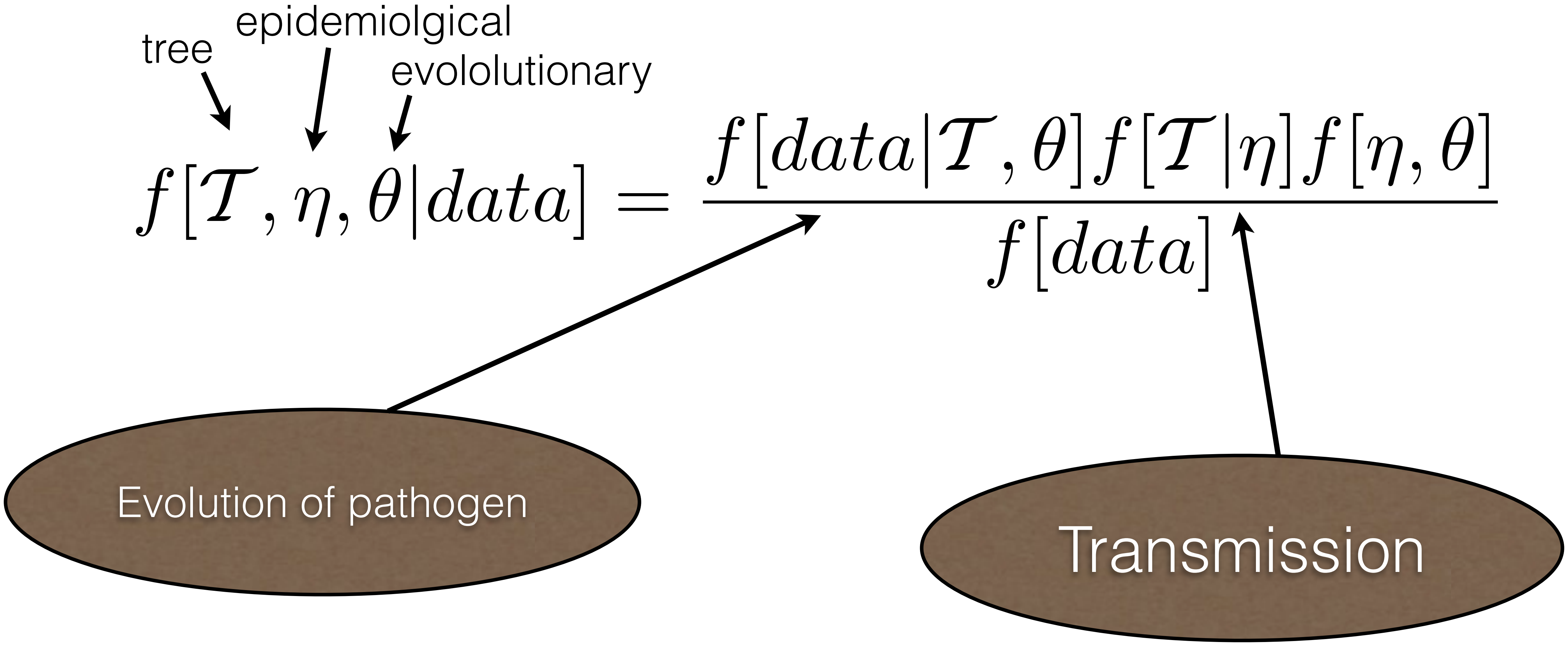
epidemiolgical

evolololutionary

$$f[\mathcal{T}, \eta, \theta | data] = \frac{f[data|\mathcal{T}, \theta] f[\mathcal{T}|\eta] f[\eta, \theta]}{f[data]}$$

Evolution of pathogen

Bayesian approach for estimating epidemiological parameters



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$$f[\mathcal{T}, \eta, \theta | data] = \frac{f[data|\mathcal{T}, \theta] f[\mathcal{T}|\eta] f[\eta, \theta]}{f[data]}$$

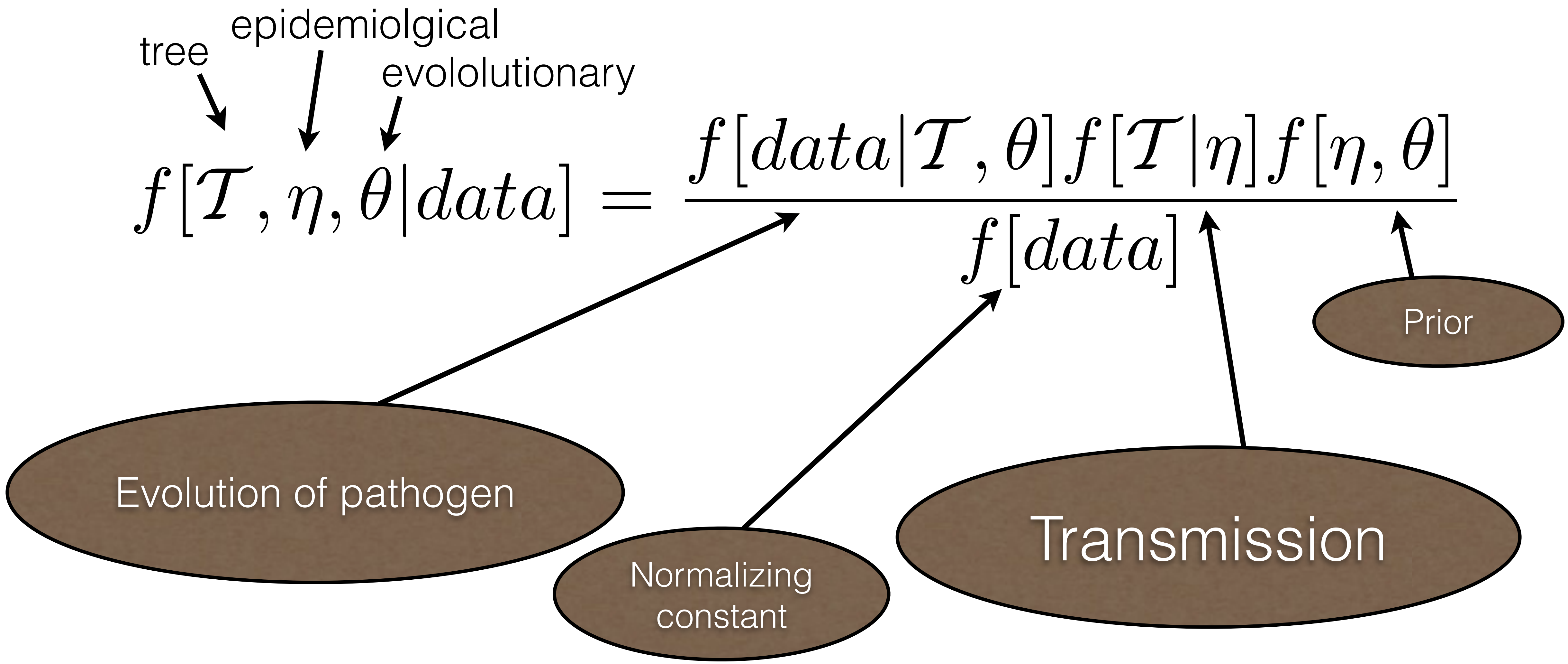
Evolution of pathogen

Transmission

Bayesian approach for estimating epidemiological parameters

$$f[\overset{\text{tree}}{\mathcal{T}}, \overset{\text{epidemiolgical}}{\eta}, \overset{\text{evololutionary}}{\theta}|data] = \frac{\underbrace{f[data|\mathcal{T},\theta]}_{\text{Evolution of pathogen}}\underbrace{f[\mathcal{T}|\eta]}_{\text{Transmission}}\underbrace{f[\eta,\theta]}_{\text{Prior}}}{f[data]}$$

Bayesian approach for estimating epidemiological parameters



tree

epidemiolgical

evolololutionary

$$f[\mathcal{T},\eta,\theta|data] = \frac{f[data|\mathcal{T},\theta]f[\mathcal{T}|\eta]f[\eta,\theta]}{f[data]}$$

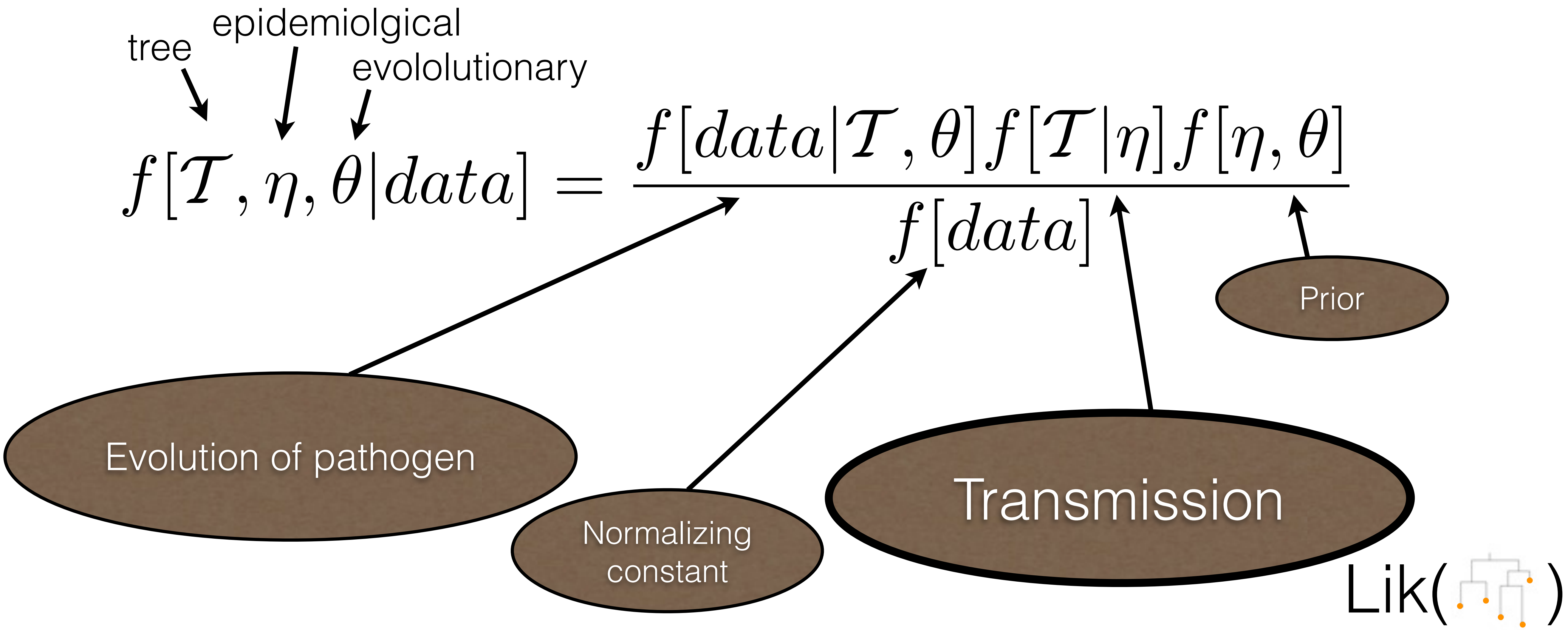
Evolution of pathogen

Normalizing constant

Transmission

Prior

Bayesian approach for estimating epidemiological parameters



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Evolution of pathogen

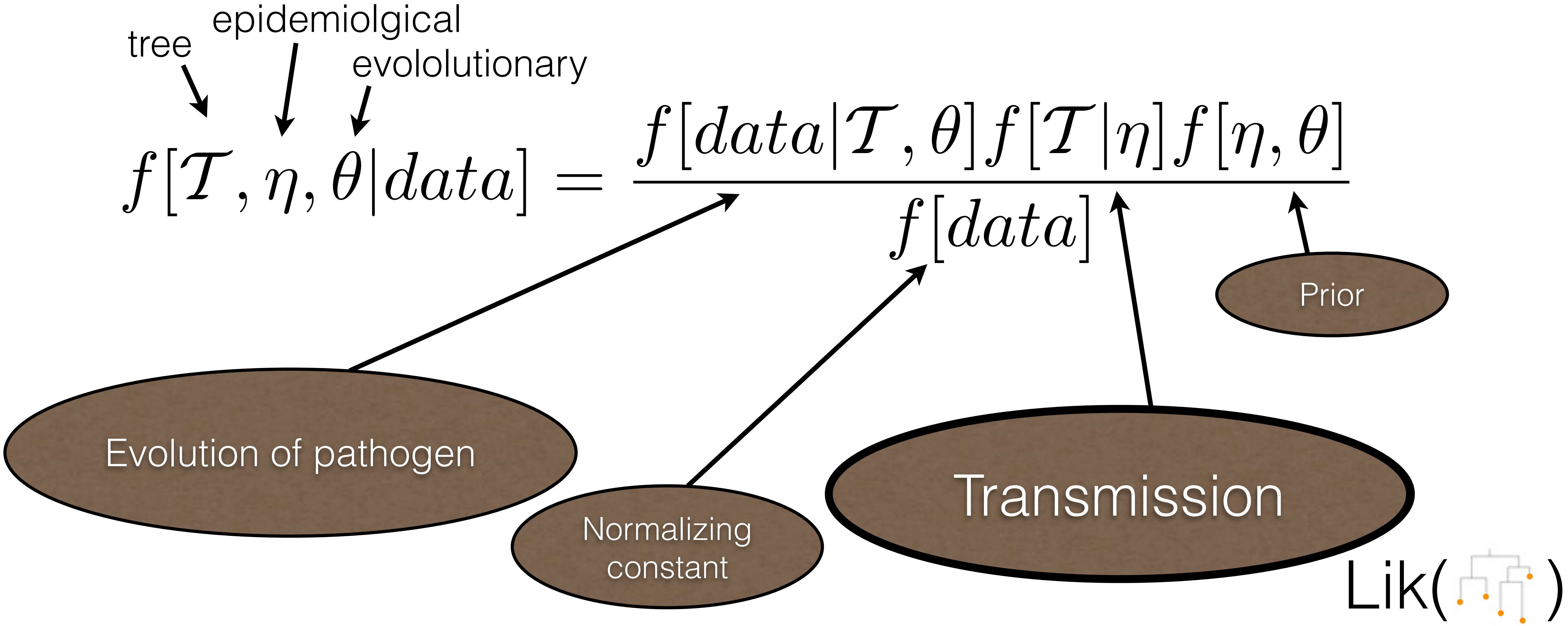
Normalizing constant

Transmission

Prior

Lik( )

Bayesian approach for estimating epidemiological parameters



tree

epidemiolgical

evololutionary

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Evolution of pathogen

Normalizing constant

Transmission

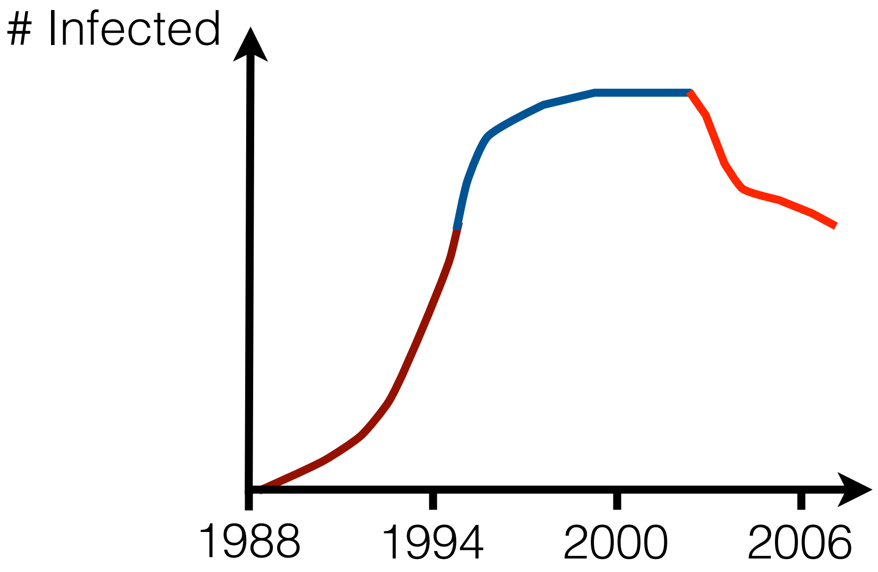
Prior

Lik( )

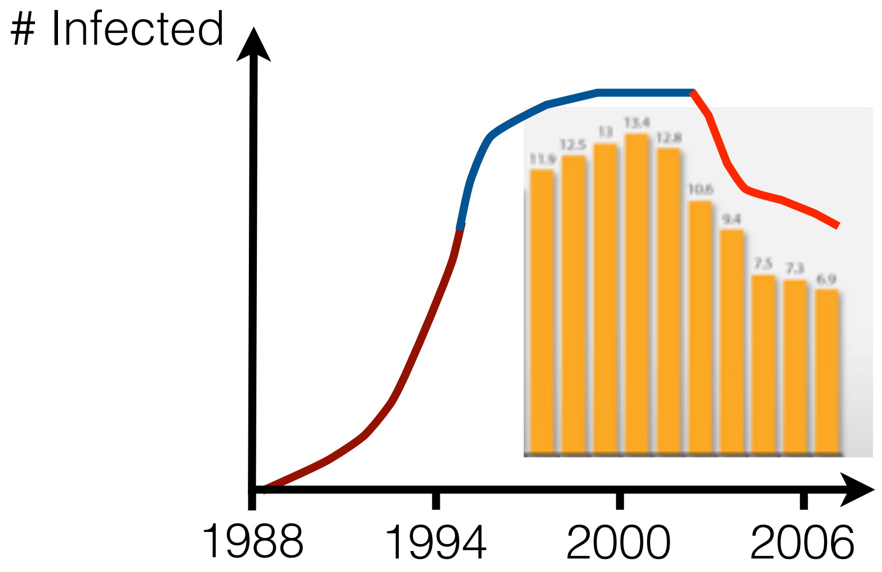
Implemented in Beast

Transmission model: coalescent or birth-death model

Phylogenetic methods for different epidemic dynamics



Phylogenetic methods for different epidemic dynamics



Phylogenetic methods for different epidemic dynamics

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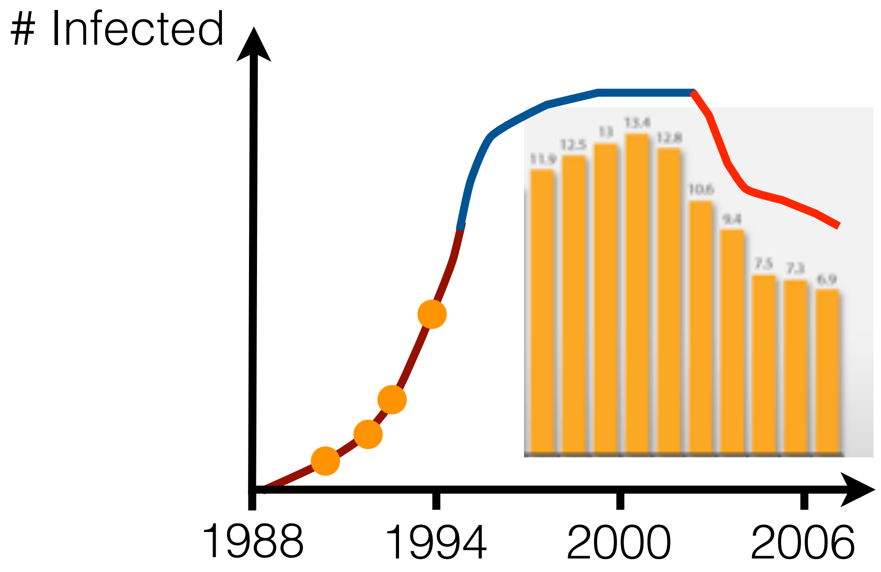
    - *C: Drummond et al. (Genetics, 2002)*
    - *BD: Stadler et al. (MBE, 2012)*



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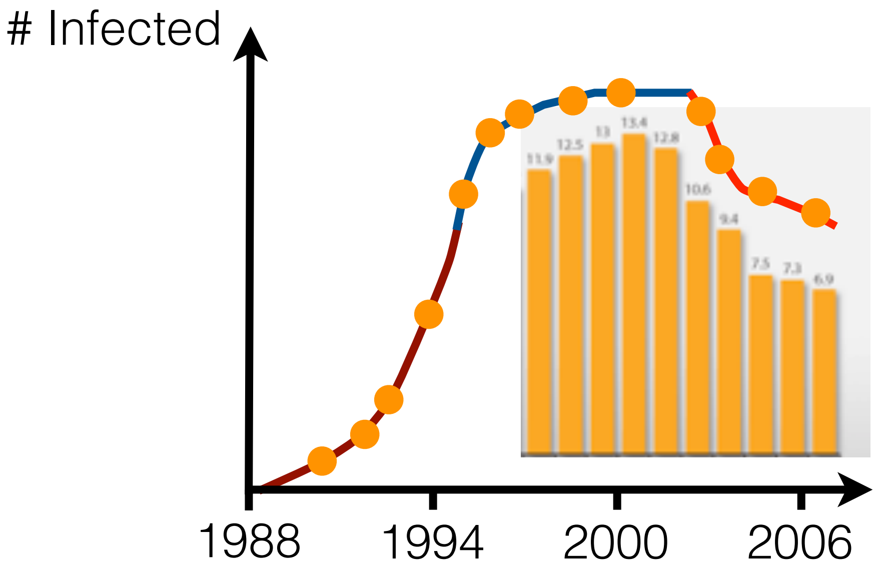

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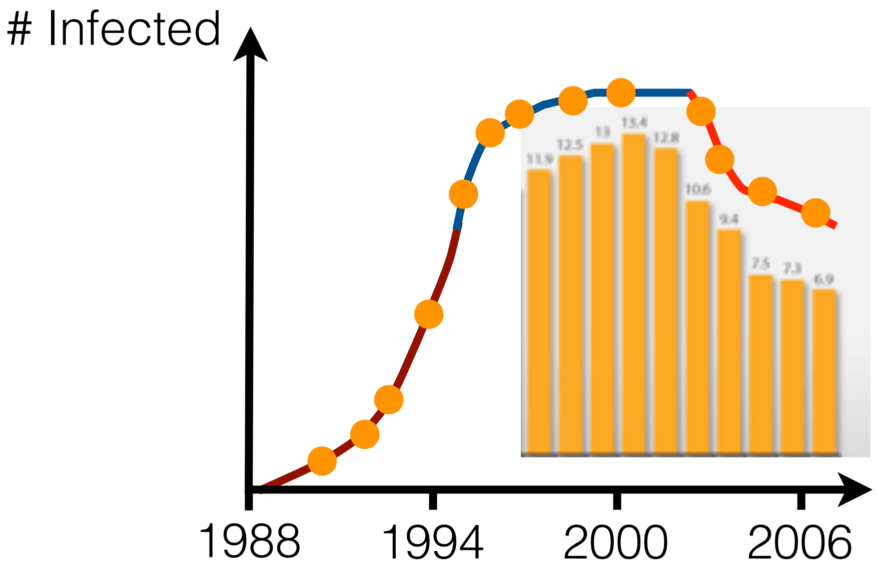

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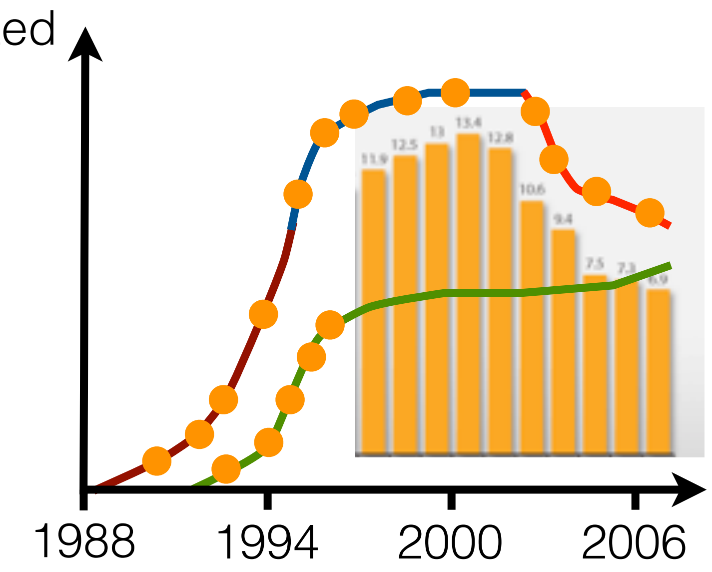
Phylogenetic methods for different epidemic dynamics



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4. ...accounting for host population structure
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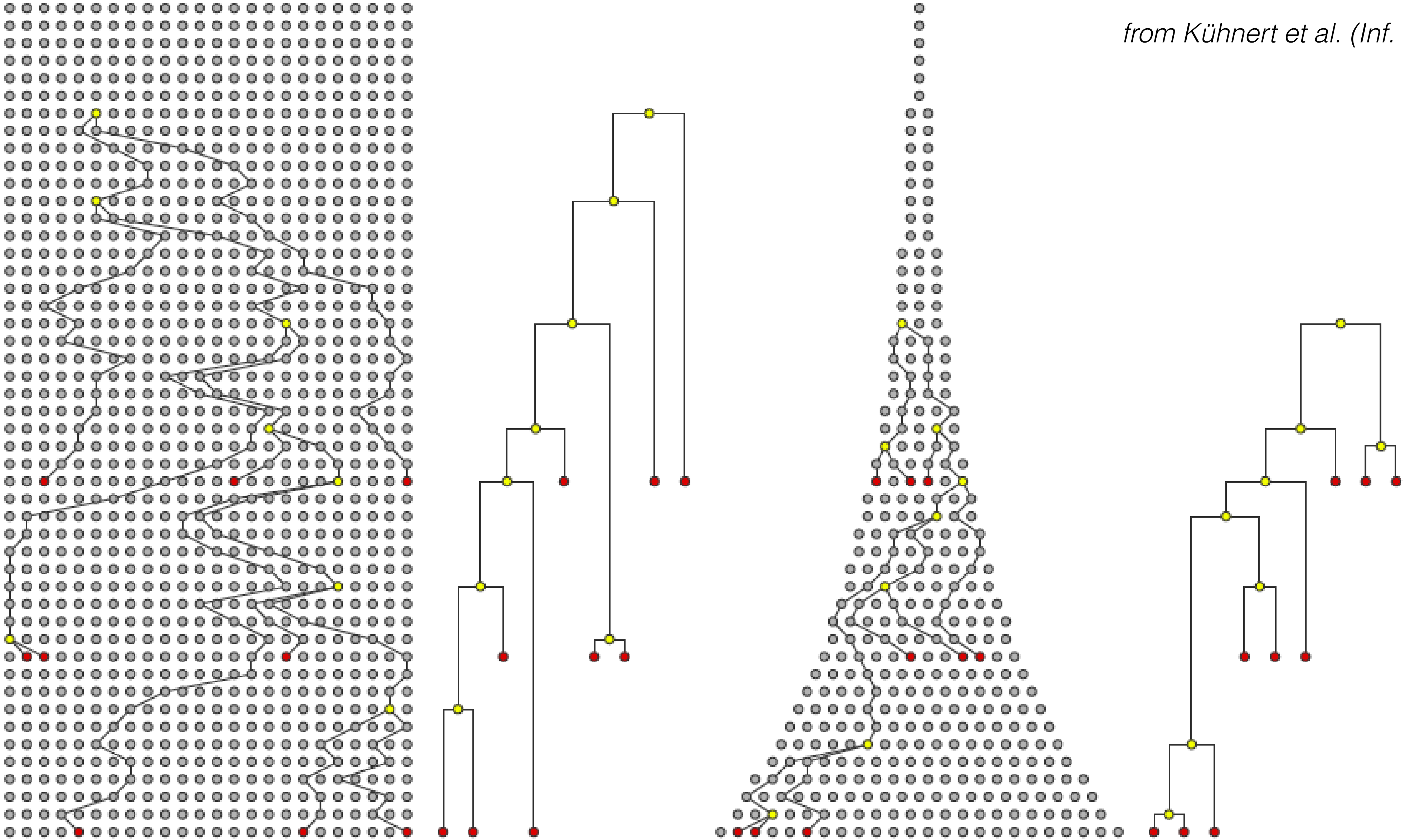
Part A

Coalescent as a model for transmission



from Kühnert et al. (Inf. Gen. Evol., 2011)

Part A

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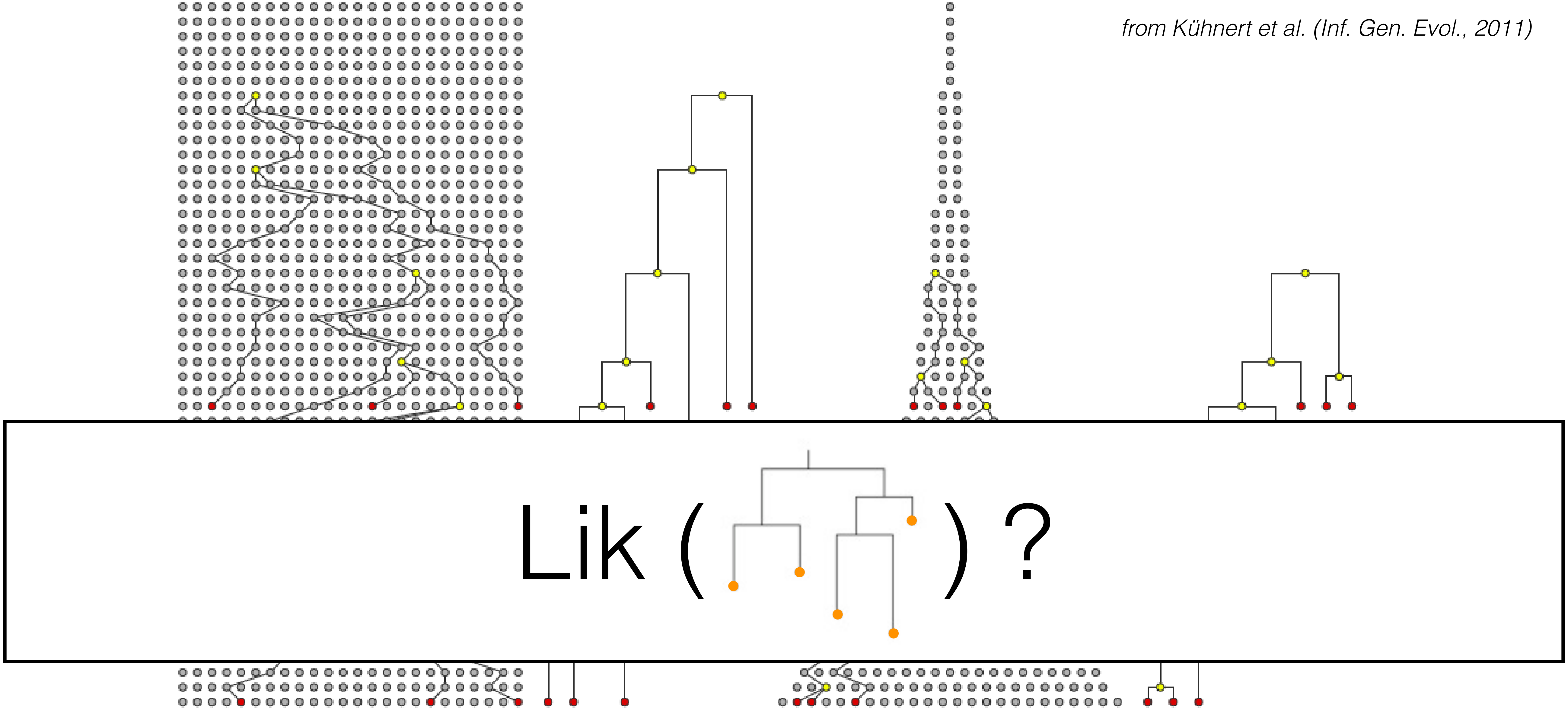

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Lik ( ) ?

Part A

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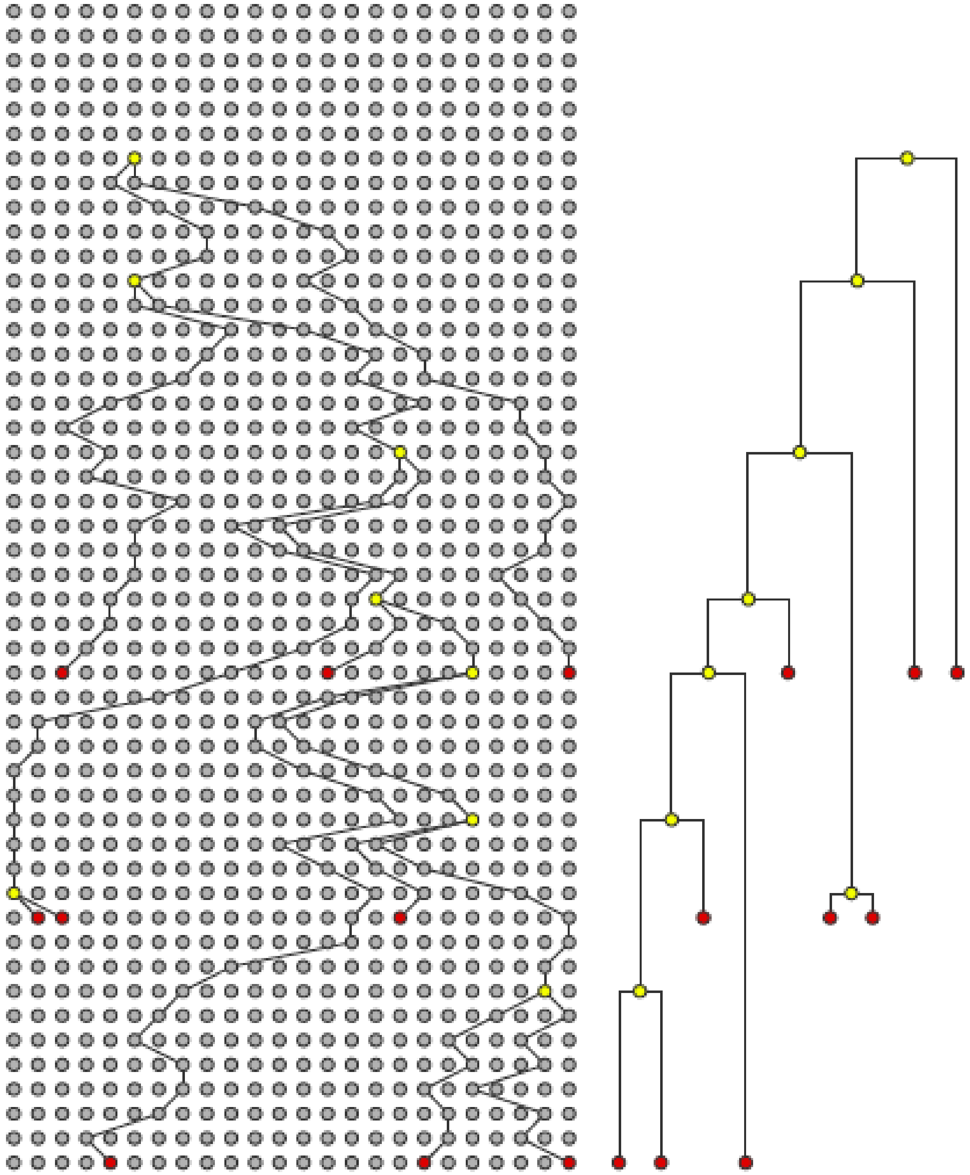

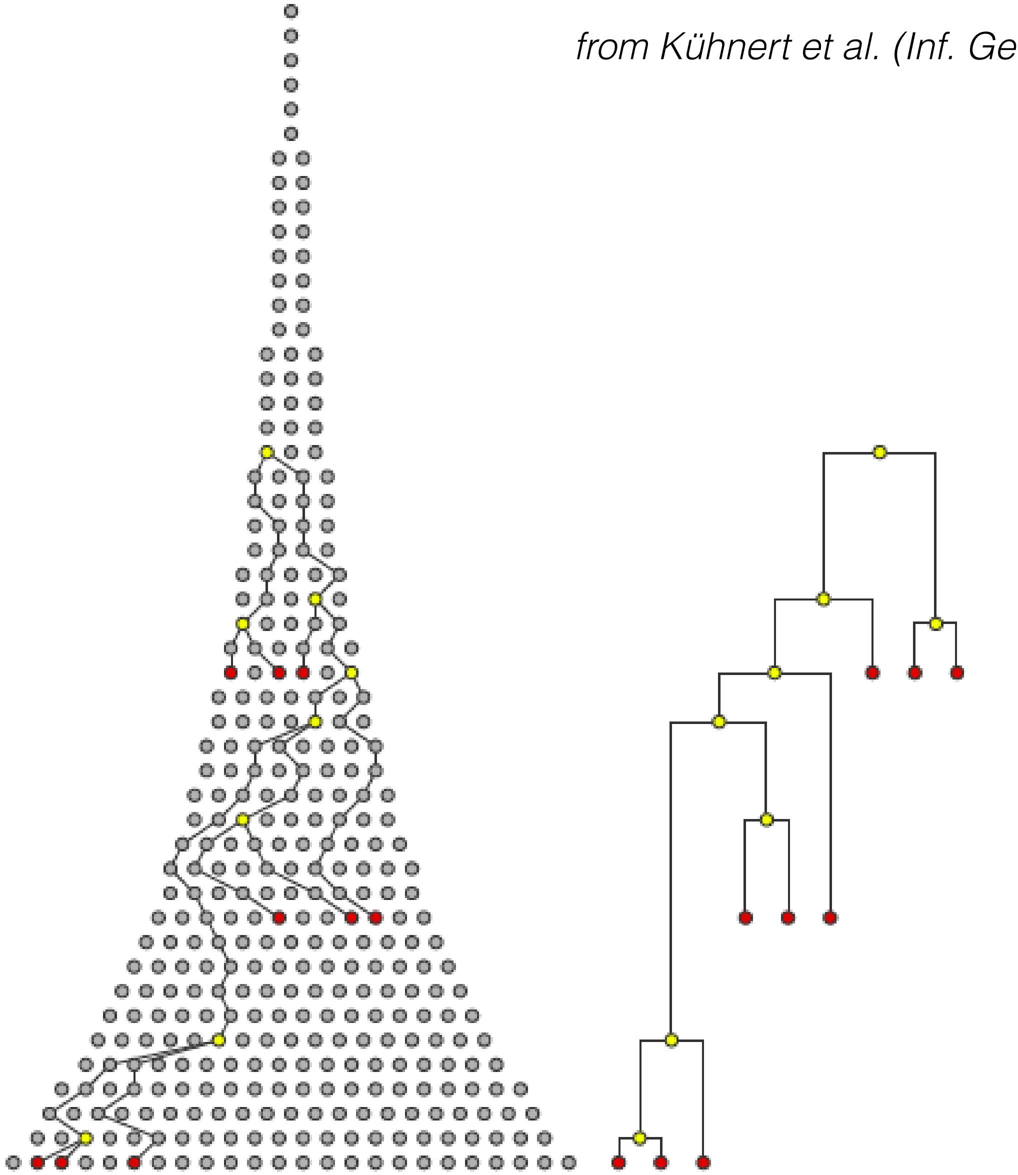

from Kühnert et al. (Inf. Gen. Evol., 2011)

$$f_G(g|\theta) = \frac{1}{\theta^{n-1}} \cdot \prod_{i=2}^{2n-1} e^{(-k_i(k_i-1)/2\theta)(t_i - t_{i-1})}$$

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from Drummend et al. (Genetics, 2002)

Estimating R_0 from sequencing data

Hepatitis C

Little known before first isolation, ie. pre-1989.

How can we determine basic reproductive number R_0?

from Pybus et al. (Science, 2001)

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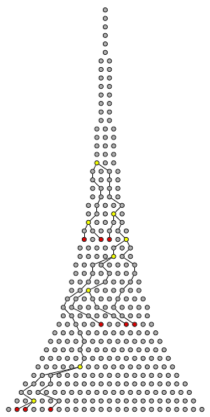
40-100 sequences per subtype

Fit exponential-growth coalescent to sequences and obtain growth rate r (i.e. $\eta=r$)

$R_0 = rD+1$ (where D is expected time of infectiousness)



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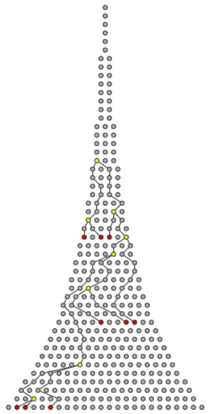
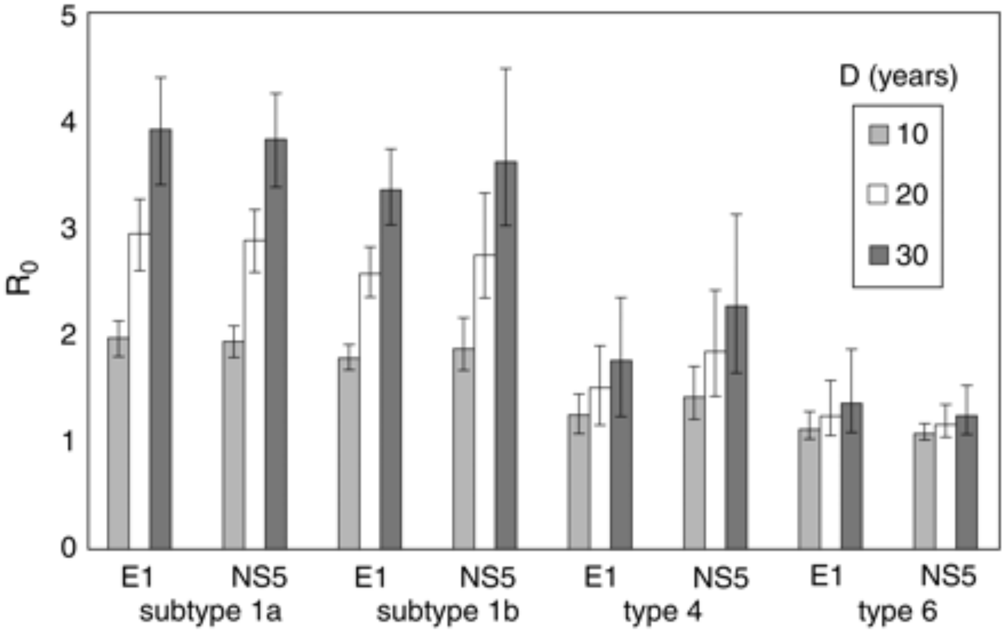


Results



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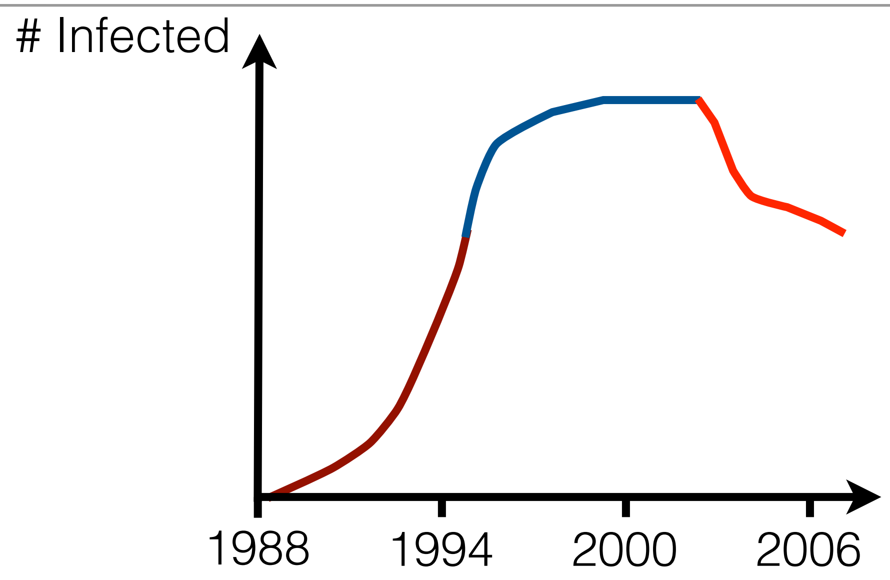
Bayesian skyline plot relaxes constant growth rate



from Drummond et al. (MBE, 2005)

Bayesian skyline plot relaxes constant growth rate

Assump-
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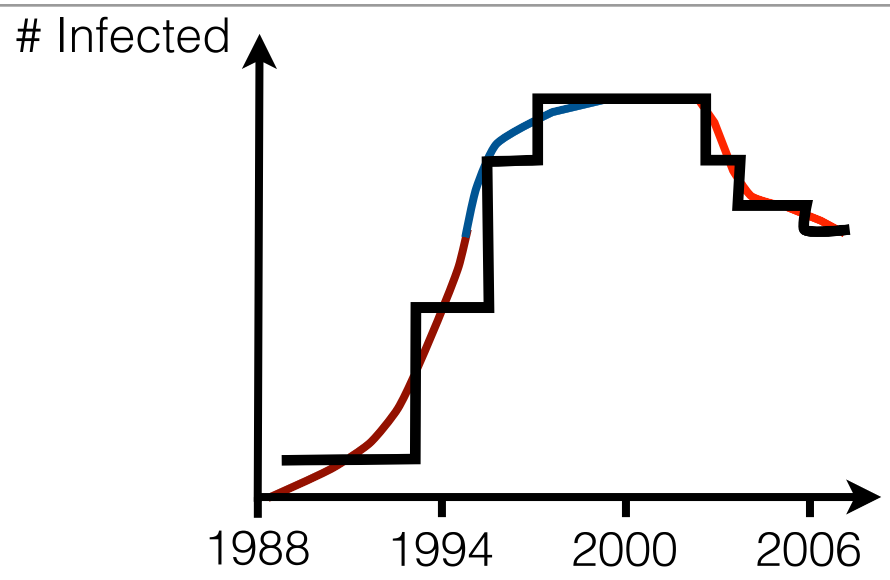
Piecewise constant population size



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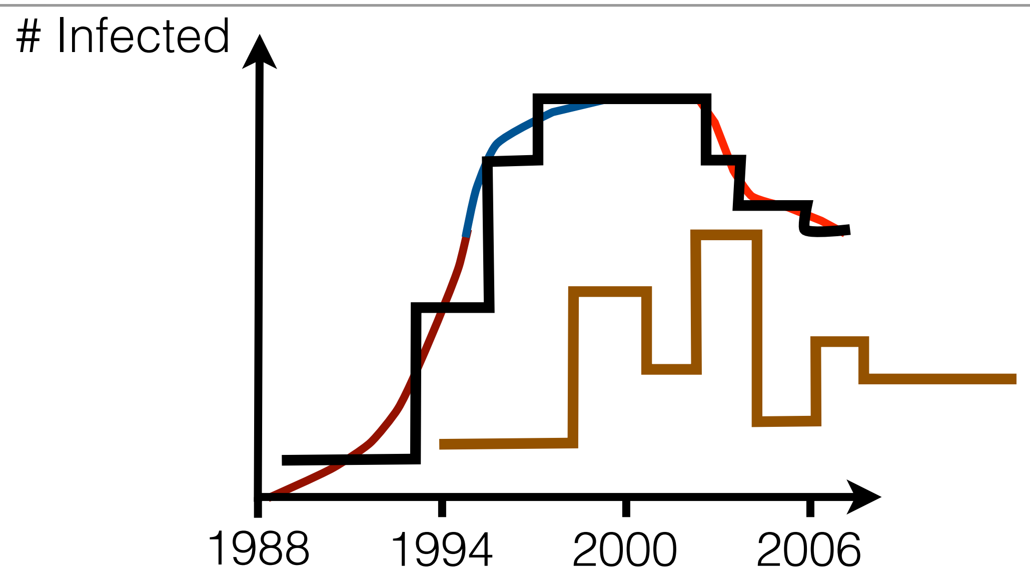

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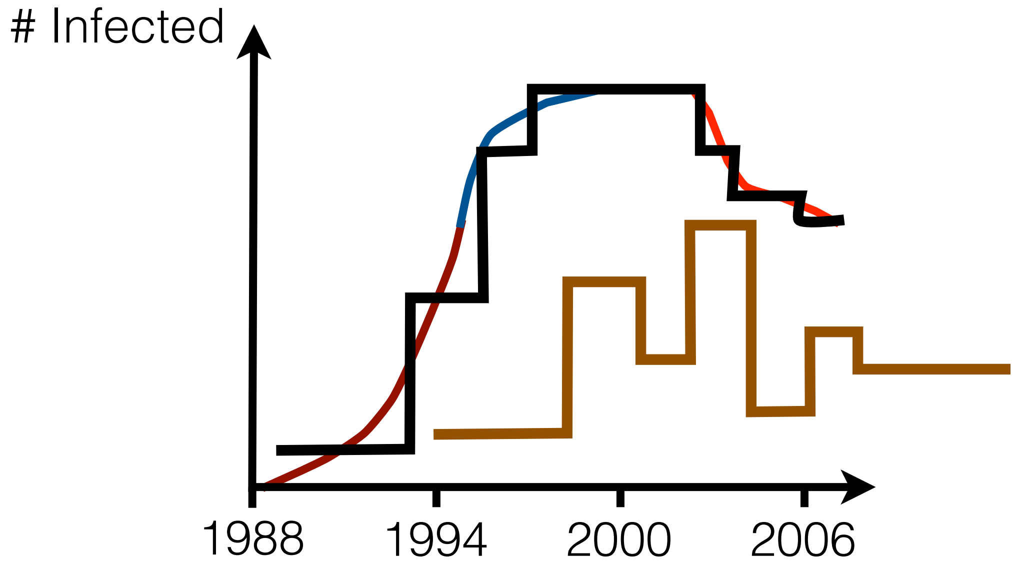
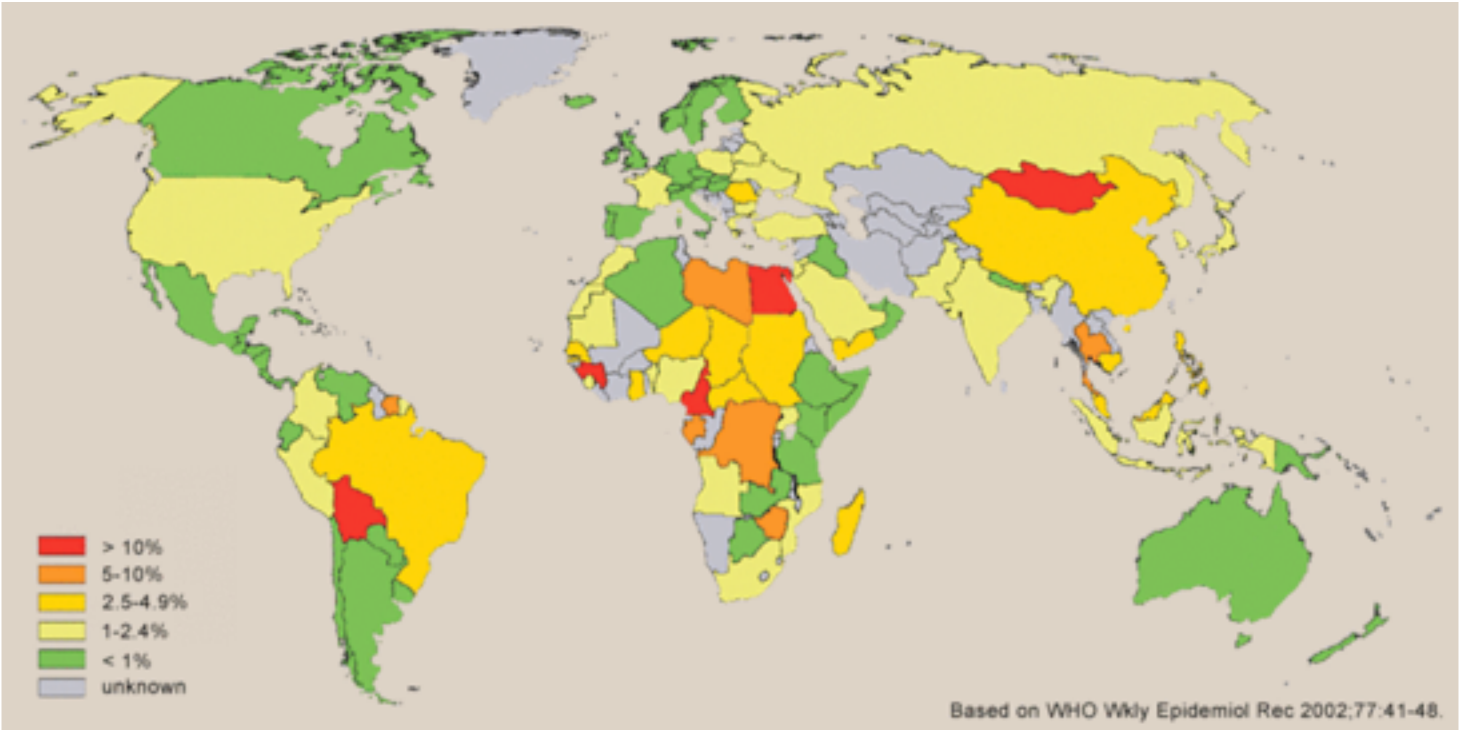


HCV in Egypt

- Egypt highest HCV prevalence worldwide (about 13 %)
- Neighboring countries low prevalence
- When did the high prevalence emerge?
- Why?



Based on WHO Wkly Epidemiol Rec 2002;77:41-48.

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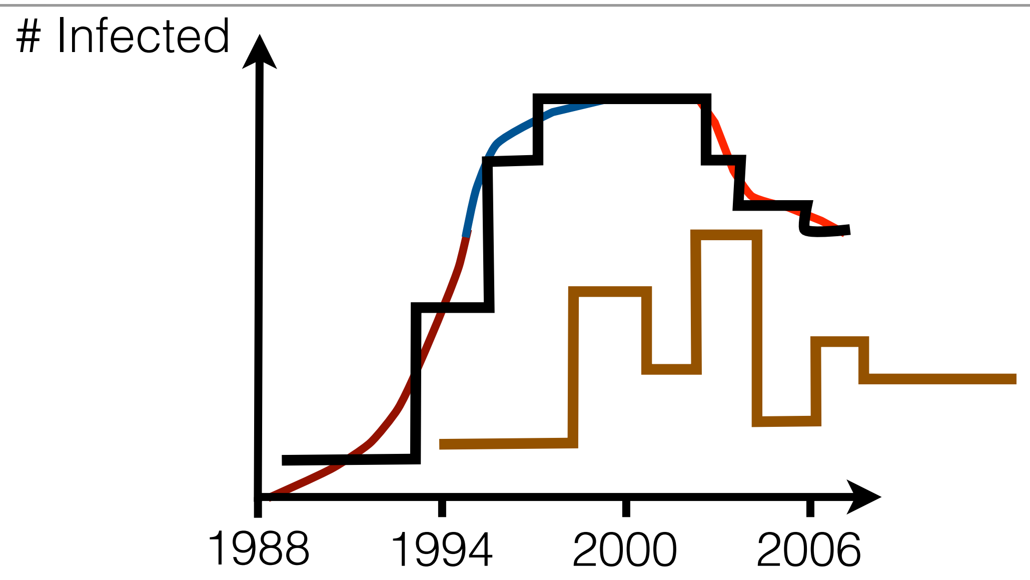

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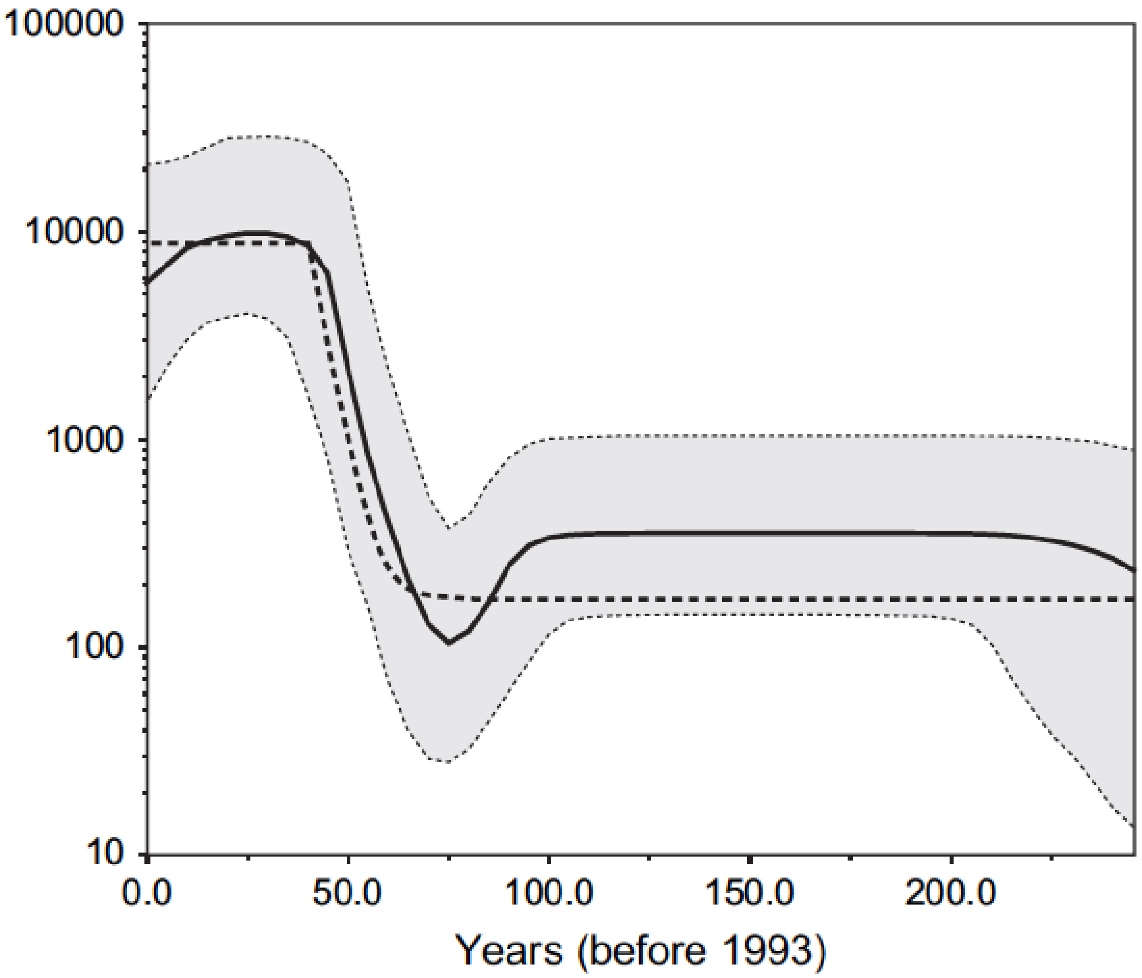

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Limitations of classic coalescent

Coalescent

Coalescent rates only depend on # infected, i.e. $\lambda_0 I$!

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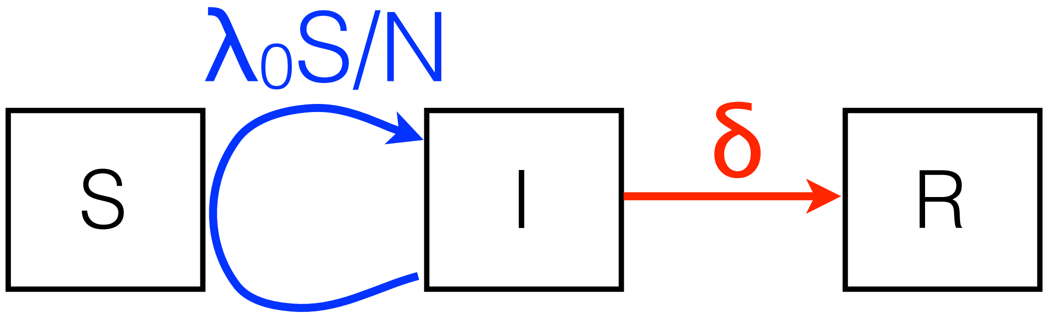
SIR extension



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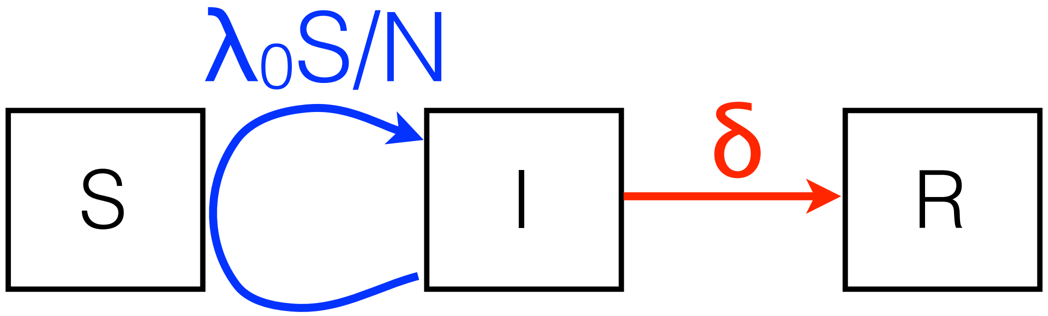

overall coalescent rate: $\lambda_0 IS/N$

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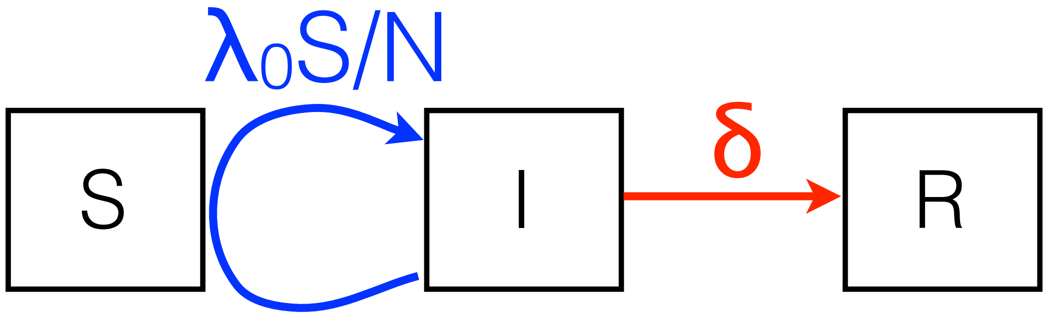

$\lambda_0 S/N$

S

I

δ

R

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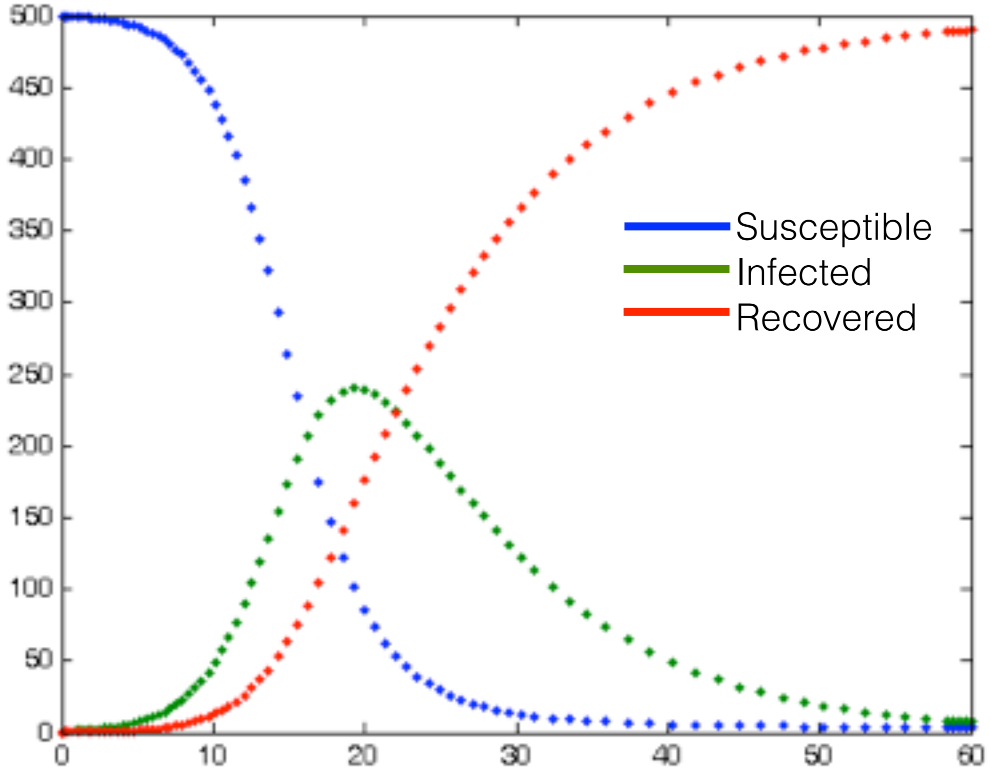

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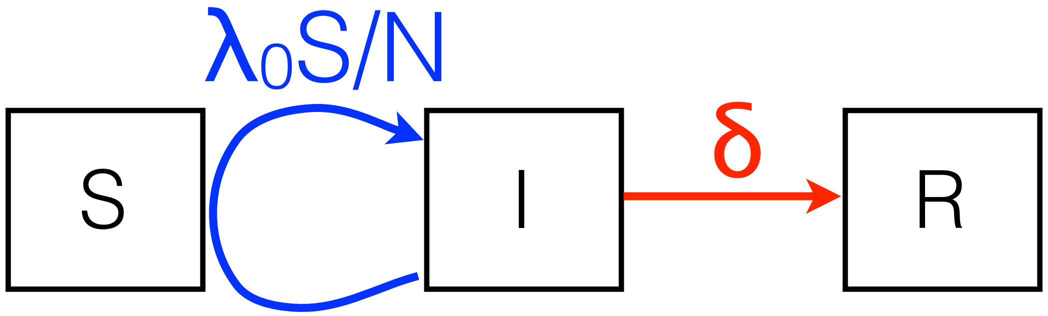

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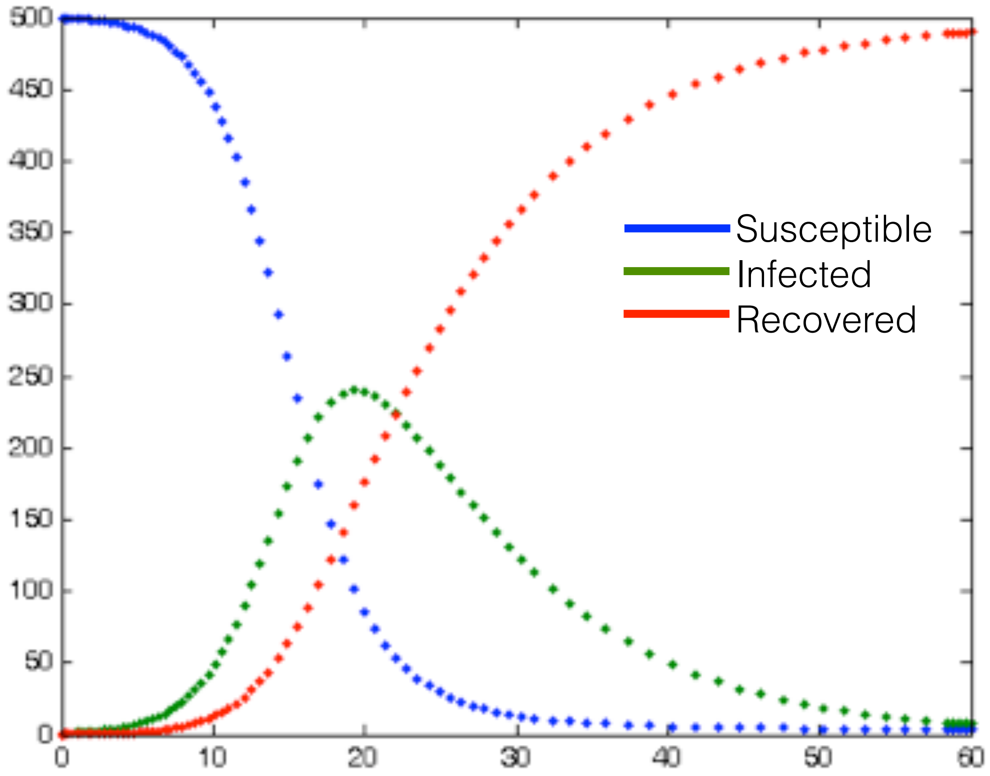

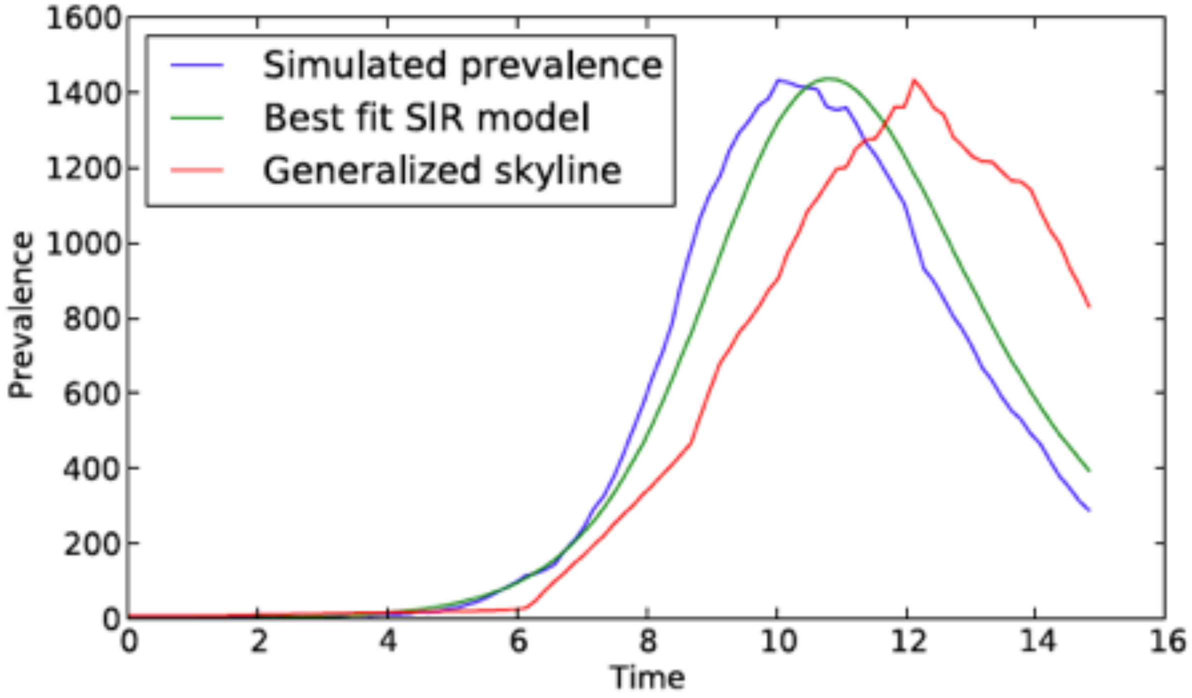

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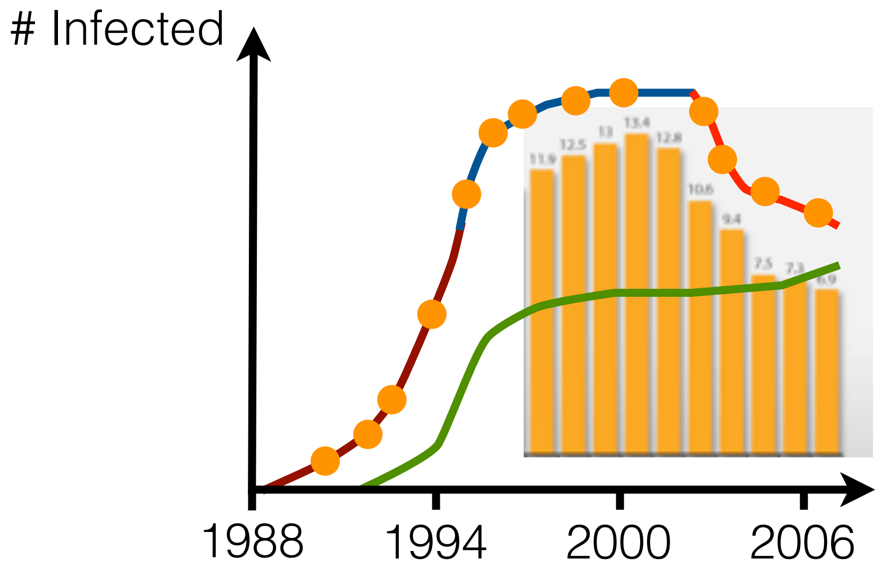
Phylogenetic methods for different epidemic dynamics



1. ...for analyzing epidemic outbreaks
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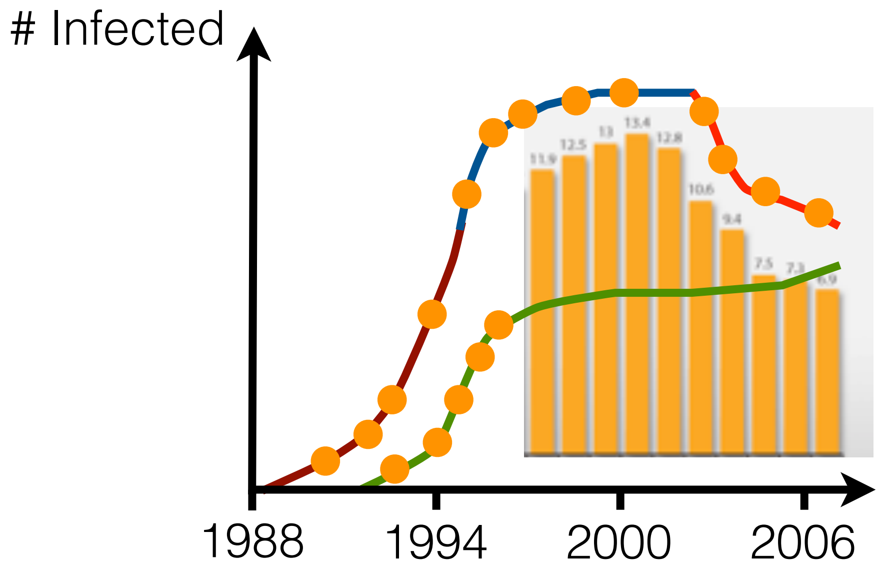

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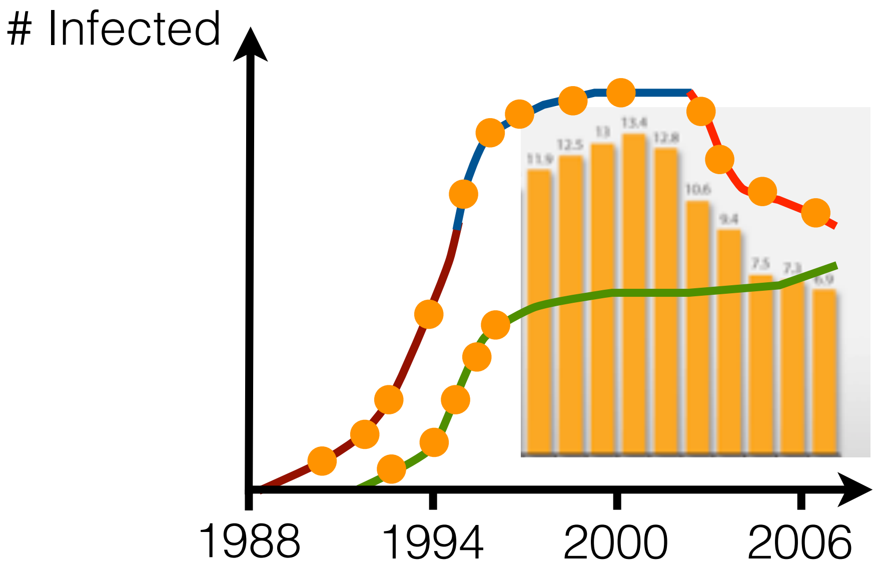

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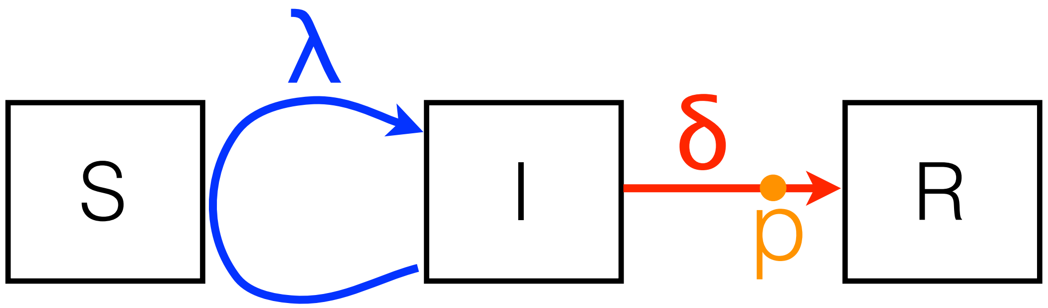
Part 2

Birth-death model for transmission

Birth-death model



- transmission rate λ
- “becoming-non-infectious” rate δ
- sampling probability p

Parameters may depend on:

1) constant (epidemic outbreak)
2) time (environmental effect)
3) # of susceptibles (SIR model)
4) type of infected individual

Stadler (JTB, 2010)

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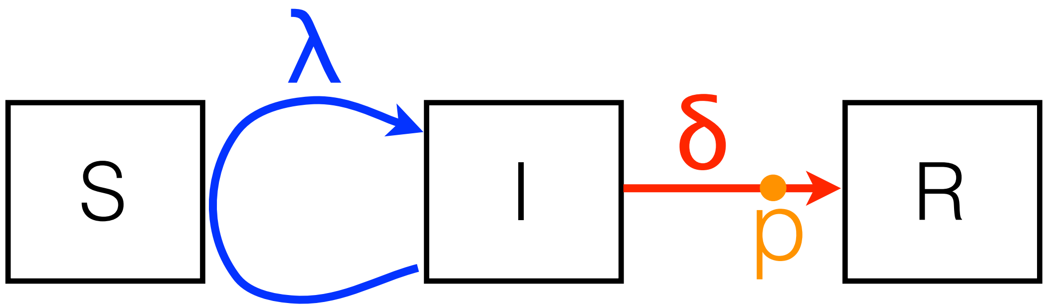

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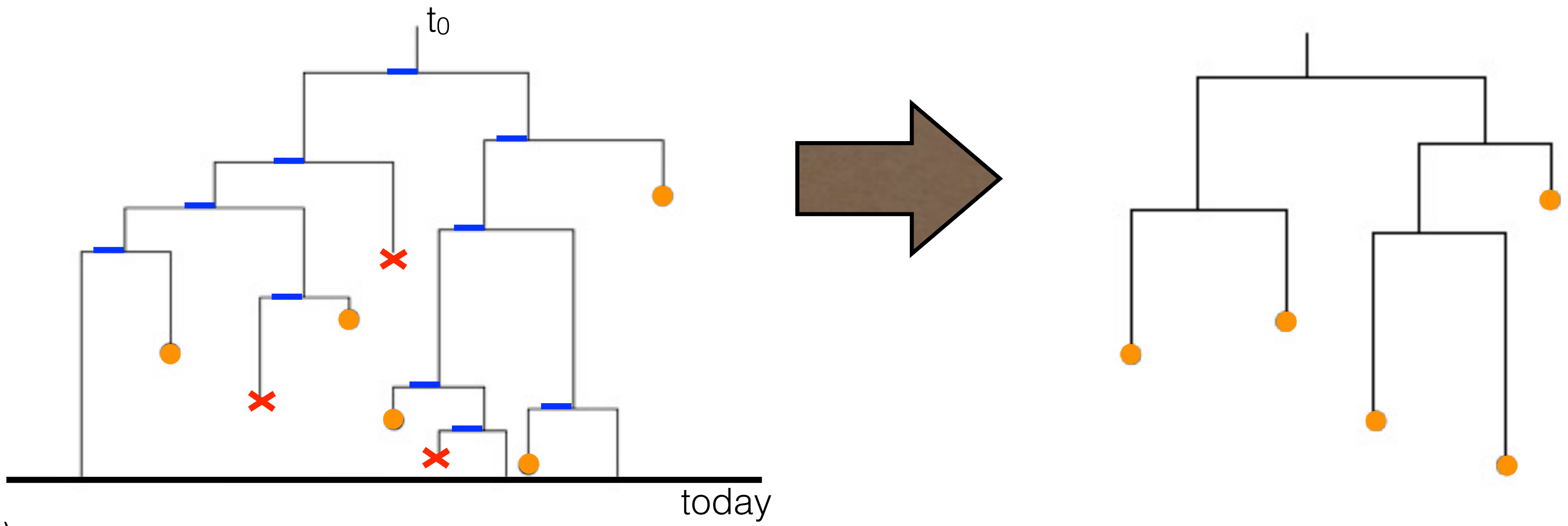
Phylo-genetic trees



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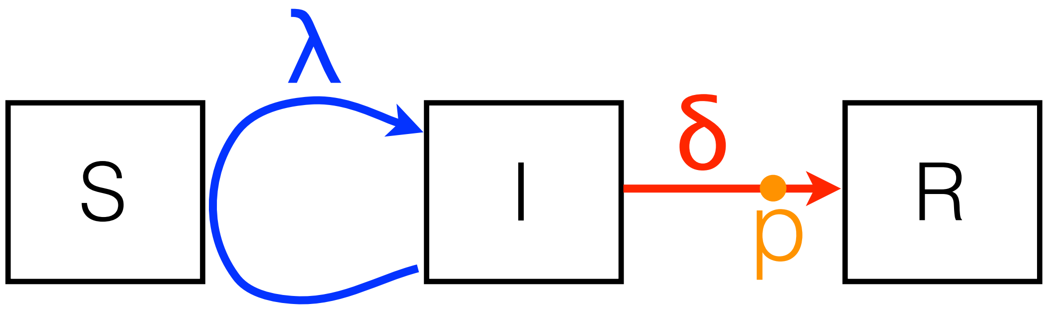

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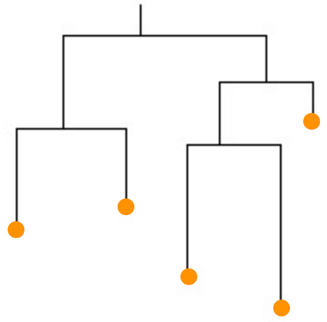
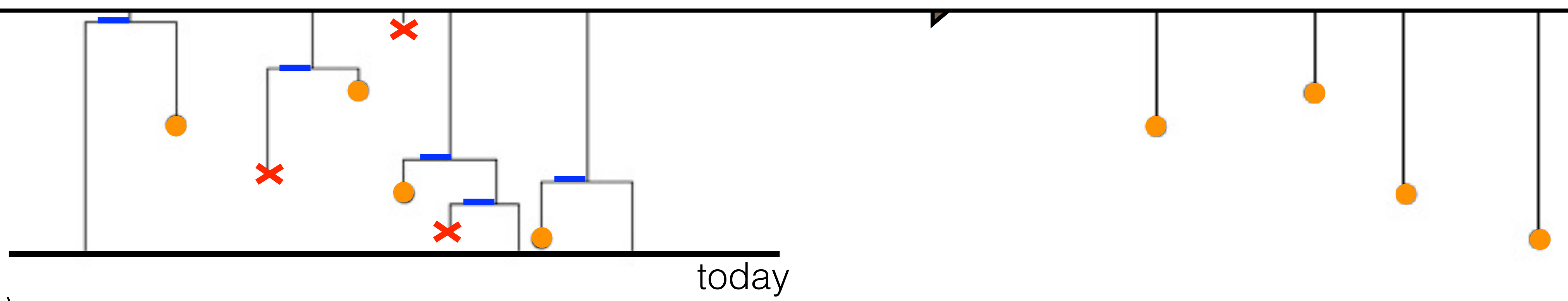
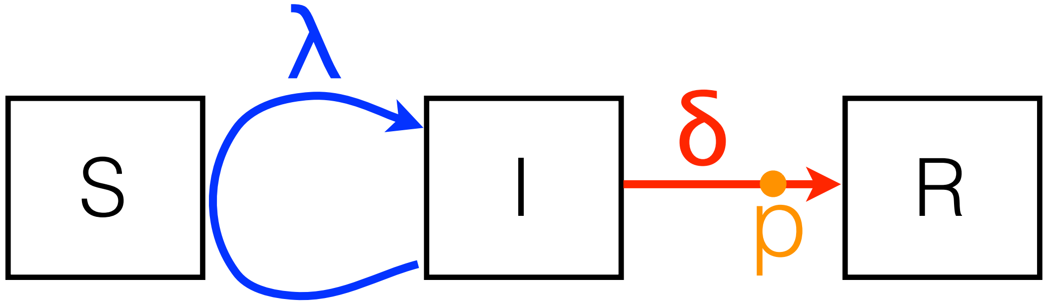
Lik () ?

genetic trees



Stadler (JTB, 2010)

1) Epidemic outbreaks



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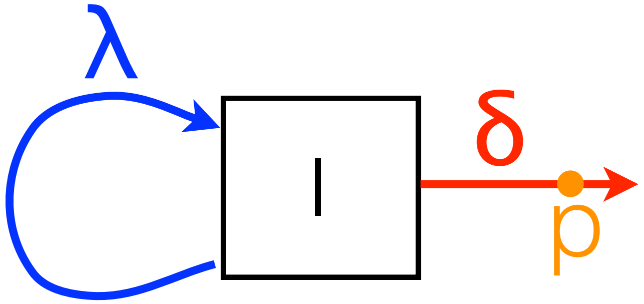

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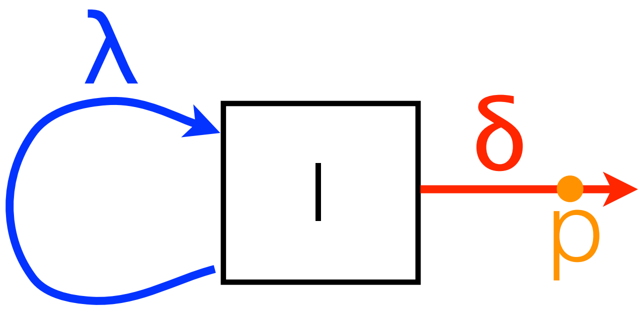

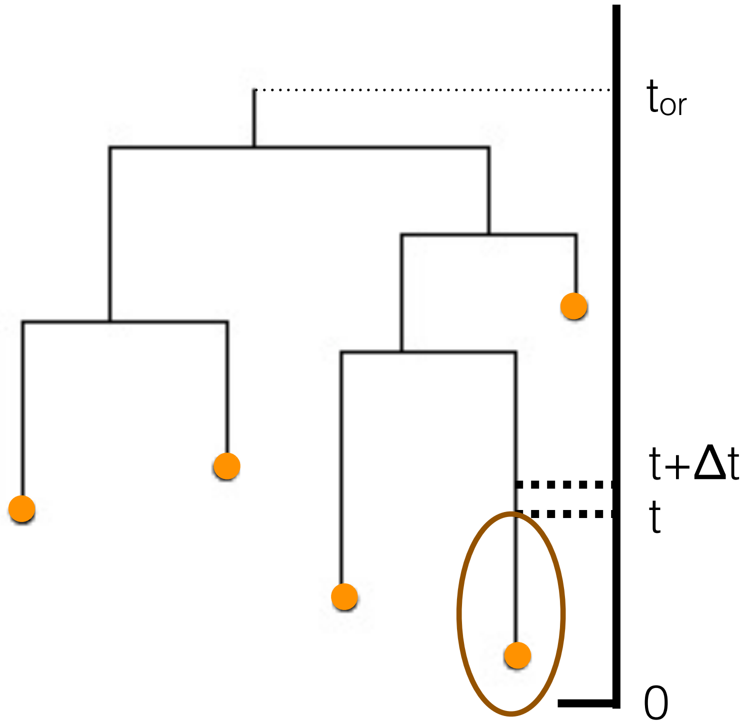

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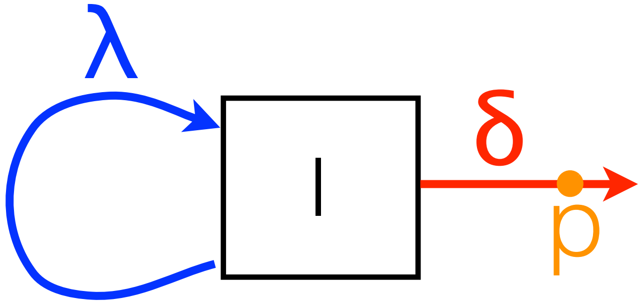

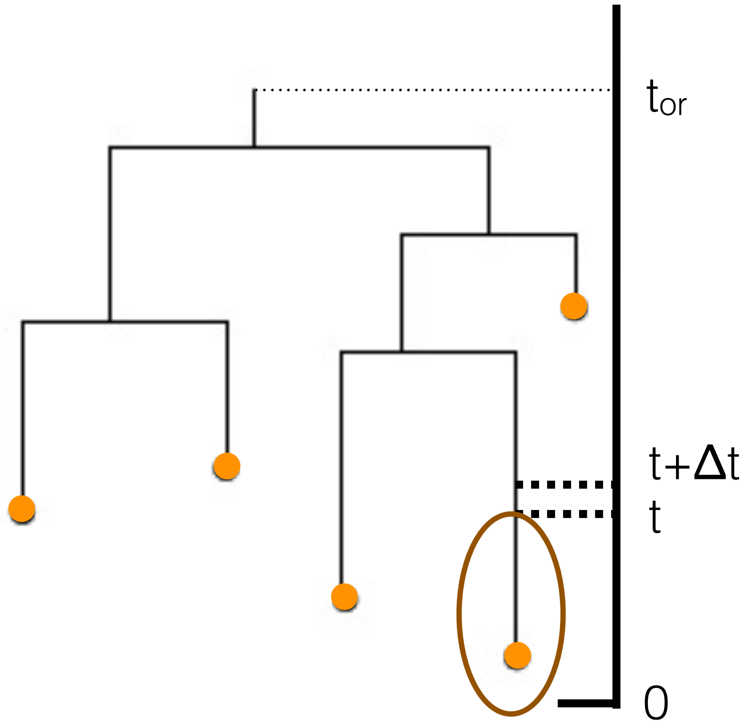

<u>p(t):</u> probability density that a given individual at time t produces an descending tree as observed.

Stadler (JTB, 2010)

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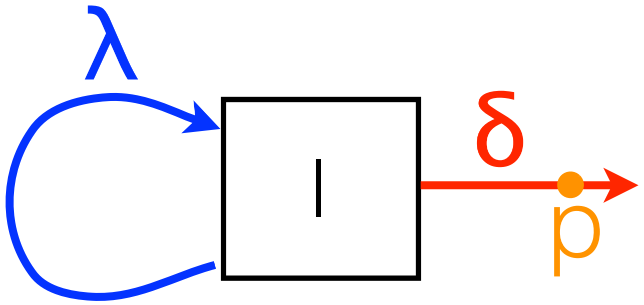

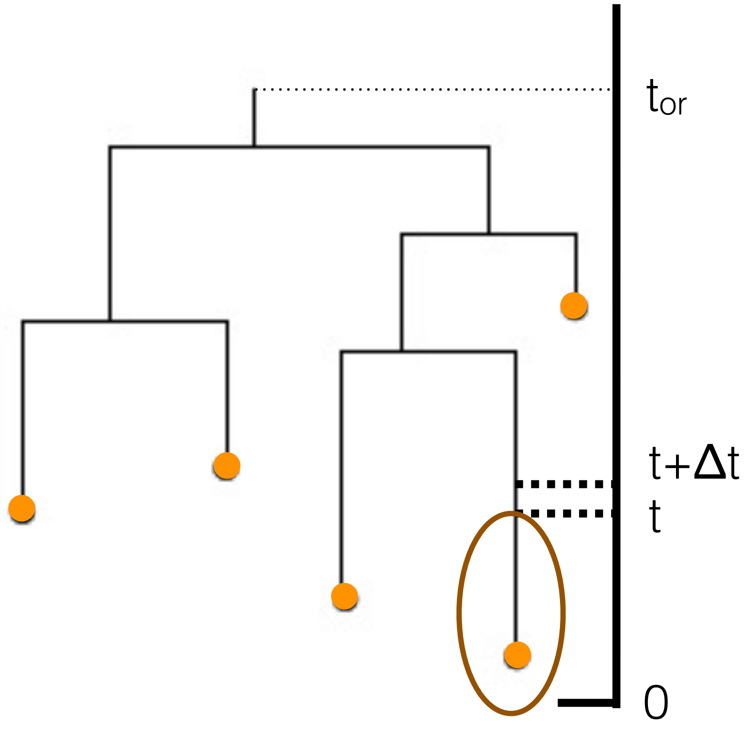

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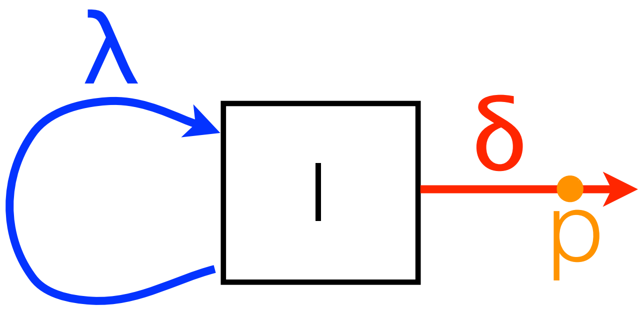

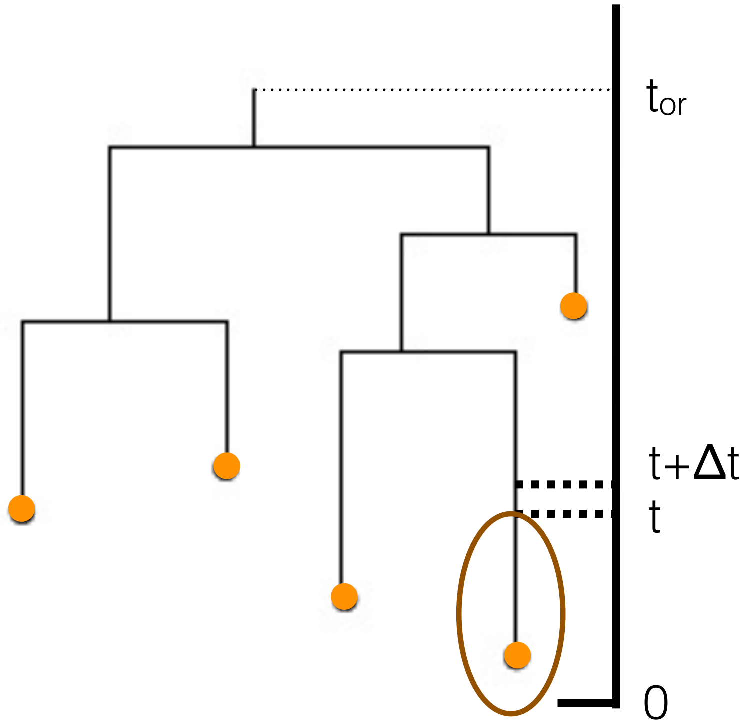

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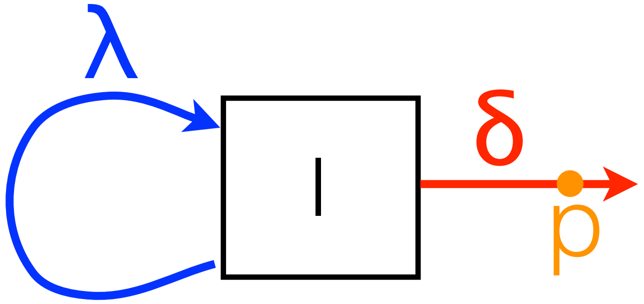

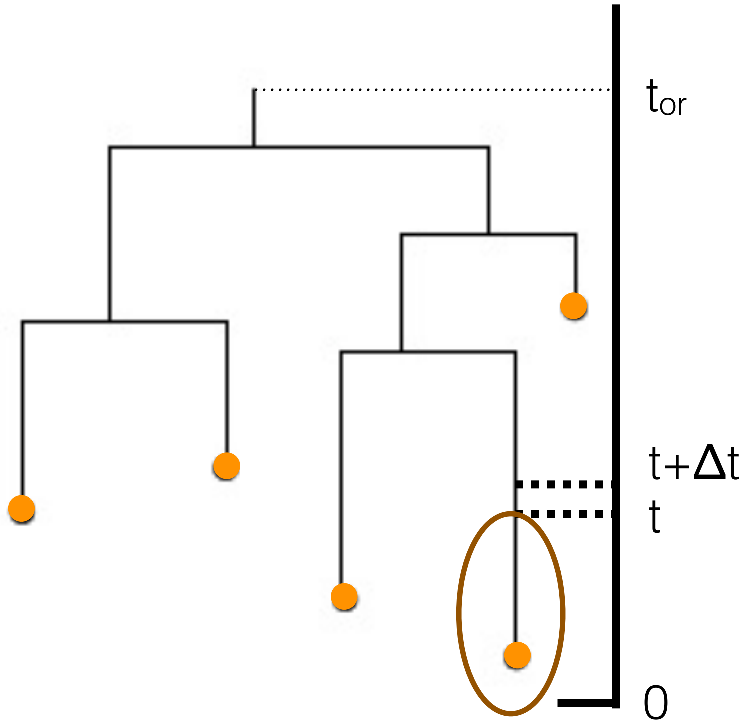

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Stadler (JTB, 2010)

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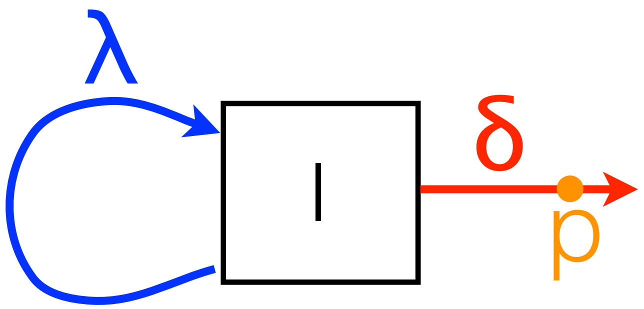

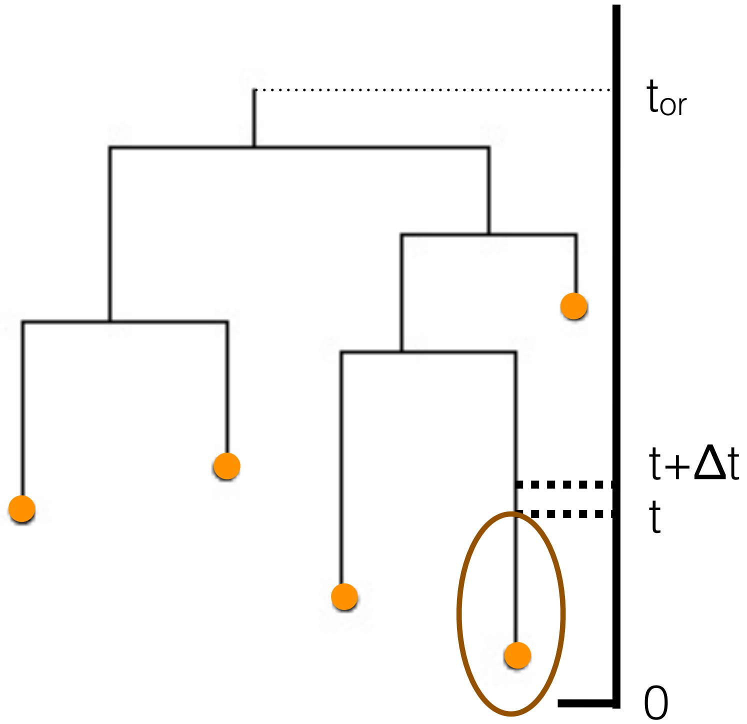

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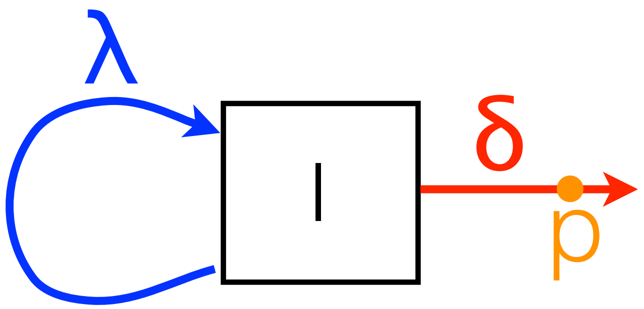
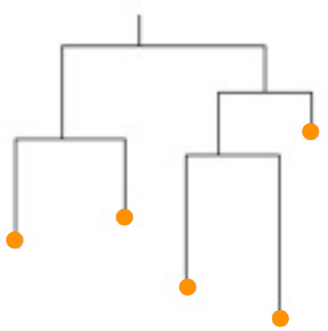
Δt → 0

$$\frac{d}{dt}p(t) = -(\lambda+\delta)p(t) + 2\lambda p_0(t)p(t)$$

Stadler (JTB, 2010)

Tree likelihood



Lik ()

$$= \lambda^{m-1} \prod_{i=0}^{m-1} \frac{1}{q(x_i)} \prod_{i=1}^{m} p\delta q(y_i)$$

where

$$q(t) = 2(1 - c_2^2) + e^{-c_1 t}(1 - c_2)^2 + e^{c_1 t}(1 + c_2)^2$$

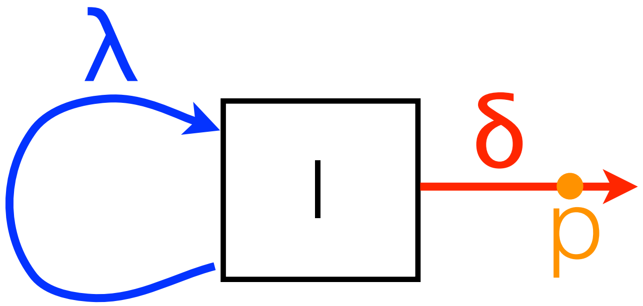
$$\begin{aligned} c_1 &= |\sqrt{(\lambda - \delta)^2) + 4p\lambda\delta}| \\ c_2 &= -\frac{\lambda - \delta}{c_1} \end{aligned}$$

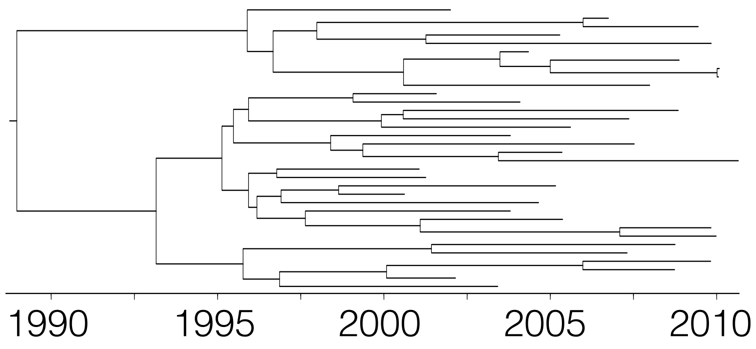
and x_i branching times, y_i sampling times.

Stadler (JTB, 2010)

Simulation study: Comparing exact method to coalescent

Simulating epidemic outbreak





Stadler et al. (Mol. Biol. Evol., 2012)

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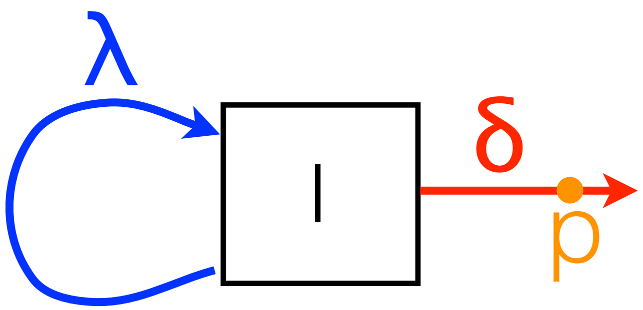
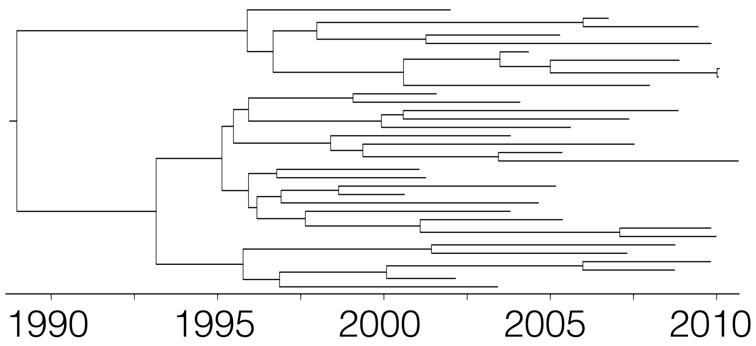




Exact method

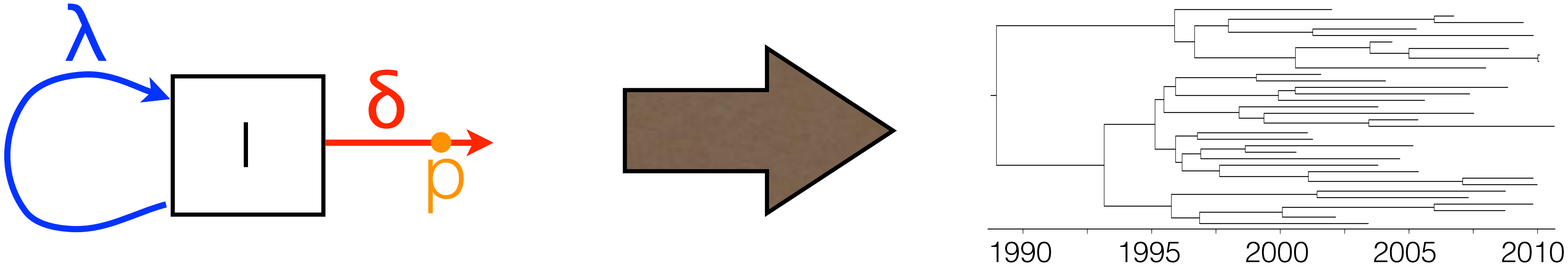
λ-δ is population size growth rate

- 95% *confidence* interval contains true value in **97%** of the simulated trees

Stadler et al. (Mol. Biol. Evol., 2012)

Simulation study:
Comparing exact method to coalescent

Simulating epidemic outbreak



Exact method

λ-δ is population size growth rate

- 95% *confidence* interval contains true value in **97%** of the simulated trees

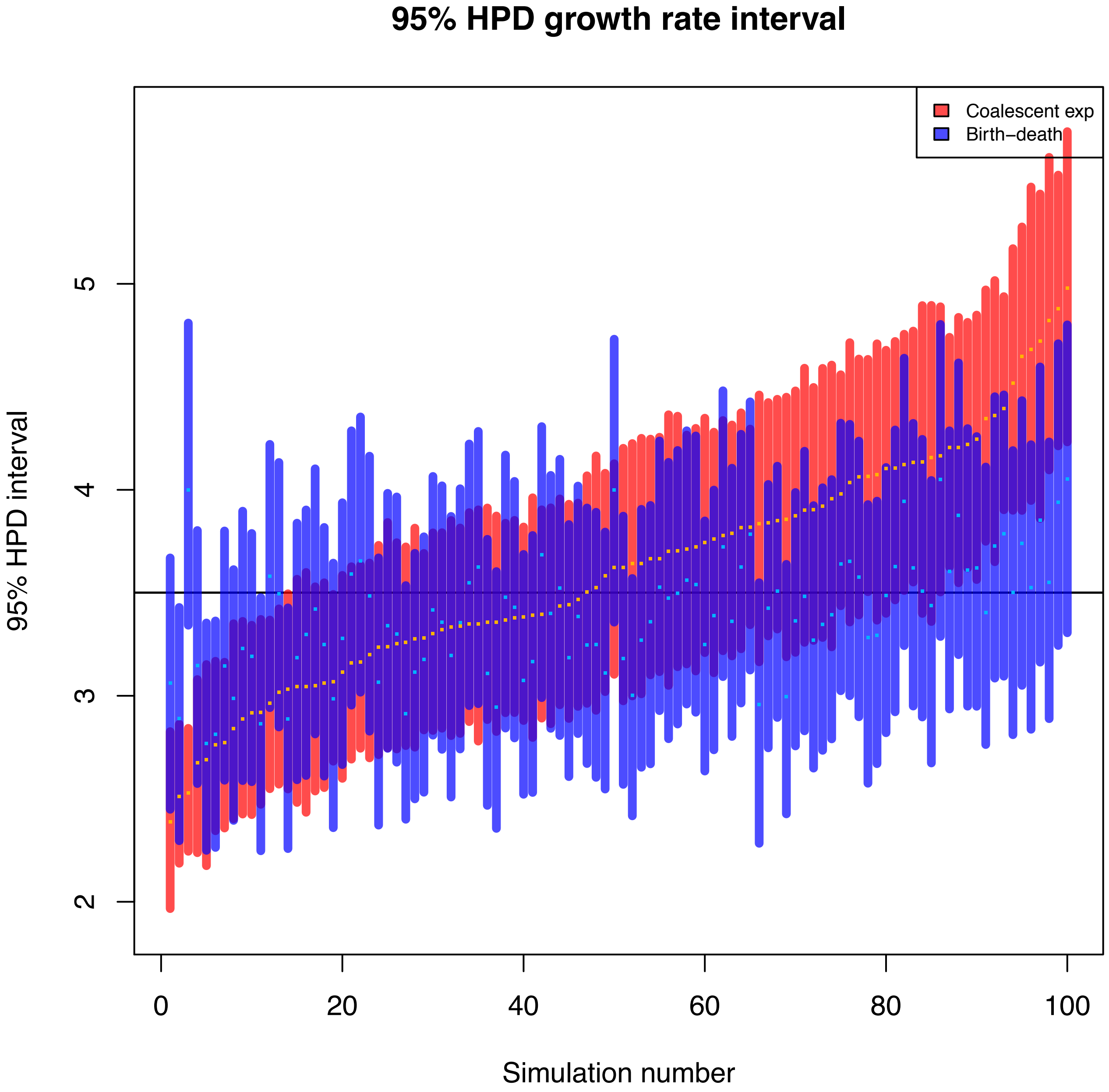
Coalescent approximation

Parameterizes deterministic population size growth

- *95% confidence* interval contains true value in **55%** of the simulated trees

Stadler et al. (Mol. Biol. Evol., 2012)

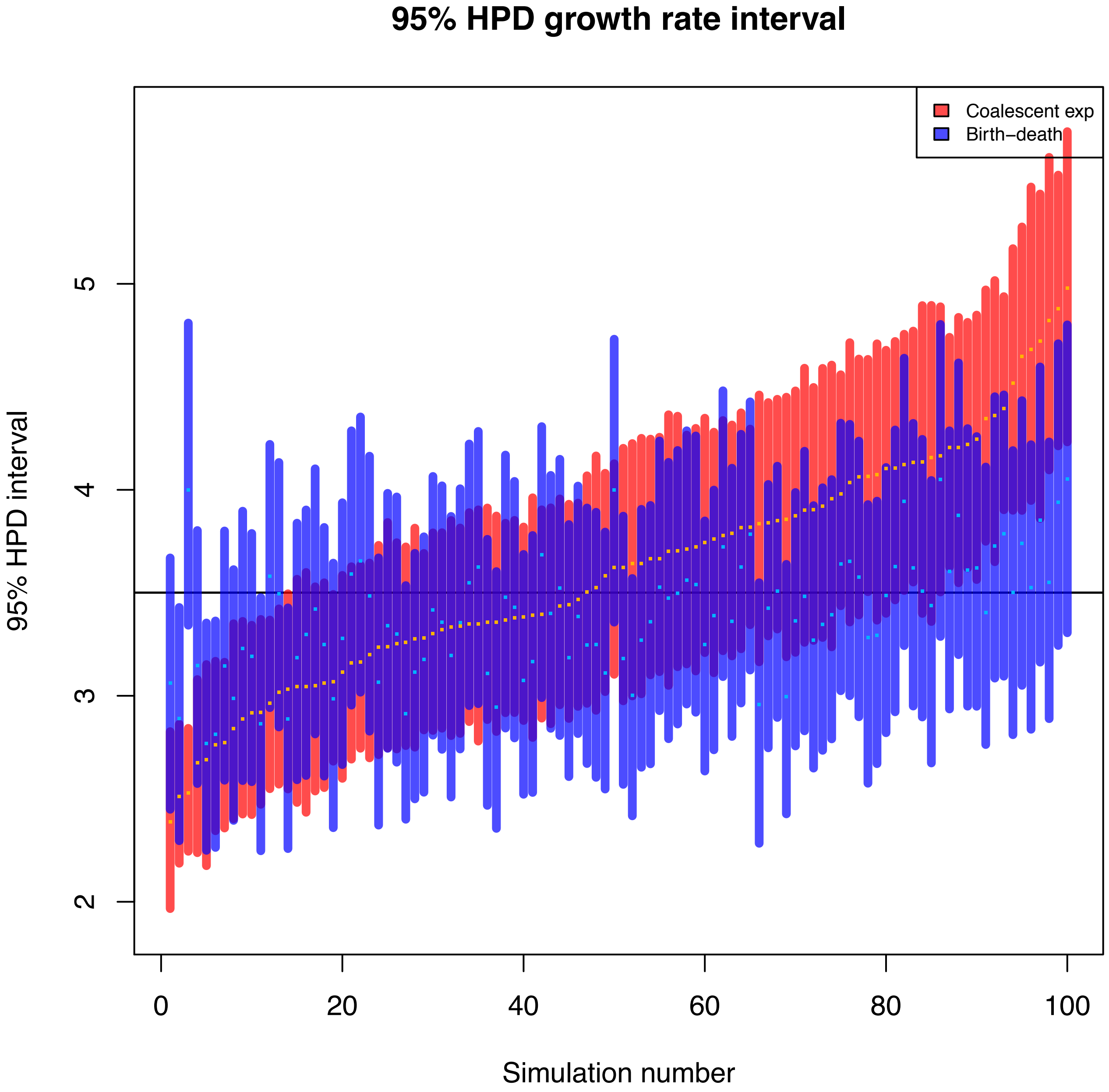
Simulating birth-death trees



p=0.5

Boskova et al., in preparation

Simulating birth-death trees



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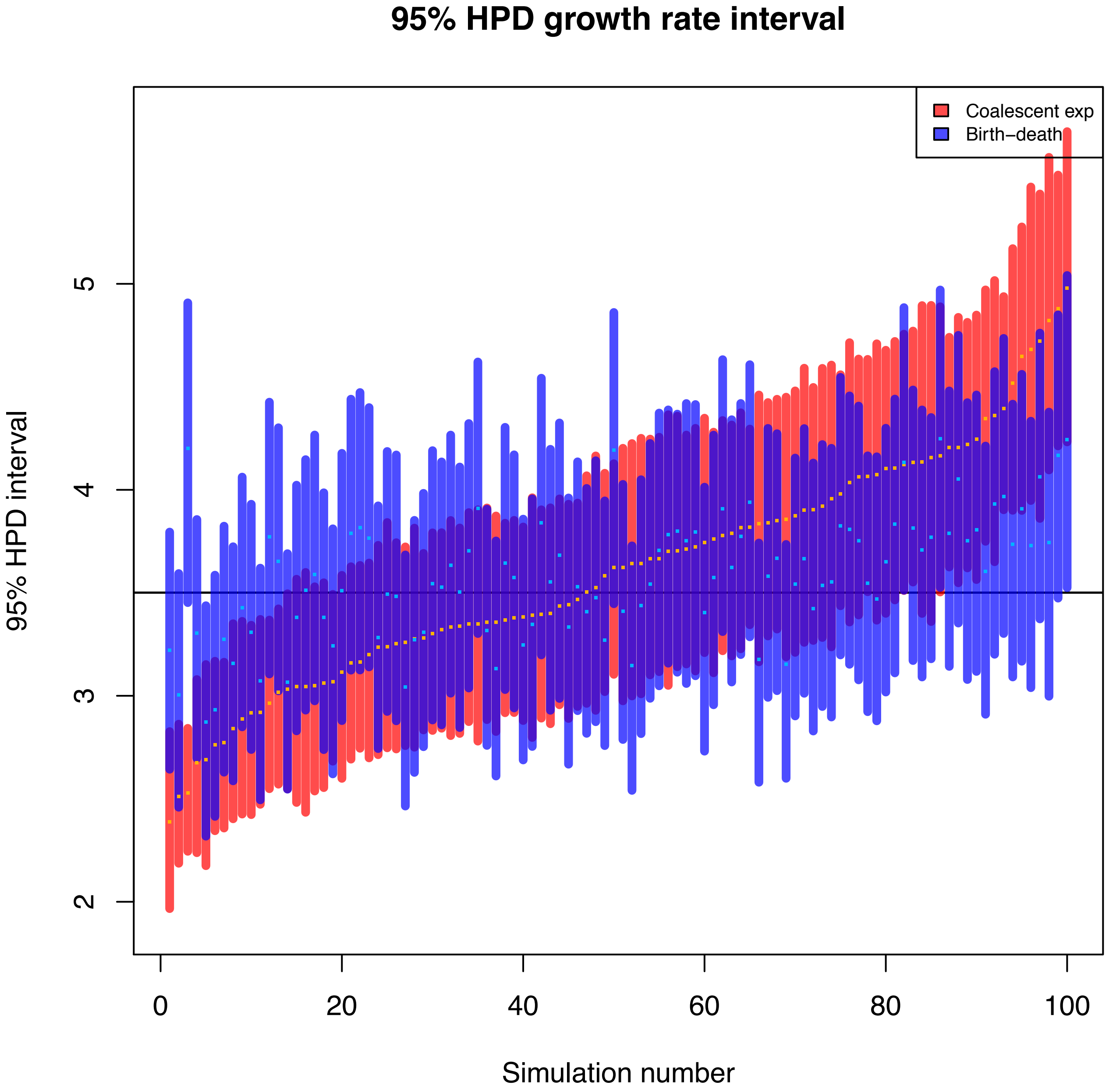
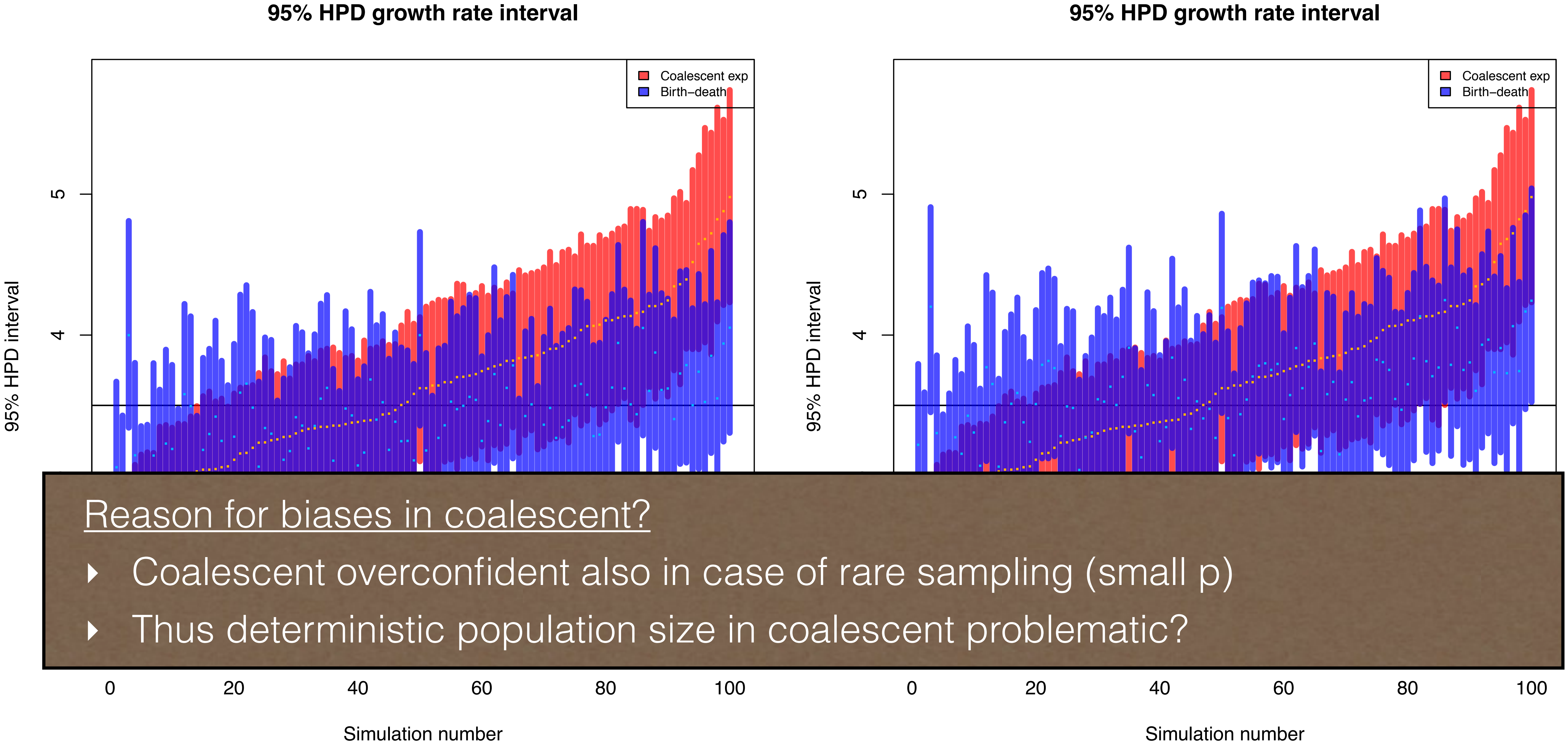


p=0.01

Boskova et al., in preparation

Simulating birth-death trees



Reason for biases in coalescent?

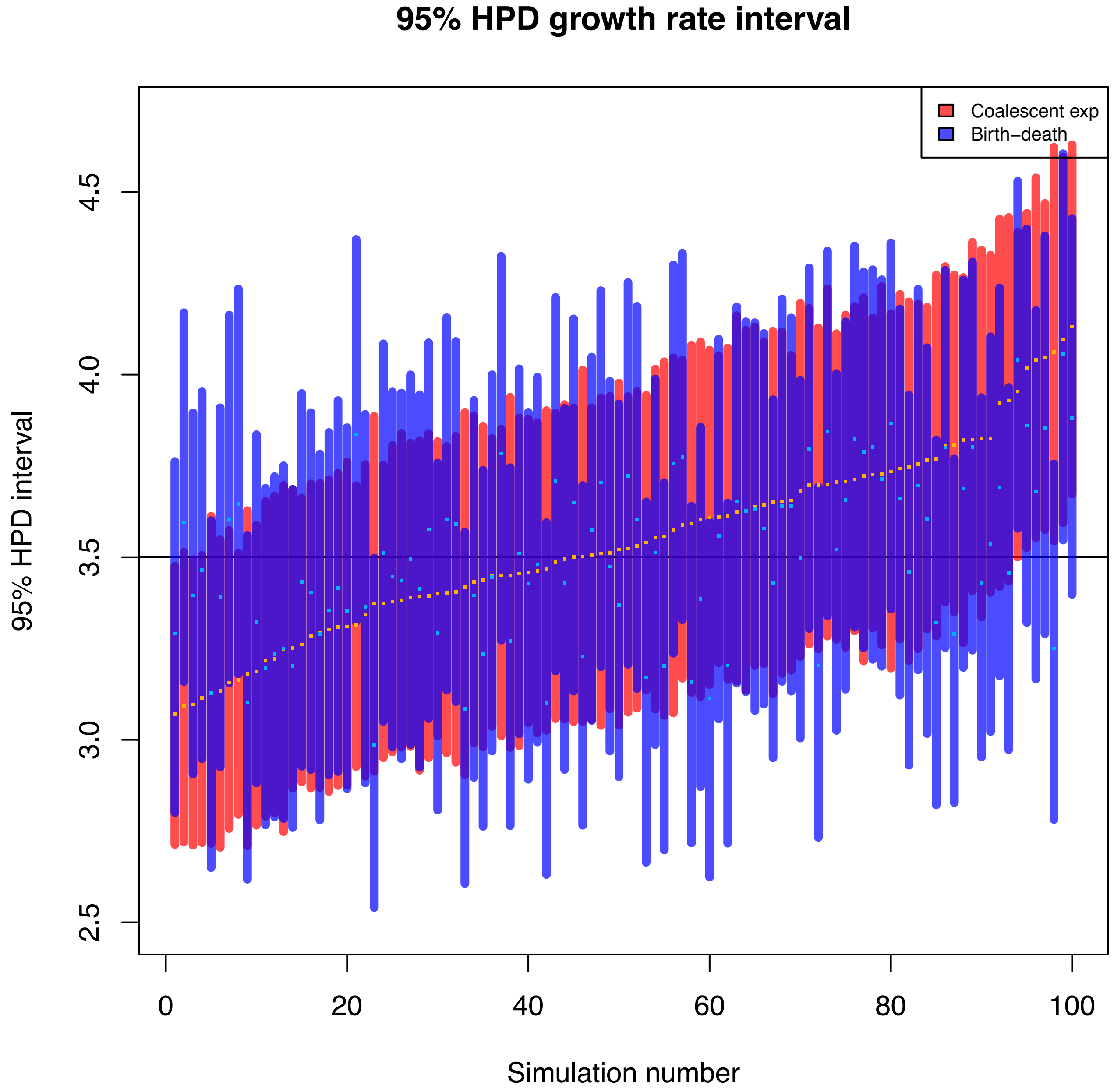
- Coalescent overconfident also in case of rare sampling (small p)
- Thus deterministic population size in coalescent problematic?

p=0.5

p=0.01

Boskova et al., in preparation

Simulating coalescent trees



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Boskova et al., in preparation

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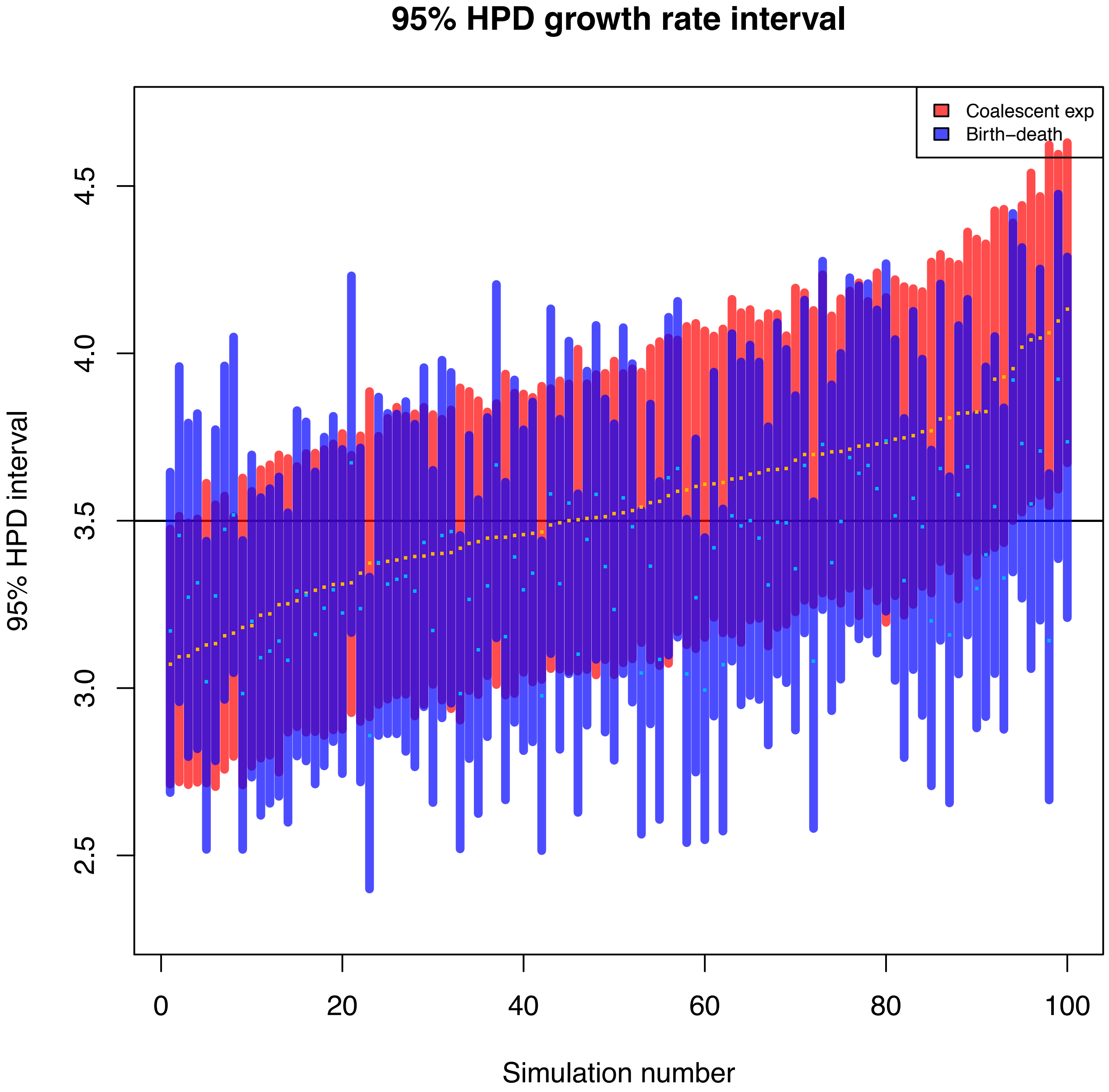

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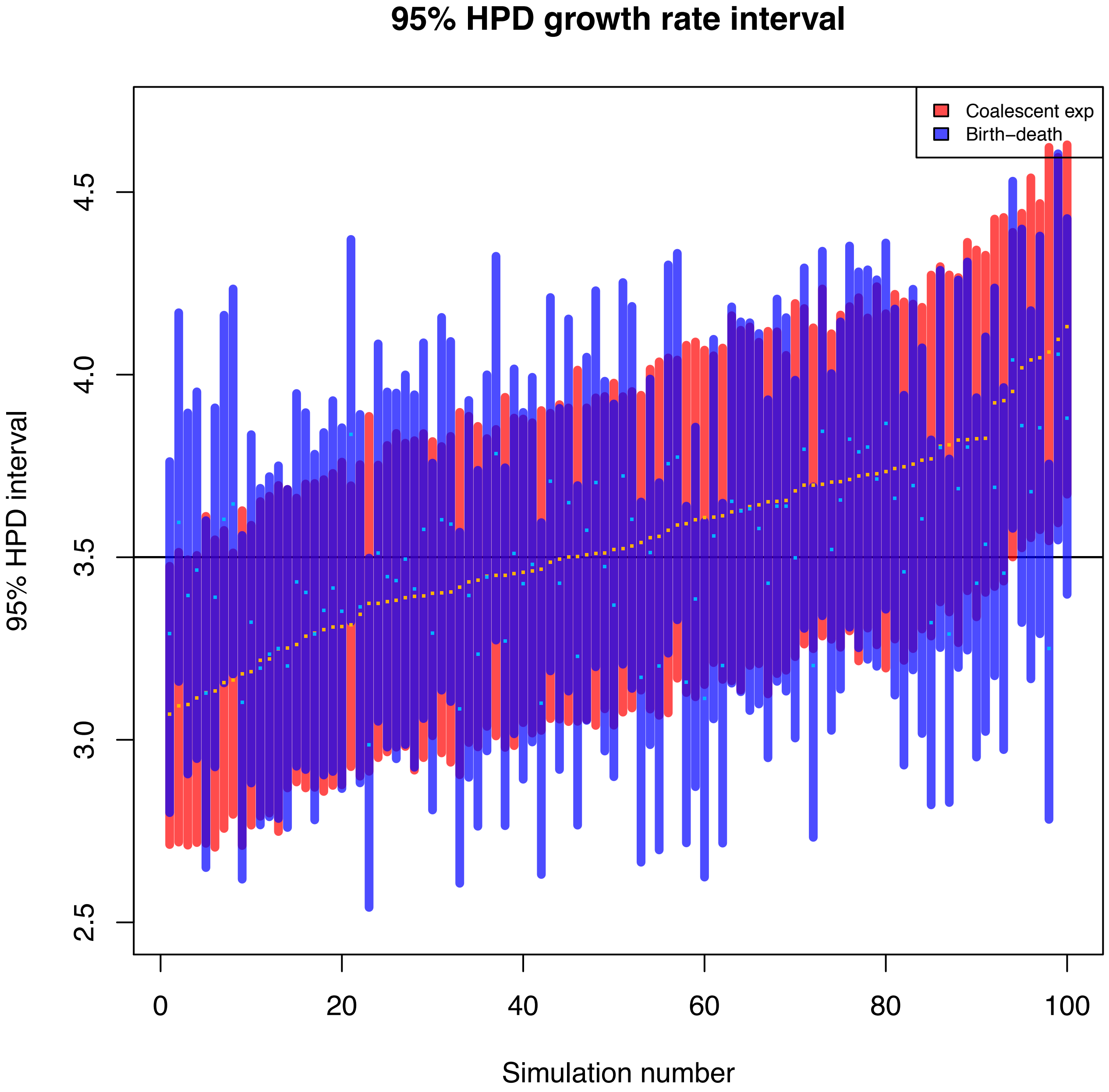

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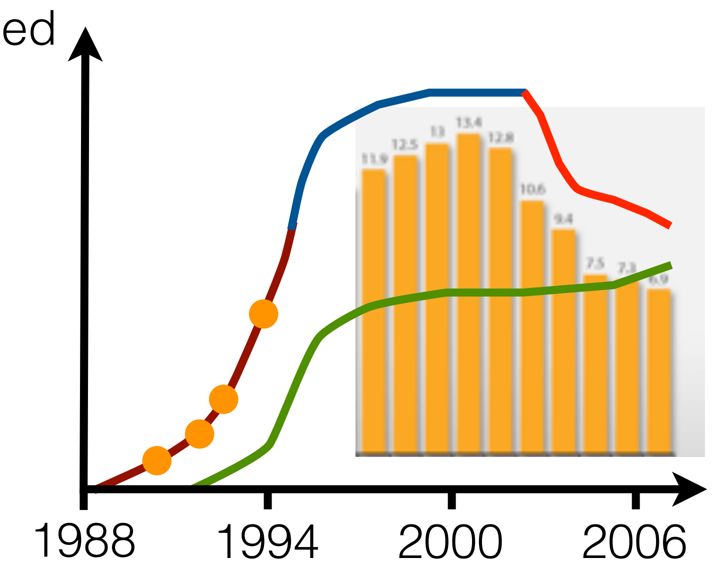
Boskova et al., in preparation

Phylogenetic methods...



1. ...for analyzing epidemic outbreaks
    - *C: Drummond et al. (Genetics, 2002)*
    - *BD: Stadler et al. (MBE, 2012)*
2. ...for identifying epidemiological changes over time
    - *C: Drummond et al. (MBE, 2005)*
    - *BD: Stadler, Kühnert et al. (PNAS, 2013)*
3. ...accounting for SIR model dynamics
    - *C: Volz et al. (Genetics, 2009)*
    - *BD: Kühnert et al., Leventhal et al. (both submitted)*
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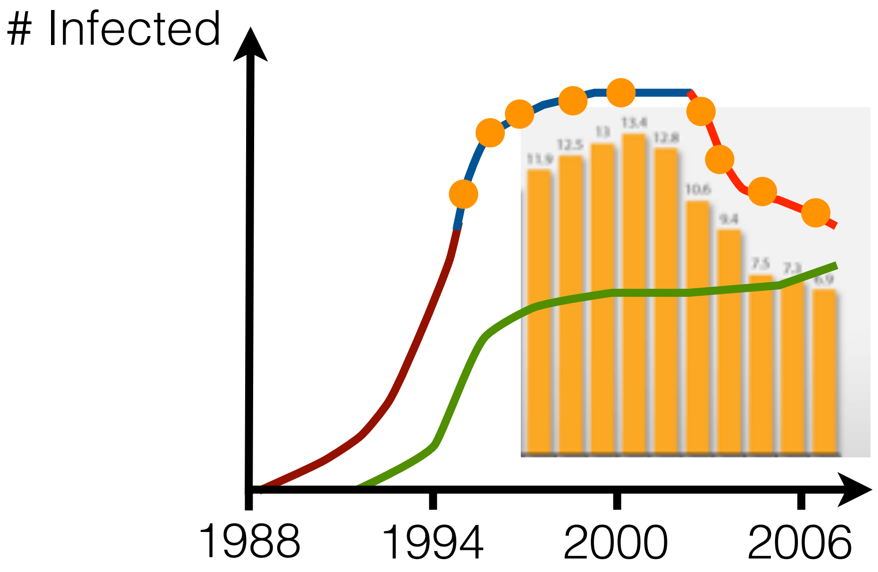

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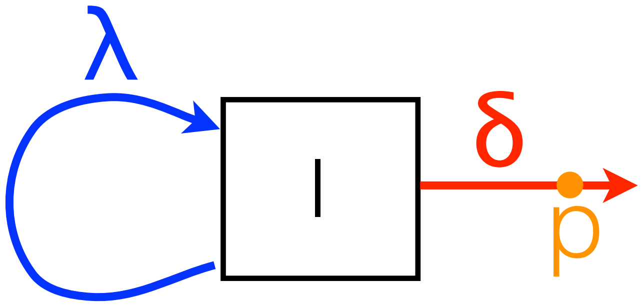
Birth-death-skyline plot

Epidemiological rates may change through time:



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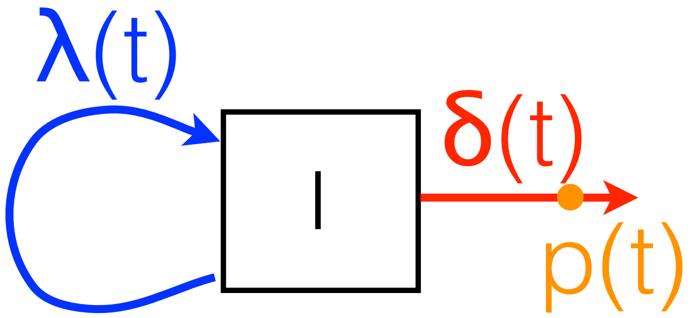

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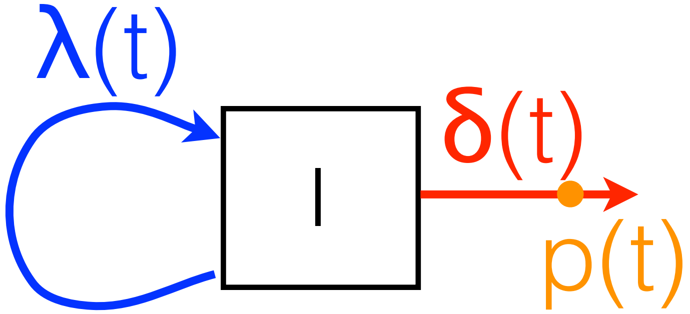
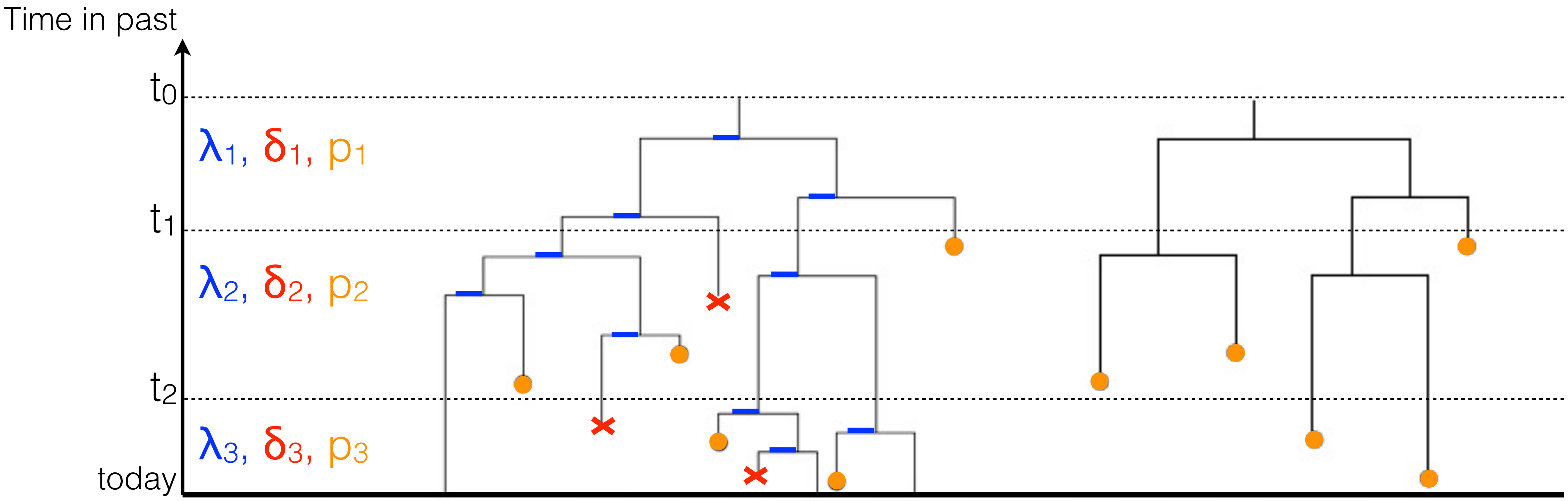
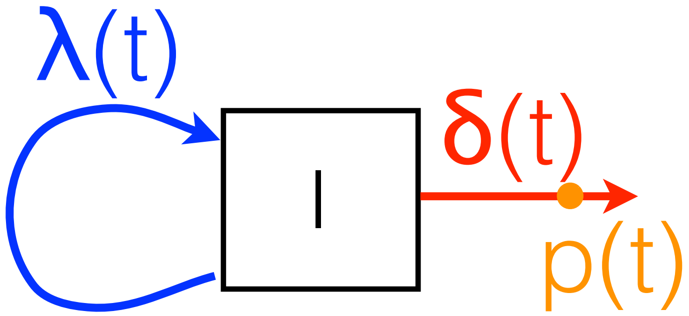




Hepatitis C virus in Egypt



Effective reproductive number $\mathbf{R_e(t)}$

generalizes

Basic reproductive number $\mathbf{R_0 = R_e(0)}$

Stadler, Kühnert et al. (PNAS, 2013)

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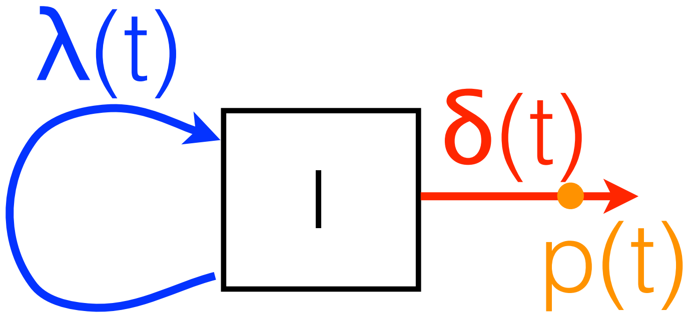

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generalizes

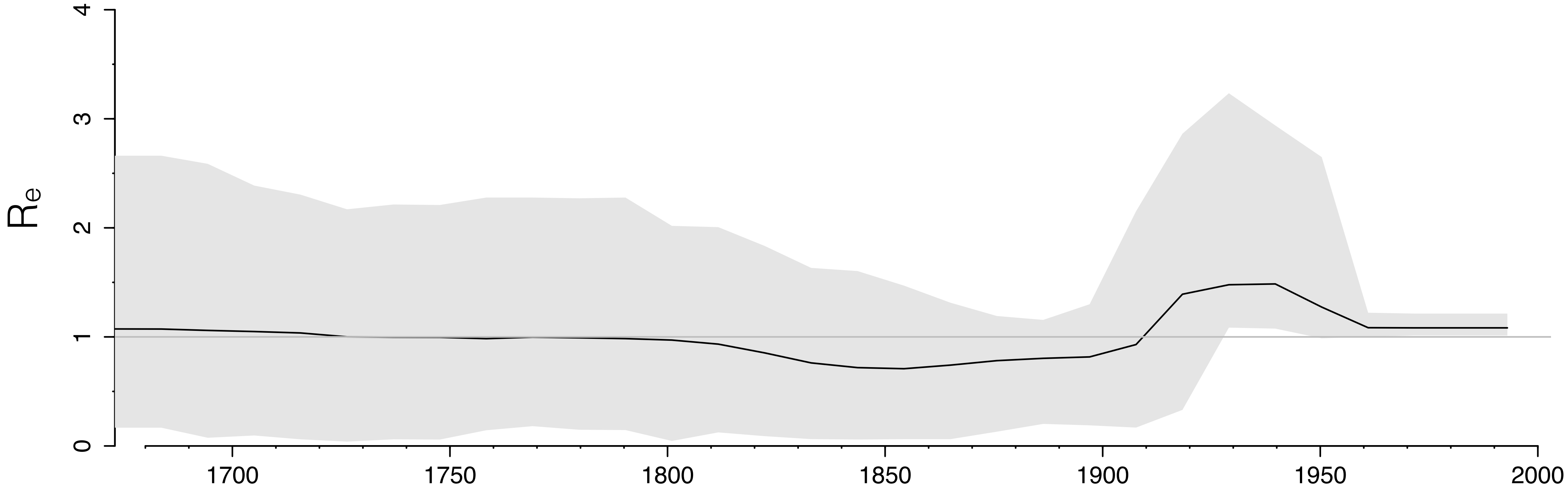
Basic reproductive number **$R_0 = R_e(0)$**

Analysis of 63 seq:

$R_e(t) = \lambda(t)/\delta(t)$

— median

▨ 95% HPD interval



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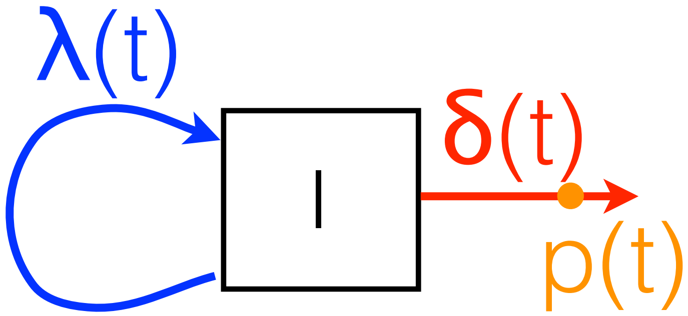

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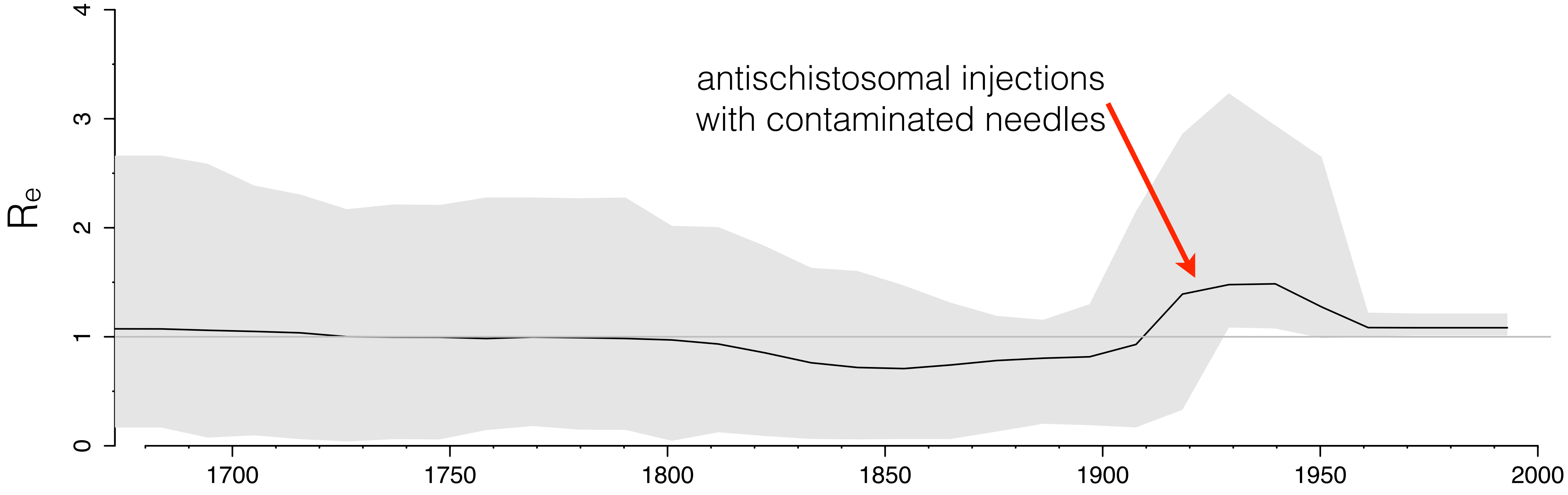
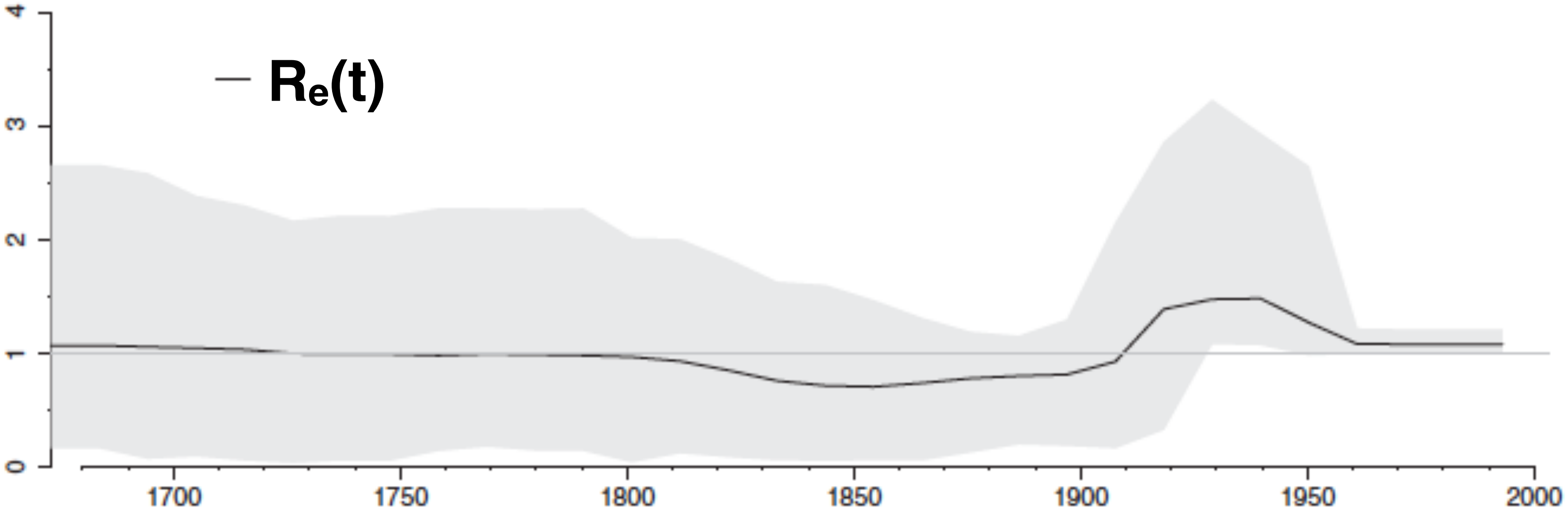


antischistosomal injections with contaminated needles

Stadler, Kühnert et al. (PNAS, 2013)

The two skyline models

Birth-death skyline plot: effective reproductive number



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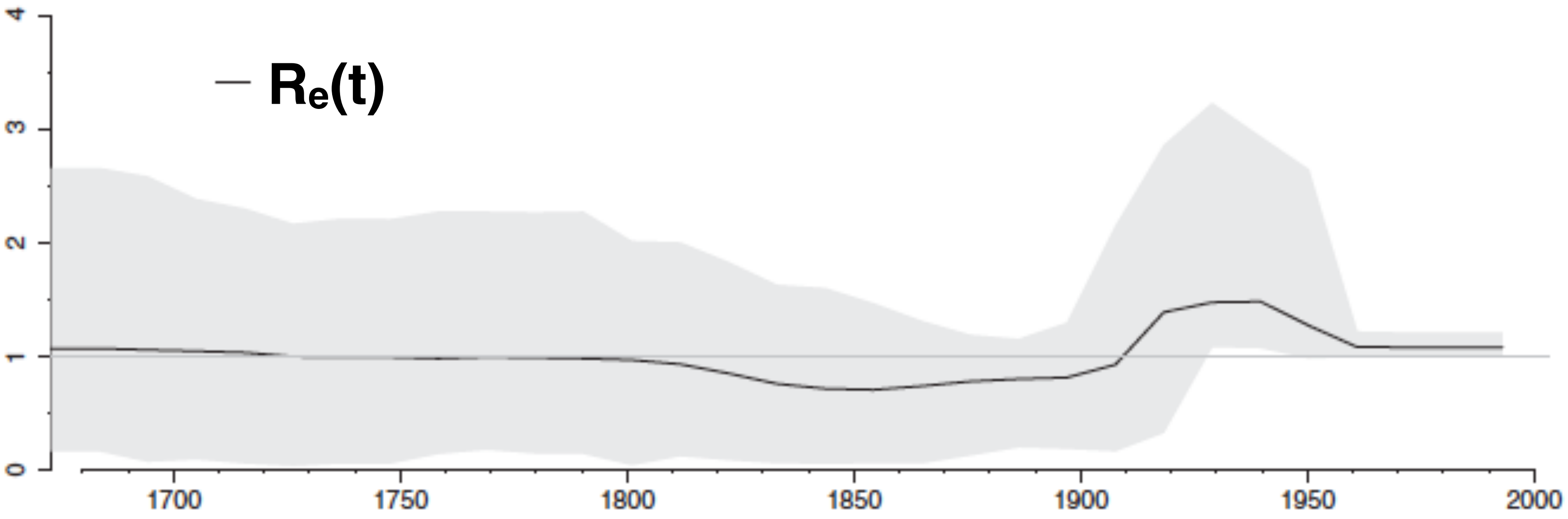
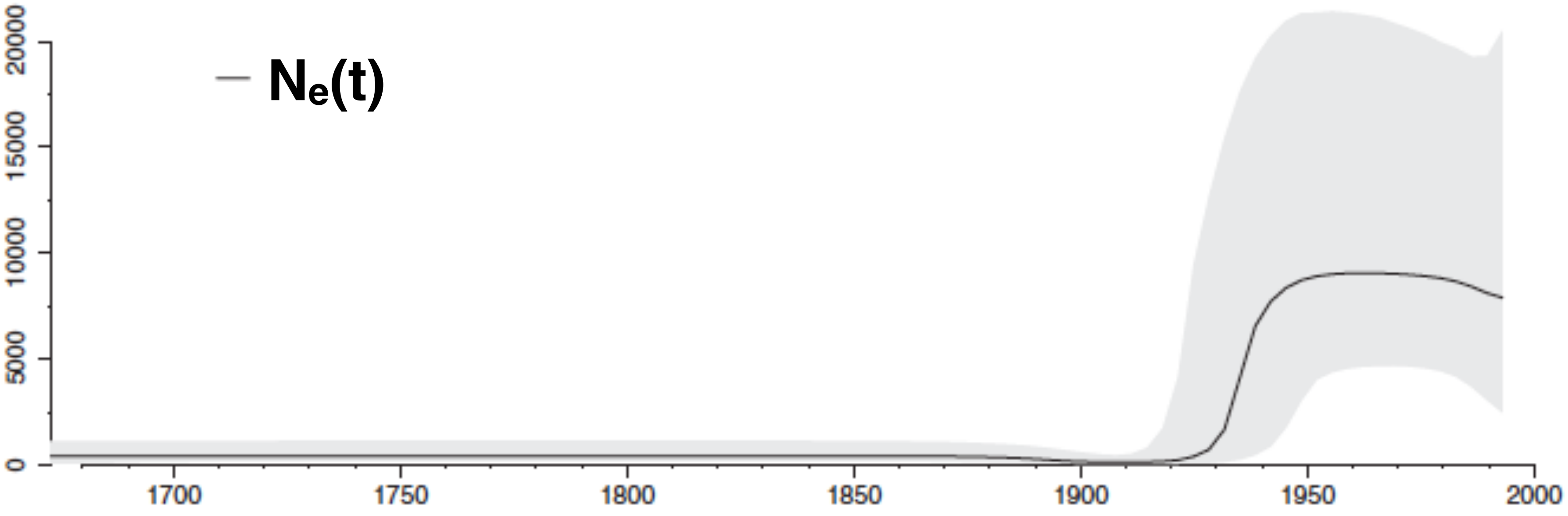
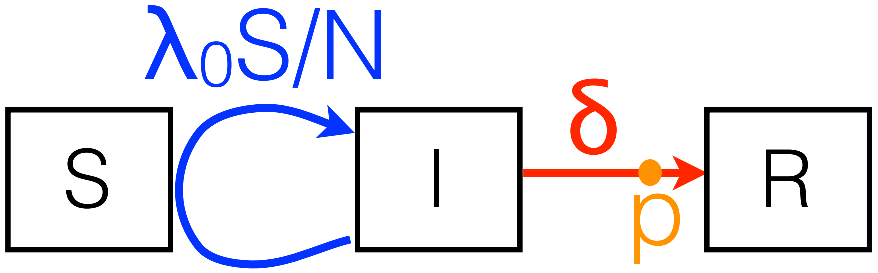


Coalescent skyline plot: effective population size



3) SIR models



SIR simulation (trees with 200 tips sampled):
population size: N=5000, start with one infected, N=S+I+R
$\lambda(S) = \lambda_0 S/N$
$R_0 = \lambda_0/\delta = 4$
host recovery rate: $\delta = 0.5$
sampling probability: $p = 0.05$

Kühnert et al. (submitted)

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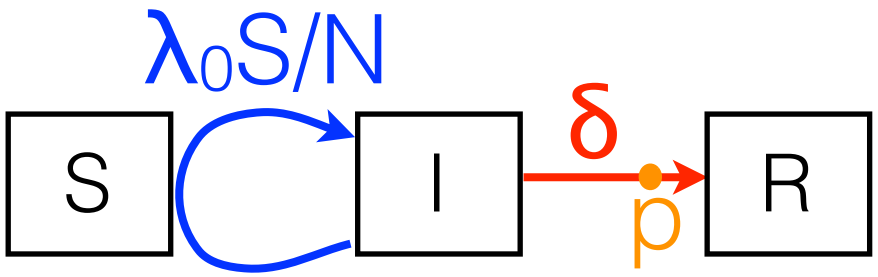

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Inference: 10 intervals for λ, δ and p constant across interval
meaning $\lambda(S)=\lambda_0 S/N$ is approximated by $\lambda(t)$

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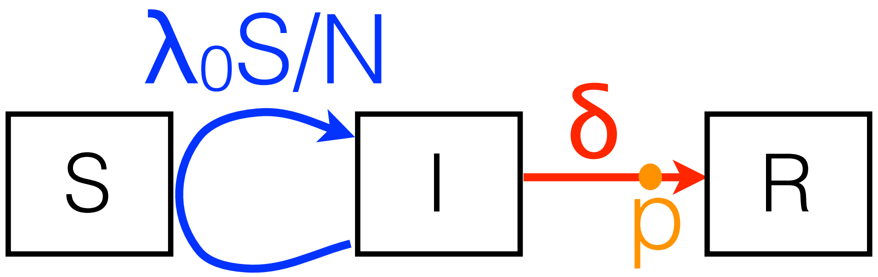

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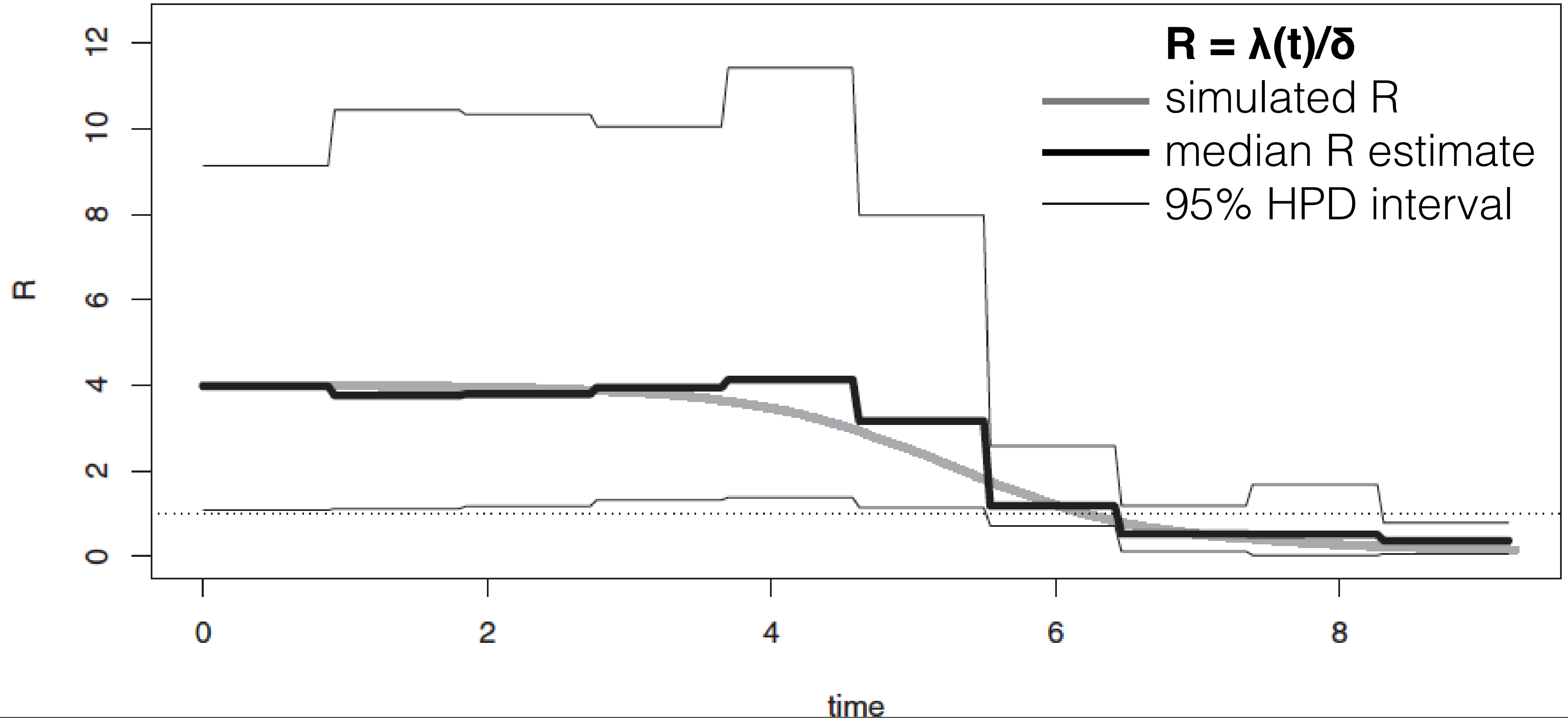

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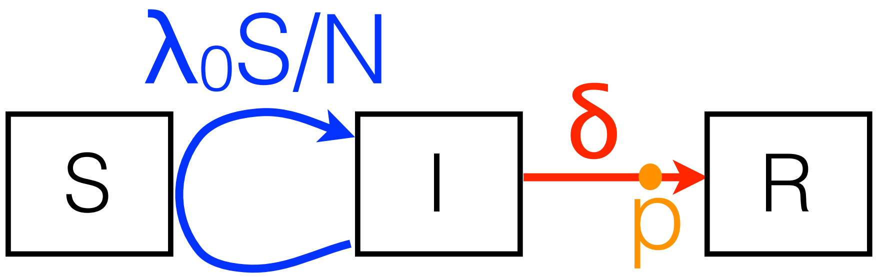

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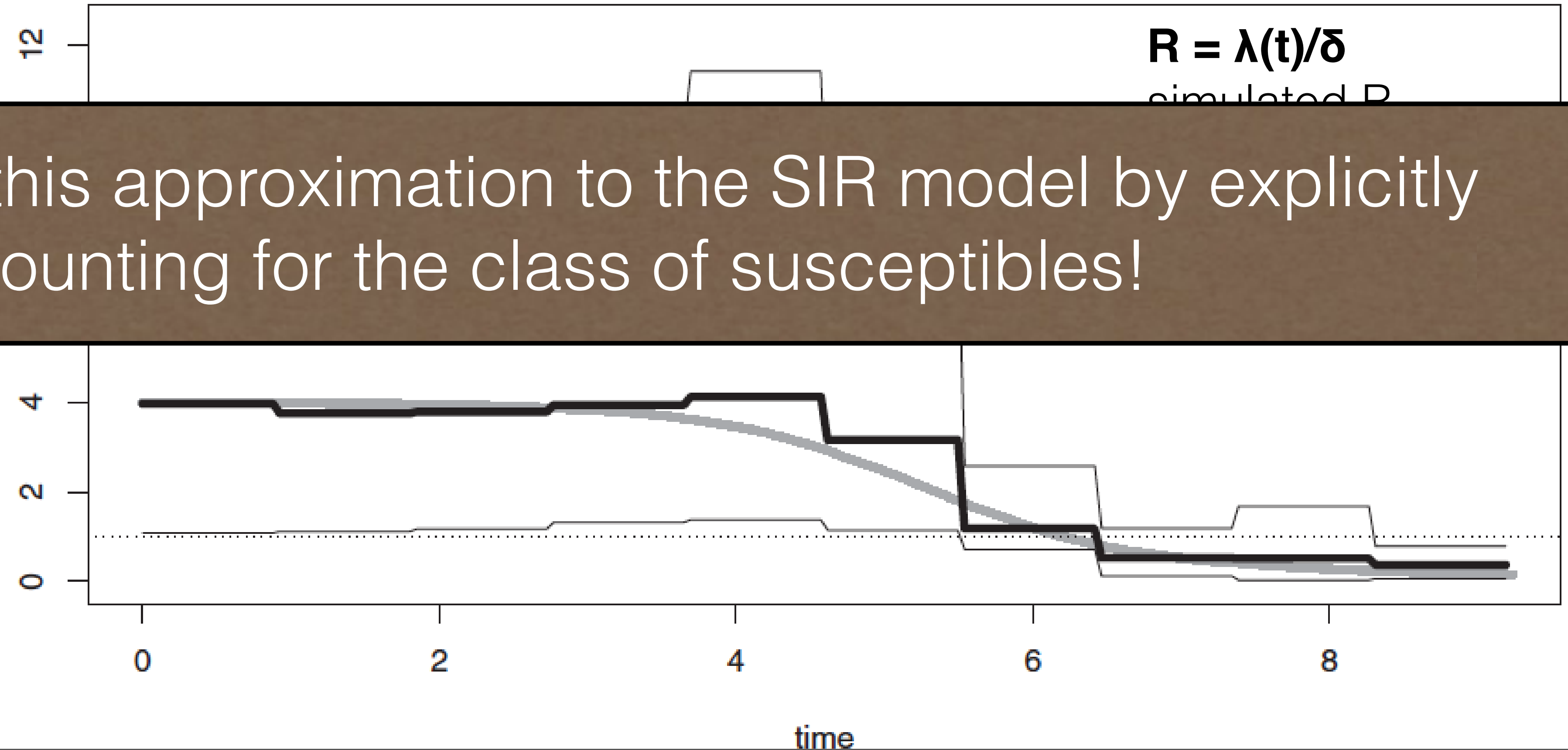
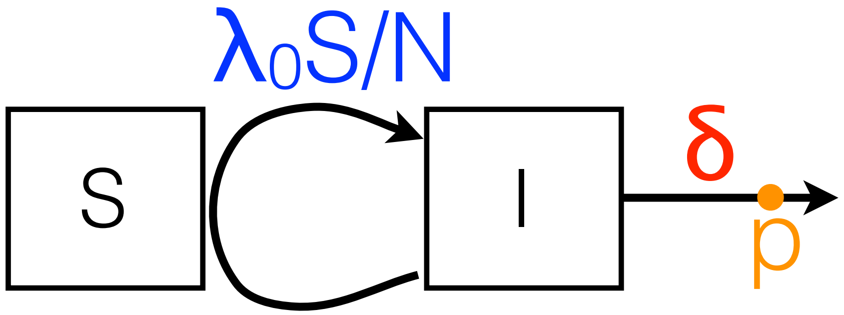


We improved this approximation to the SIR model by explicitly accounting for the class of susceptibles!

Kühnert et al. (submitted)

SI dynamics - exact method

Para-
meters

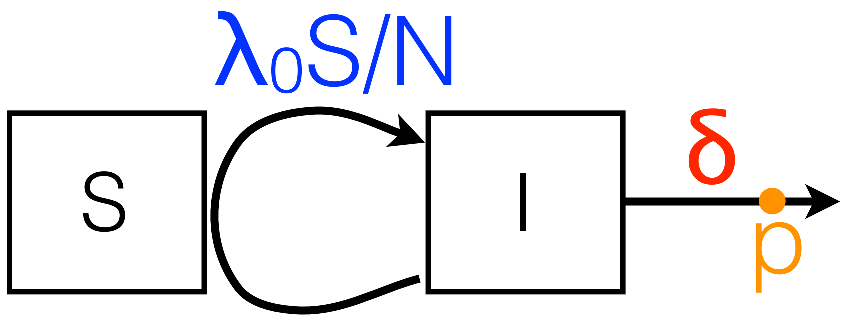


N=S+I (constant)

Leventhal et al. (submitted)

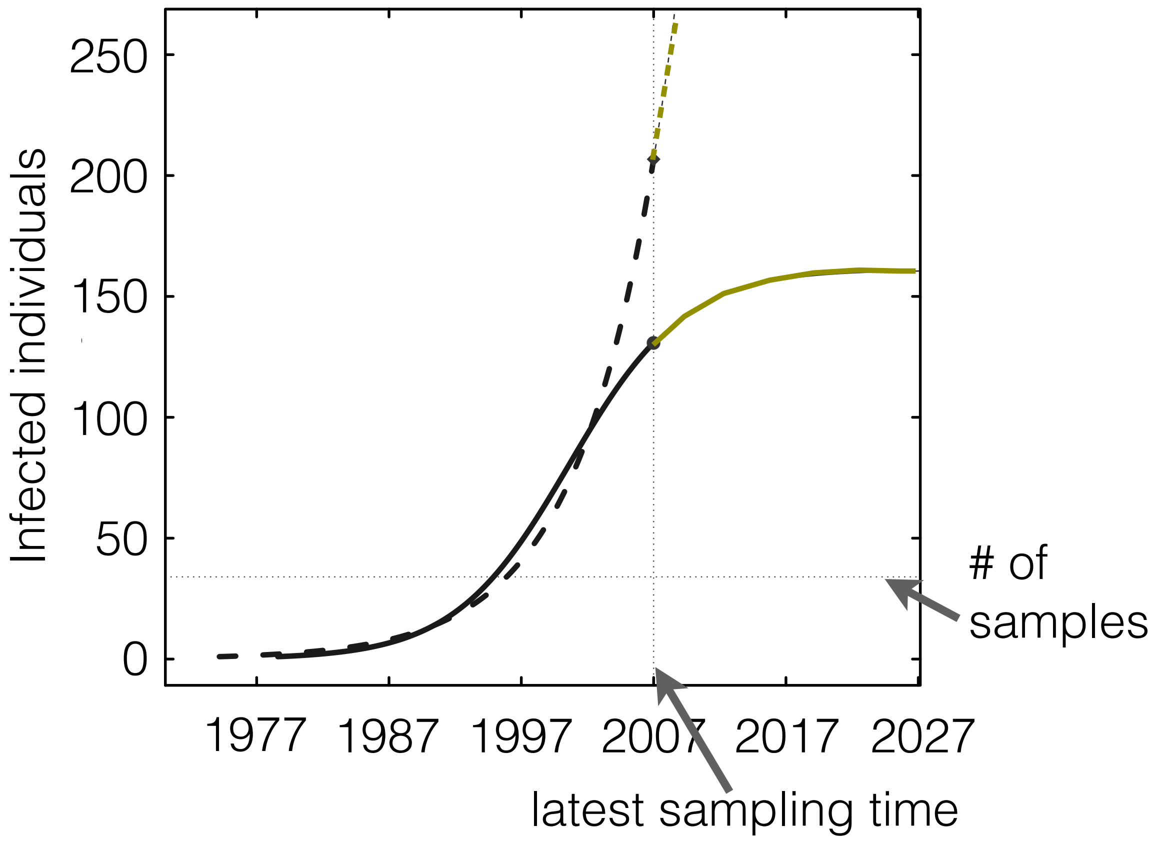
SI dynamics - exact method

Para-meters



N=S+I (constant)

HIV transmission cluster in Switzerland

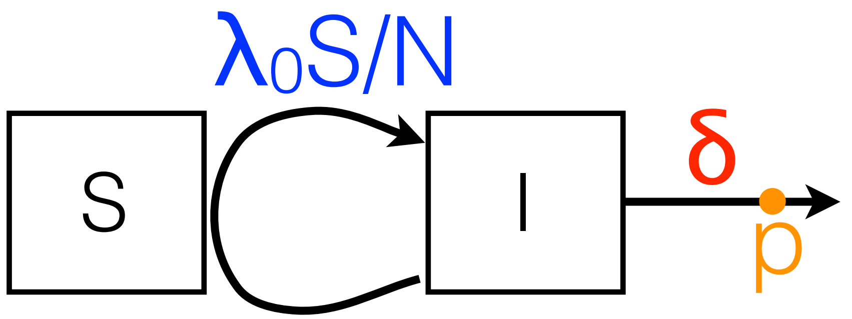


— SI model
- - - - epidemic outbreak model

Leventhal et al. (submitted)

SI dynamics - exact method

Para-meters



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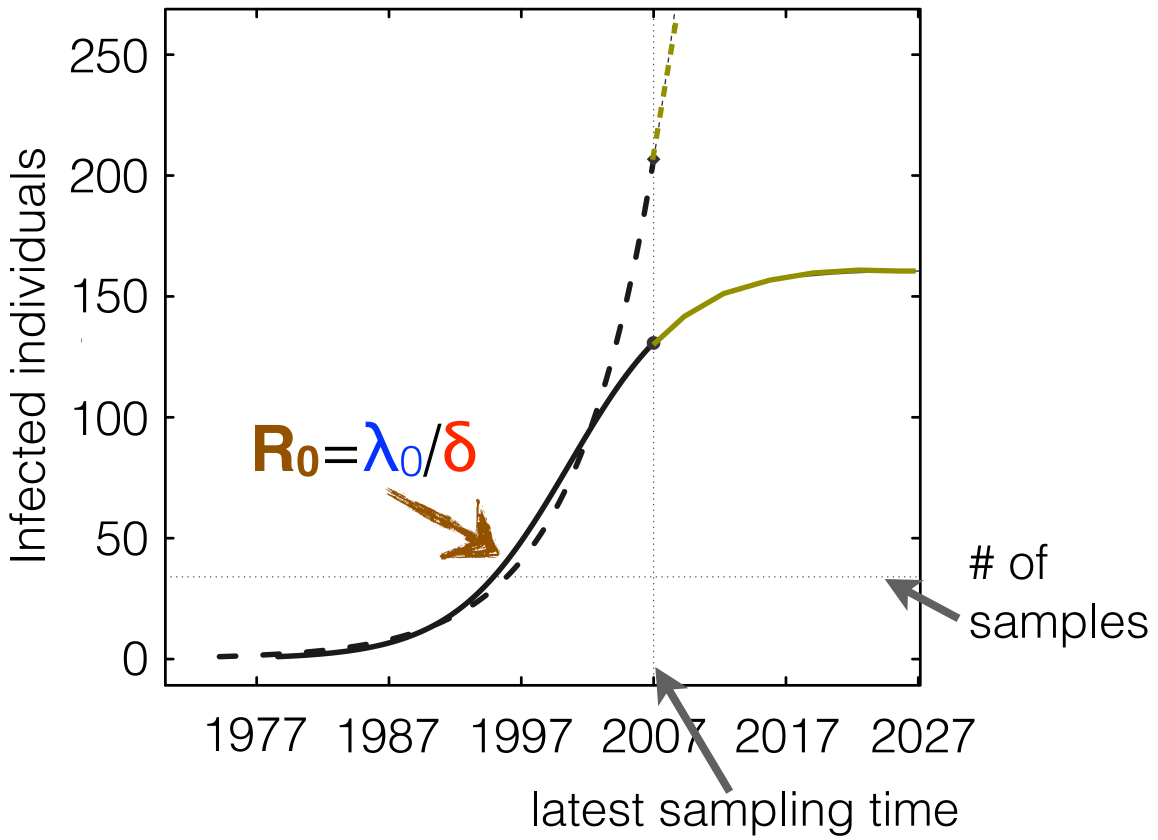


R_0=λ_0/δ

# of samples

latest sampling time

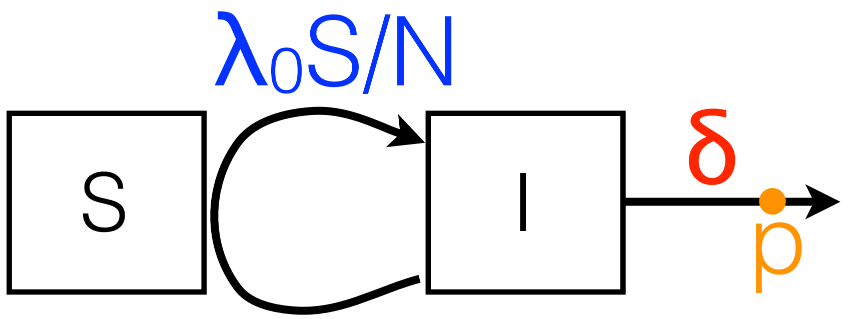
— SI model

- - - - epidemic outbreak model

Leventhal et al. (submitted)

SI dynamics - exact method

Para-meters



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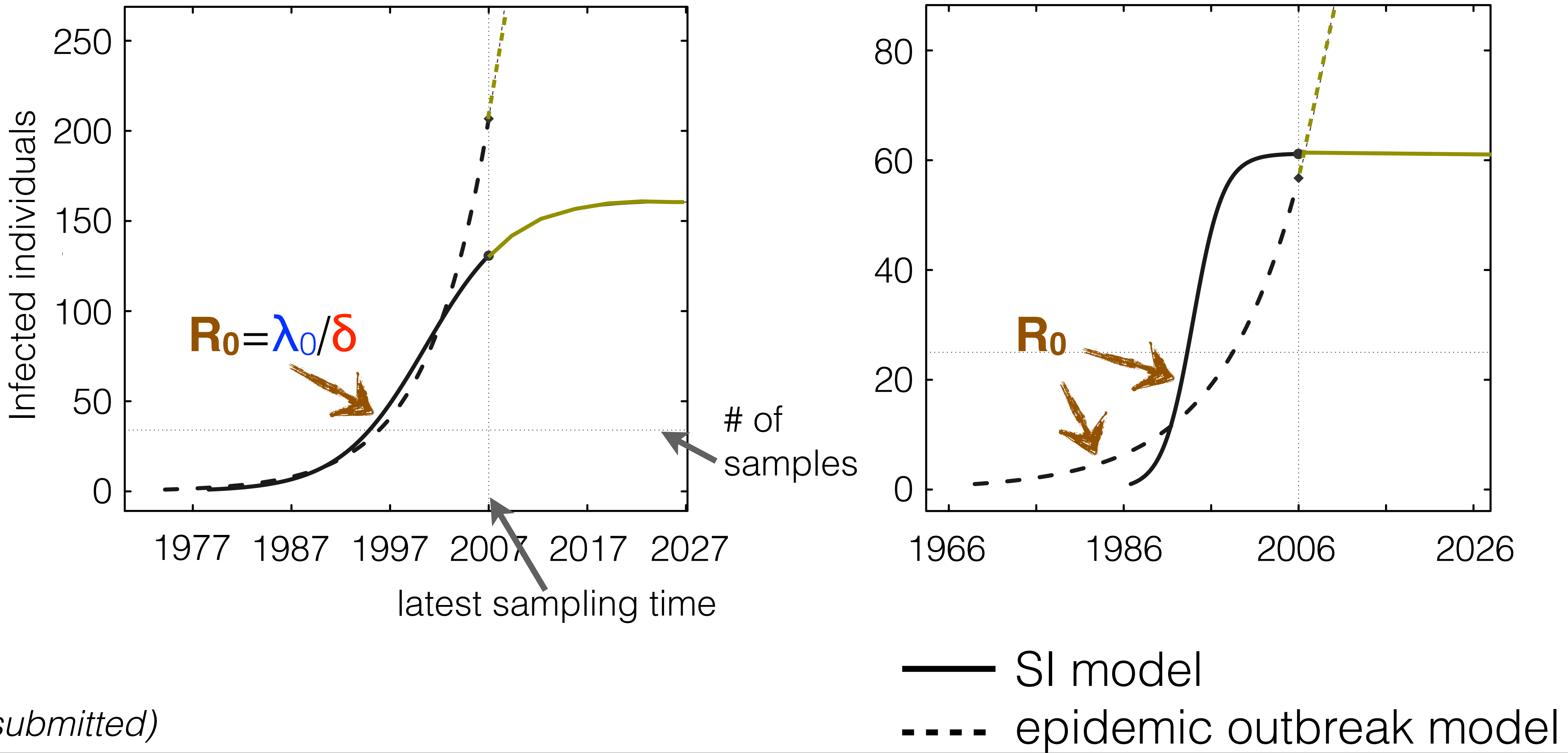
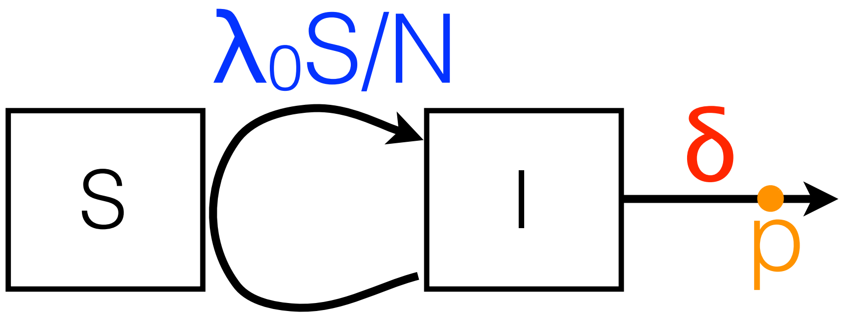


Leventhal et al. (submitted)

SI dynamics - exact method

Parameters



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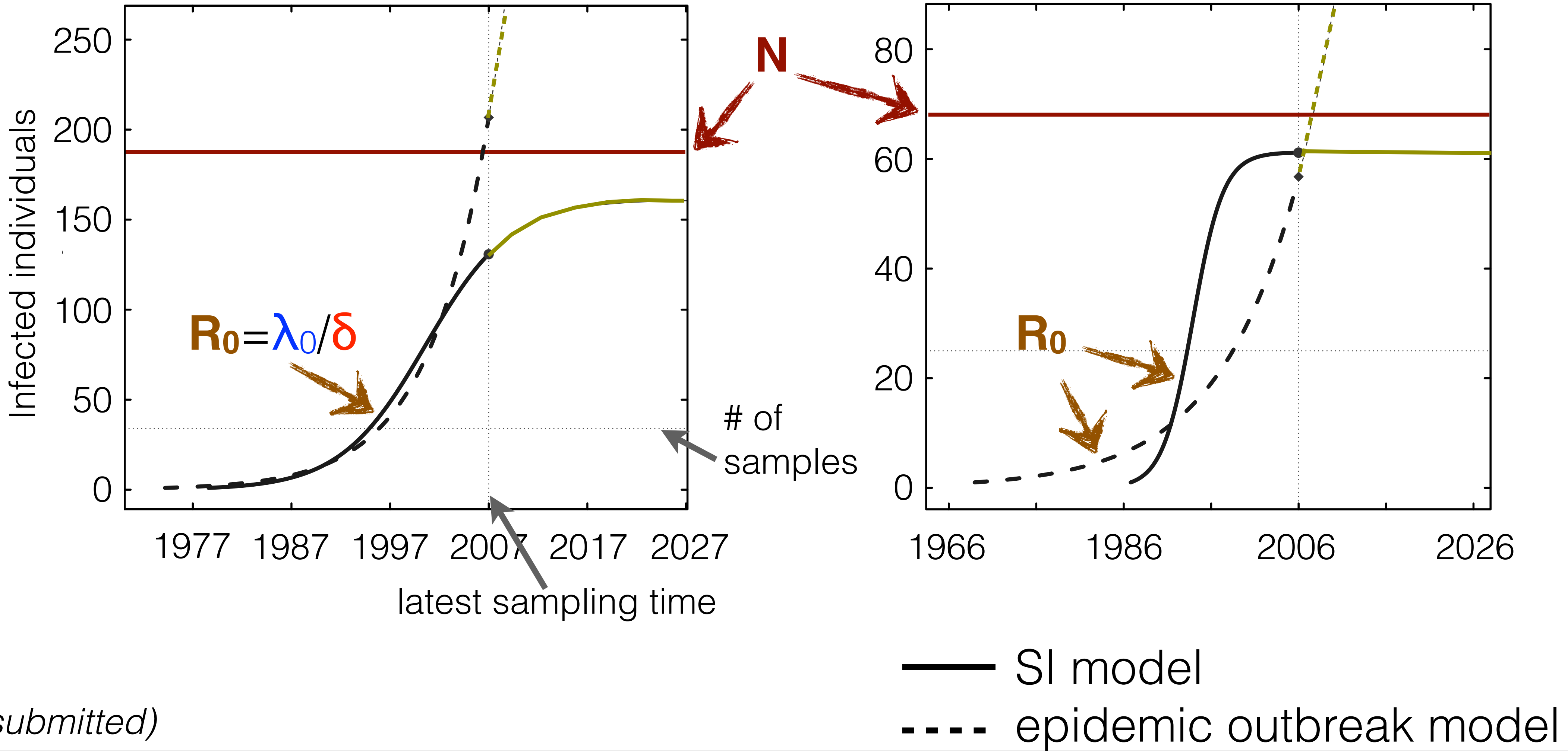

N

R_0=λ_0/δ

R_0

# of samples

latest sampling time

Leventhal et al. (submitted)

SIR models: Birth-death or coalescent?

Coalescent approximation

Volz et al., Genetics, 2009

So far sampling at one time point, not in Beast

Tim Vaughan implements it in Beast for comparison

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Birth-death approxi-mation

BDSIR add-on in Beast v2.0

Simulations show good performance

Flexible framework (SI,SIS,SIR,SEIR, etc)

Poster: Denise Kühnert

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Poster: Denise Kühnert

Birth-death exact

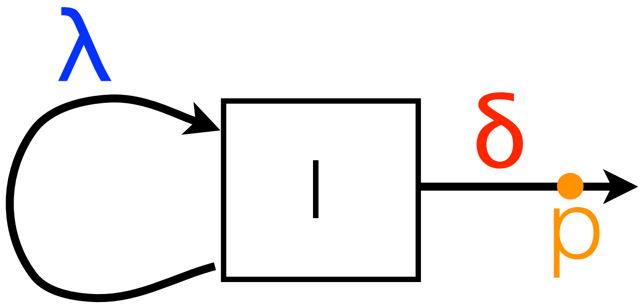
expoTree (R package)

Promising to estimate overall population size N=S+I

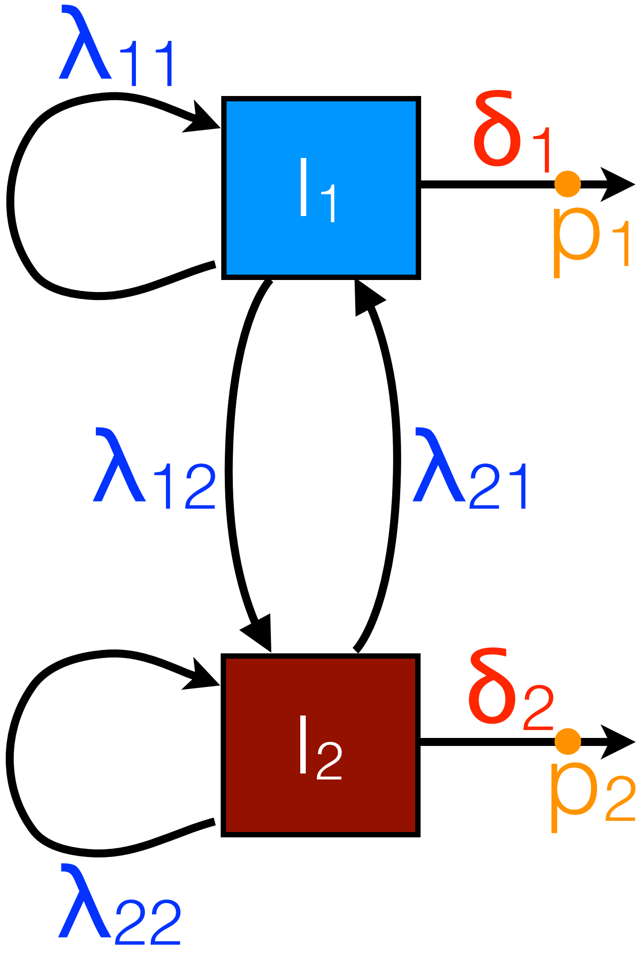
Future study will identify potential limitations of approximate method

Poster: Gabriel Leventhal

4) Host population structure



4) Host population structure



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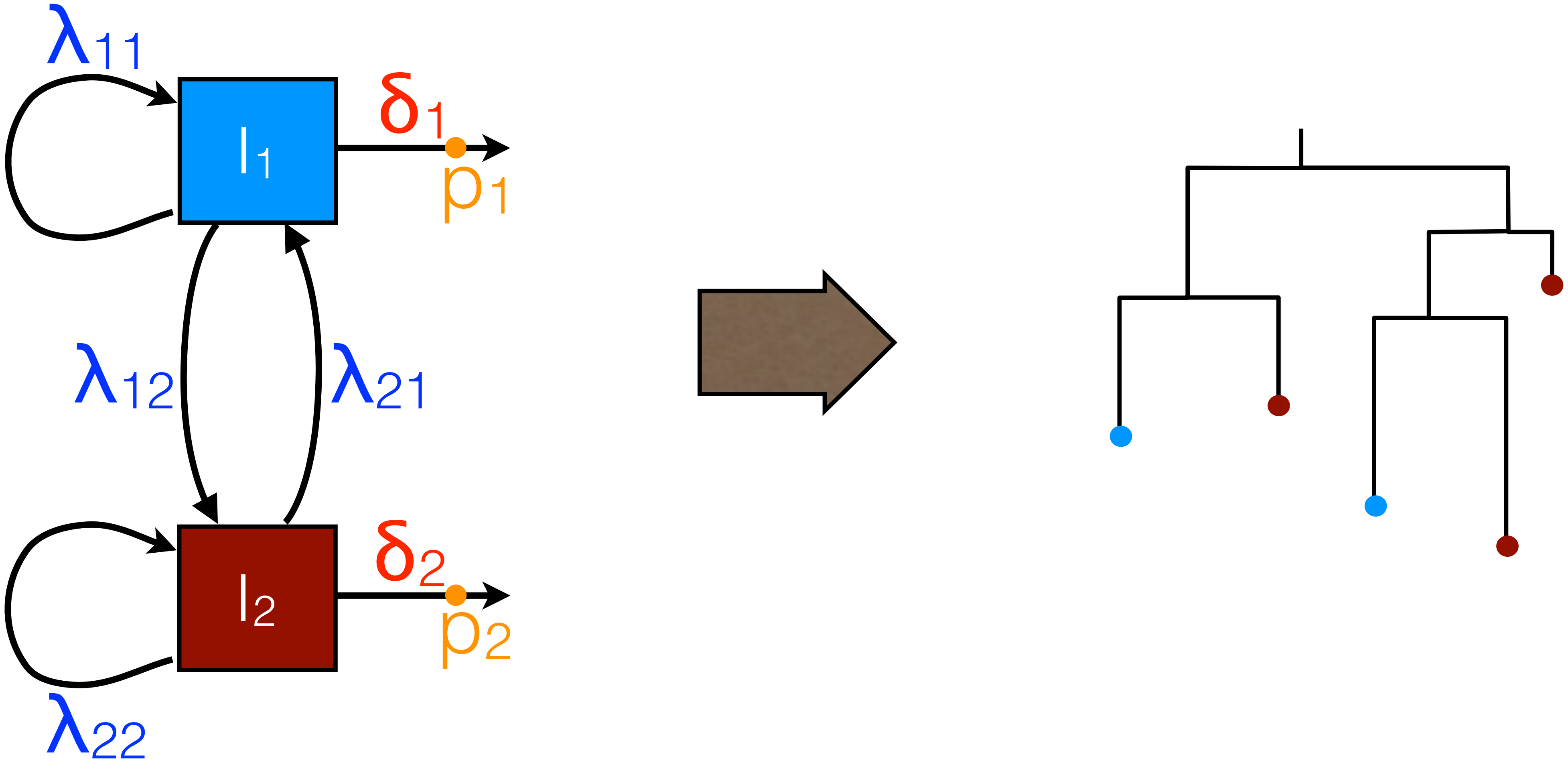

Quantification of risk-group dependent spread of HIV

Two states

Heterosexual

Intravenous drug user

Stadler et al. (Phil. Trans. Roy. Soc. B, 2013)

Quantification of risk-group dependent spread of HIV

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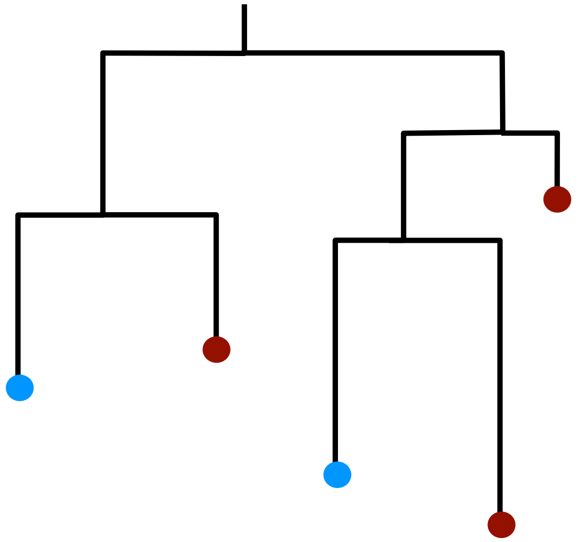
Intravenous drug user

Data



220 Latvian sequences from
Balode et al. (2012)

Stadler et al. (Phil. Trans. Roy. Soc. B, 2013)

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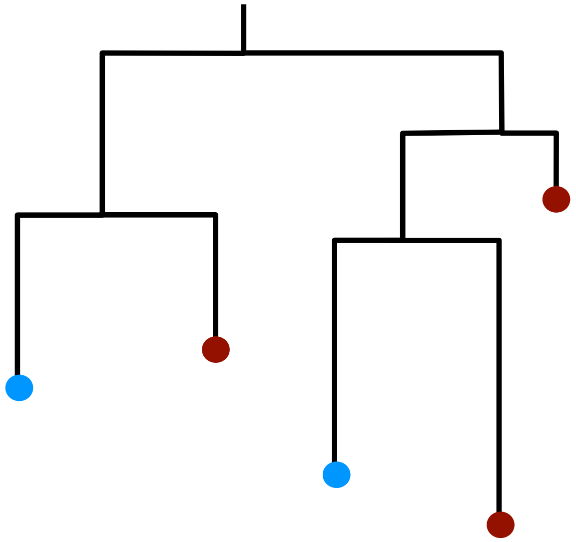

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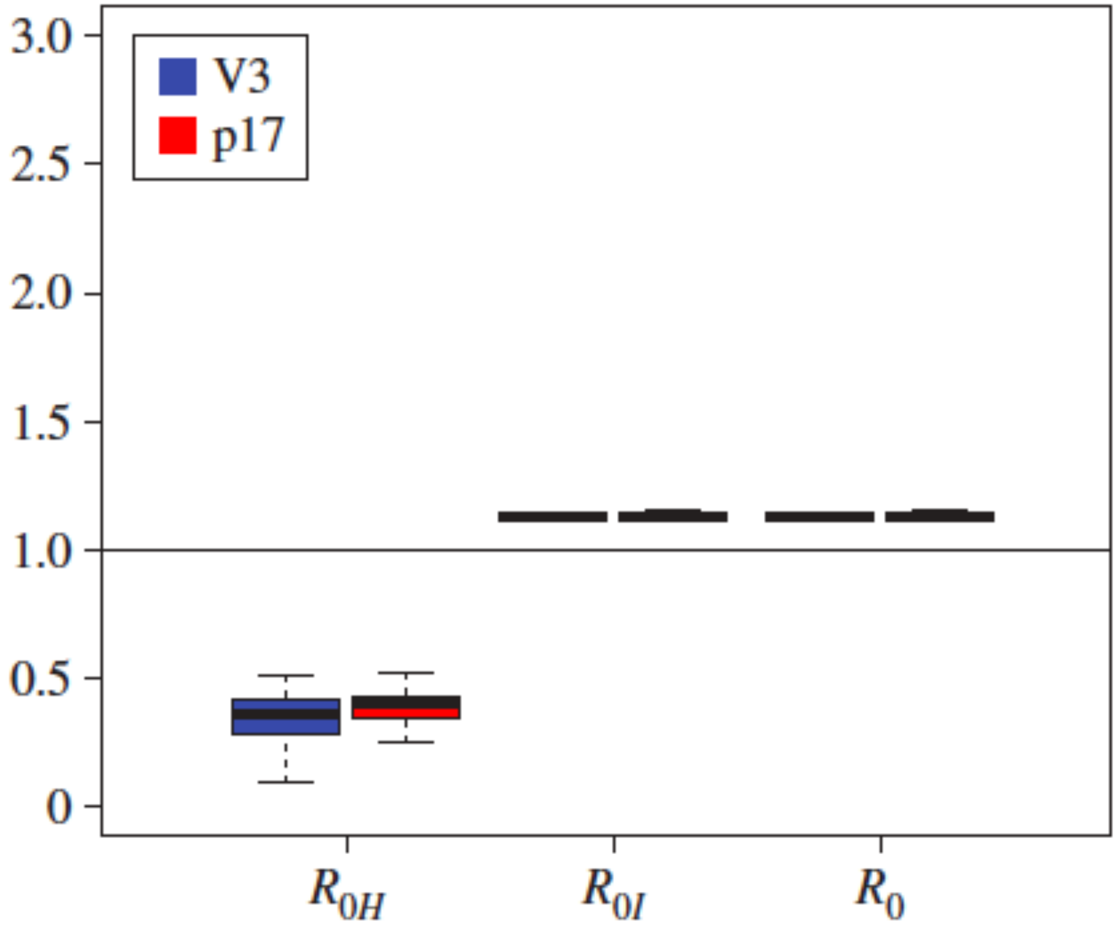

Stadler et al. (Phil. Trans. Roy. Soc. B, 2013)

Quantification of super-spreading in HIV

Two states

Super-spreader

Normal-spreader

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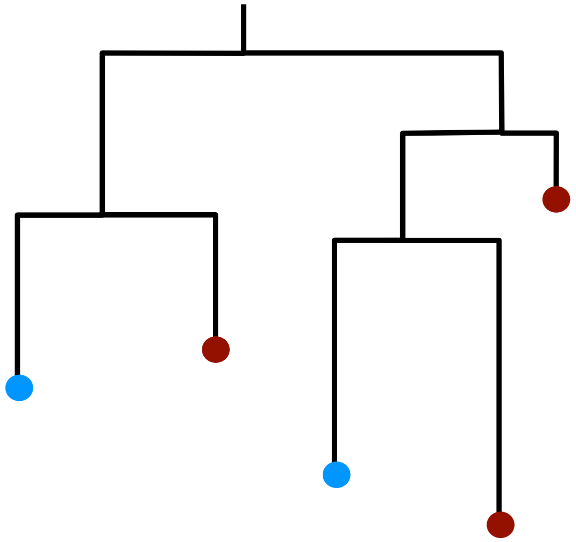

40 Latvian sequences from
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Quantification of super-spreading in HIV

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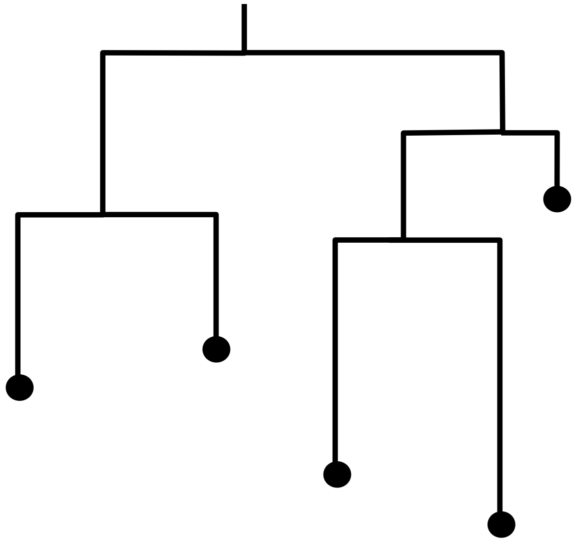

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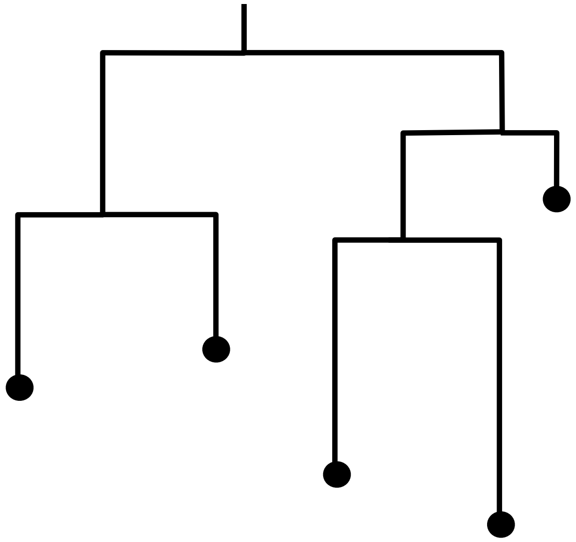

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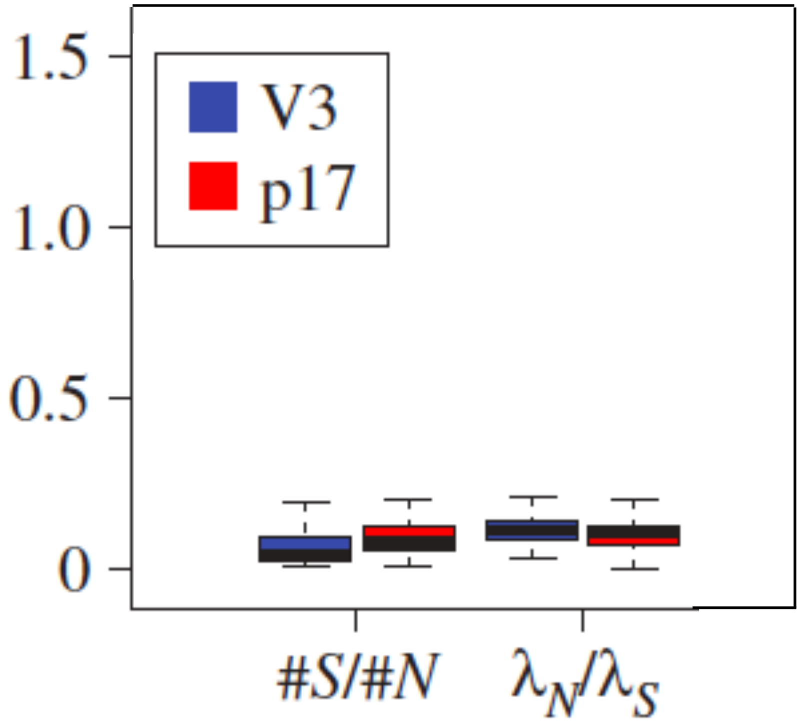


Stadler et al. (Phil. Trans. Roy. Soc. B, 2013)

Key questions in infectious disease ecology approached through phylogenetics

Human pathogens

PUBLIC HEALTH

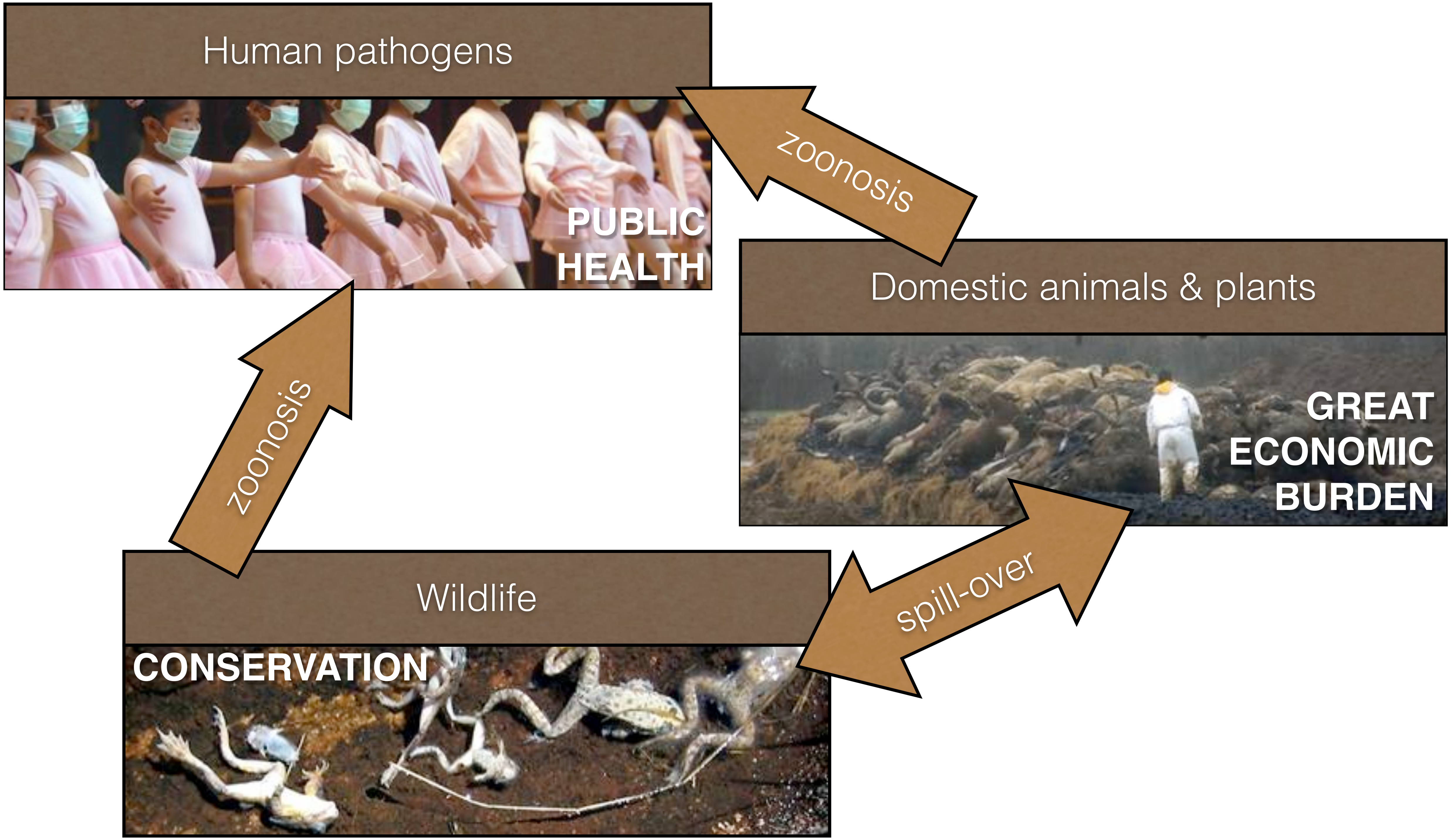
Domestic animals & plants

GREAT ECONOMIC BURDEN

Wildlife

CONSERVATION

Key questions in infectious disease ecology approached through phylogenetics



Human pathogens

PUBLIC HEALTH

zoonosis

Domestic animals & plants

GREAT ECONOMIC BURDEN

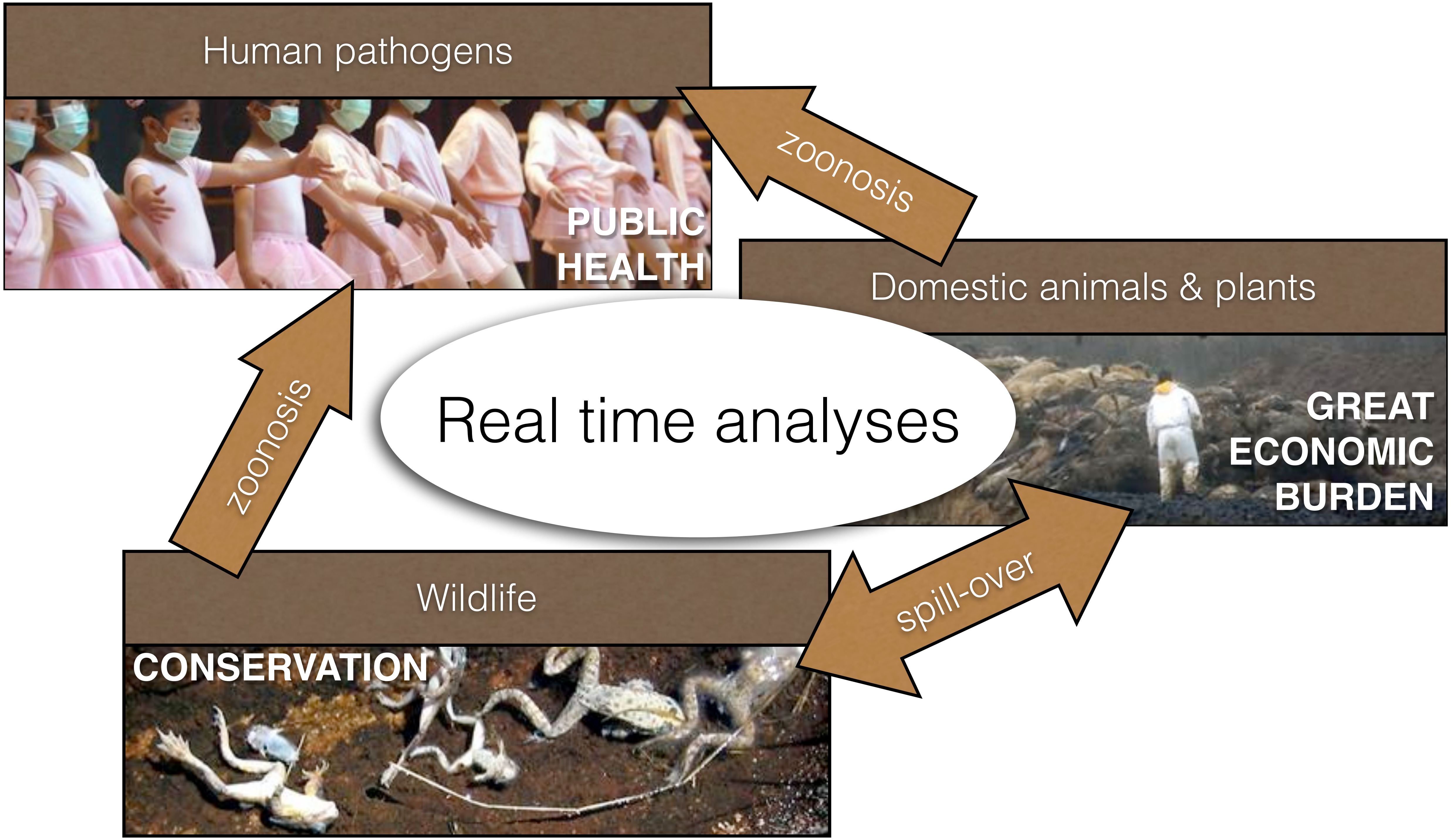
zoonosis

spill-over

Wildlife

CONSERVATION

Key questions in infectious disease ecology approached through phylogenetics



Human pathogens

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GREAT ECONOMIC BURDEN

Real time analyses

zoonosis

Wildlife

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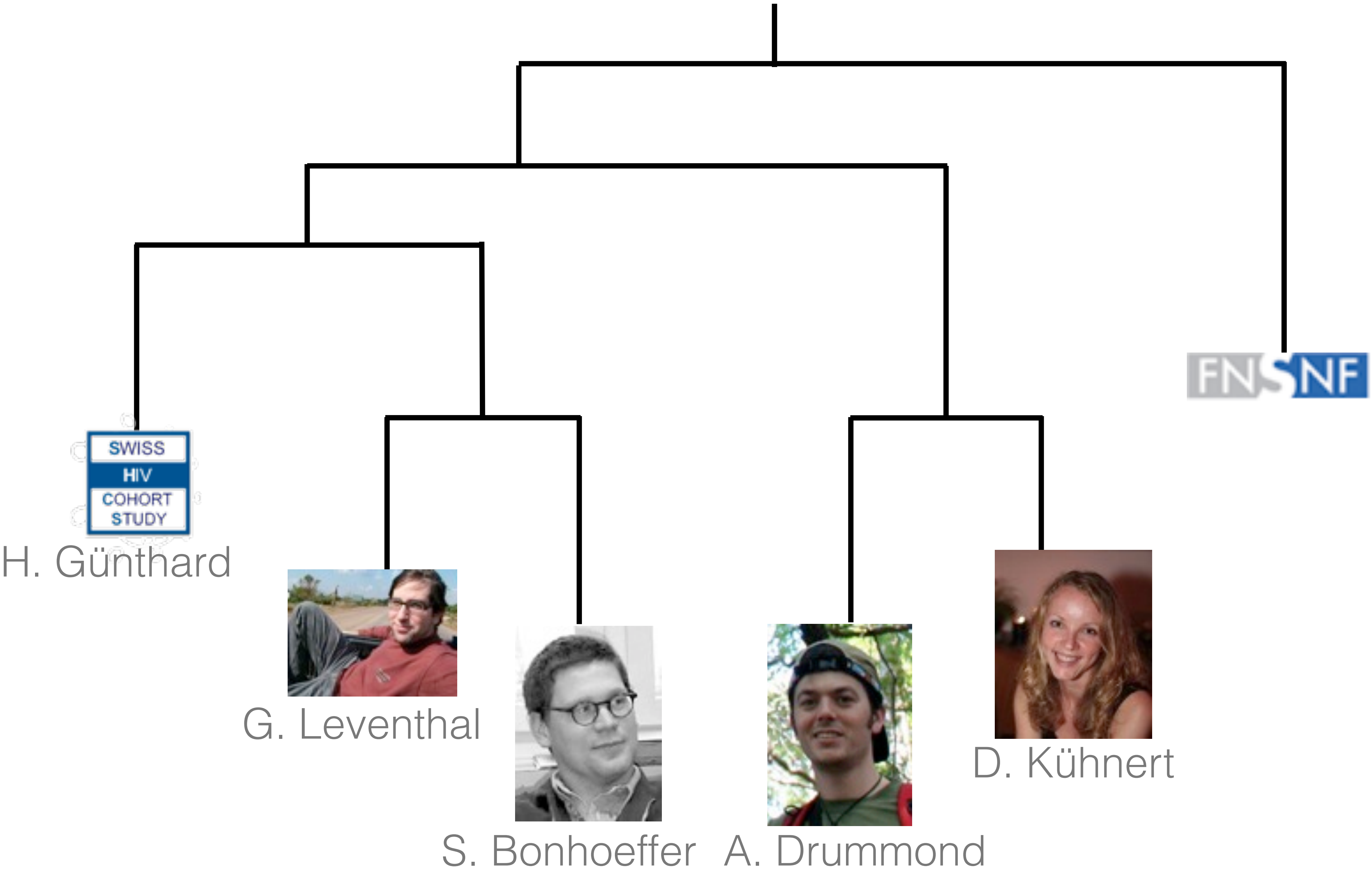
spill-over

Phylogeny of Acknowledgements



SWISS HIV COHORT STUDY

H. Günthard

G. Leventhal

S. Bonhoeffer

A. Drummond

D. Kühnert

FNSNF