Lecture 2: Non-phylogenetic transmission reconstruction

Epidemiological vs genomic outbreak reconstruction

Epidemiological outbreak data alone can be used for outbreak reconstruction (e.g. contact tracing), but genomic data offer a high-resolution source of information

What can genomic data offer?

- Extra detail
- Resolve transmission where epi data are hard to obtain and/or have ‘gaps’
- Genomic data becoming ever easier, cheaper and faster to obtain

To infer ***who infected whom*** and ***key parameters associated with transmission***

Challenge: create a single framework/likelihood incorporating genomic & epidemiological data

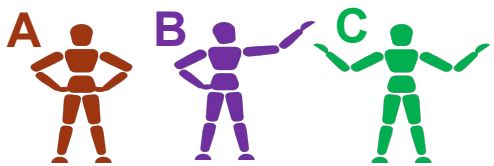
All of the methods we'll see today must balance these 2 data sources. This leads to questions around:

- Do we evaluate the epi data first, and then further discriminate based on genomic data?
- Or, do we do the opposite?
- Or, do we find a way to jointly evaluate both data sources?
- But, the units are completely different!?
- What if the genomic and epi data seem to disagree?

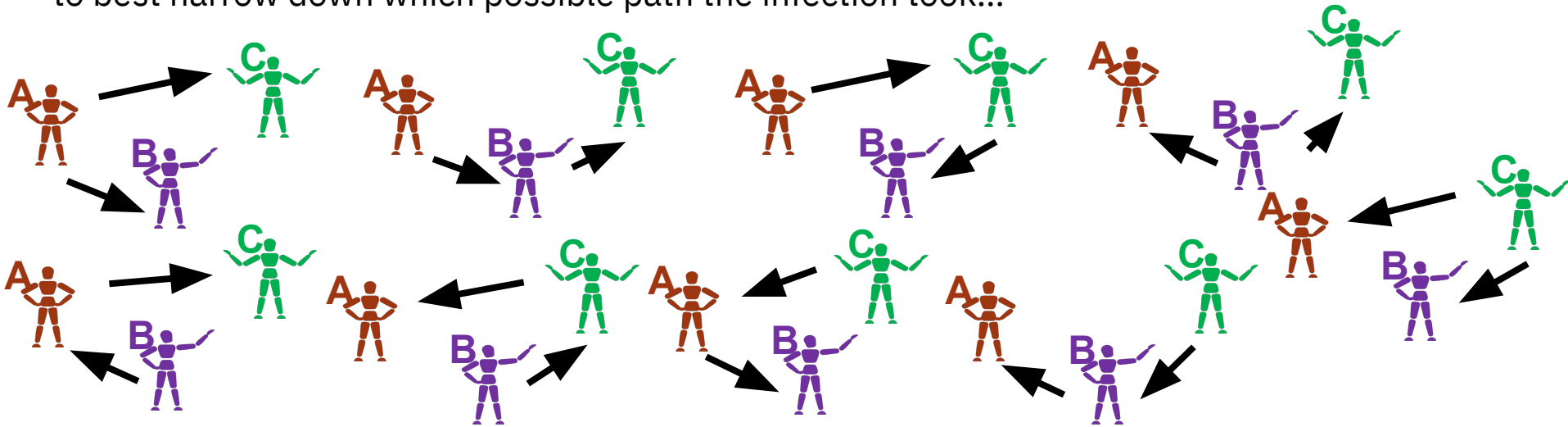
Each method will have its own approach to answering these questions

Challenge: create a single framework/likelihood incorporating genomic & epidemiological data

Imagine we have 3 people infected in an outbreak…



We want to combine our genomic information and our epidemiological information, to best narrow down which possible path the infection took…



2 of the earliest approaches

Many of the earliest methods tackled the 2 data streams separately

PROCEEDINGS OF THE ROYAL SOCIETY B

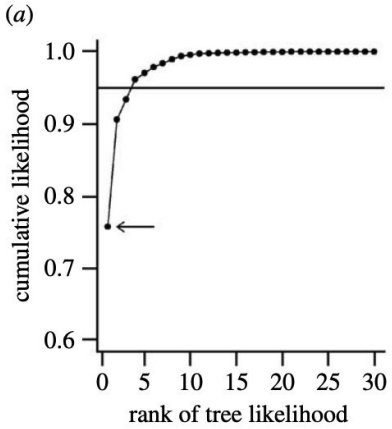
Proc. R. Soc. B (2008) **275**, 887–895
doi:10.1098/rspb.2007.1442
Published online 29 January 2008

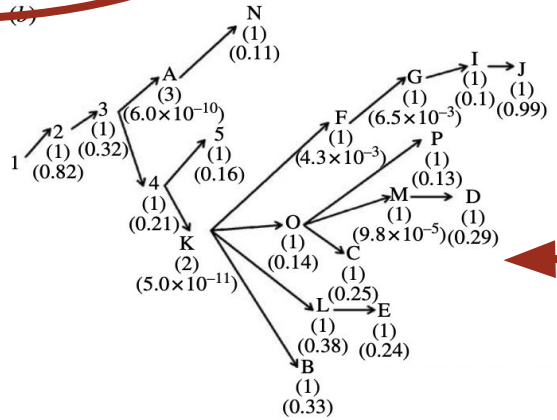
Integrating genetic and epidemiological data to determine transmission pathways of foot-and-mouth disease virus

Eleanor M. Cottam[1,2], Gaël Thébaud[2,†], Jemma Wadsworth[1], John Gloster[3,‡], Leonard Mansley[4], David J. Paton[1], Donald P. King[1] and Daniel T. Haydon[2,*]

Cottam et al. 2008

- 3-step maximum likelihood approach
- Rank the likelihood of the set of plausible trees
- Applied to 20 farms from 2001 UK Foot-and-mouth disease outbreak, to obtain a most likely transmission tree





Cottam et al. model

Begin with a set of **all** possible transmission trees given the set of sampled cases

1. Select only trees that are consistent with **known infection pairs**
2. Select only remaining trees that are consistent with **the genomic data**
3. Calculate the **likelihood** of each remaining tree based on the **epi data** – describing both the chance each host (farm) was infected on a given day and able to infect others on a given day.

Cottam et al. model

Begin with a set of **all** possible transmission trees given the set of sampled cases

1. Select only trees that are consistent with **known infection pairs**
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3. Calculate the **likelihood** of each remaining tree based on the **epi data** – describing both the chance each host (farm) was infected on a given day and able to infect others on a given day.

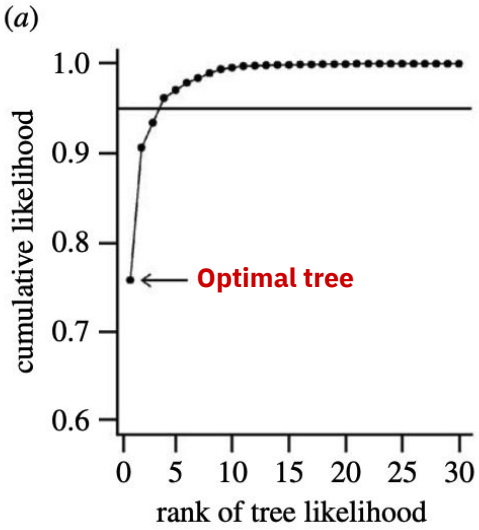
Because there are many possible trees

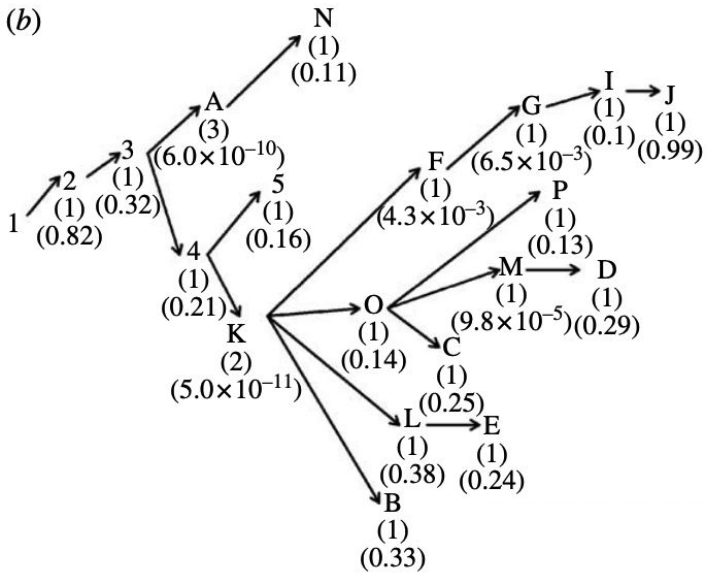
Potentially demanding

Also potentially demanding

Depending on the size of the data and how many trees you were able to exclude

Cottam et al. model





Finally, either

(a) pick 1 optimal tree, or

(b) pick a set of optimal trees (and look for similarities between them)

This is done by ranking the remaining trees by their likelihood

SeqTrack - a graph based approach

A second method from 2011 also tackles first the genomic and then the epi data

Heredity (2011) 106, 383–390

www.nature.com/hdy

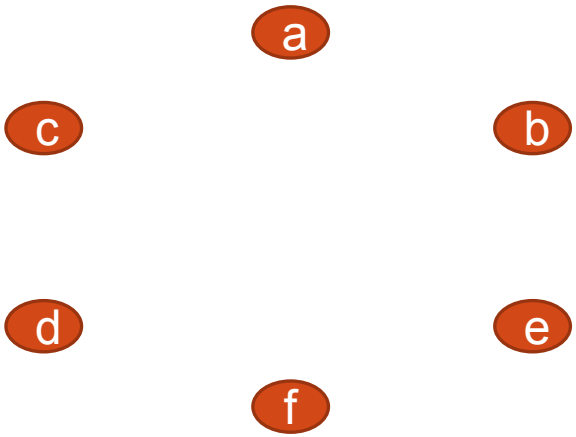
ORIGINAL ARTICLE

Reconstructing disease outbreaks from genetic data: a graph approach

T Jombart, RM Eggo, PJ Dodd and F Balloux
Department of Infectious Disease Epidemiology, MRC Centre for Outbreak Analysis and Modelling, Imperial College Faculty of Medicine, London, UK

- **Graph theory** approach to find 'genetically parsimonious' transmission trees
- Algorithm *SeqTrack* finds the optimum branching in a directed graph

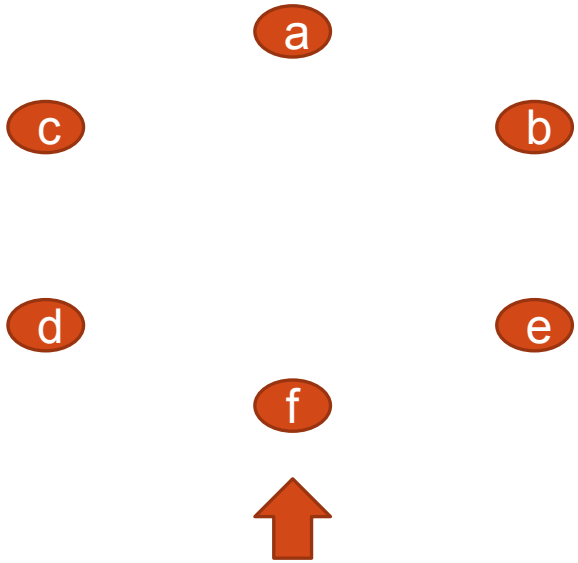
Imagine we have an outbreak with 6 cases, a:f



Imagine we have an outbreak with 6 cases, a:f

Genomic distance matrix

	a	b	c	d	e	f
a	0	1	3	2	5	9
b		0	2	4	7	5
c			0	1	4	12
d				0	1	3
e					0	8
f						0



Sample collection dates:

a: t=3 d: t=5
b: t=1 e: t=4
c: t=2 f: t=7

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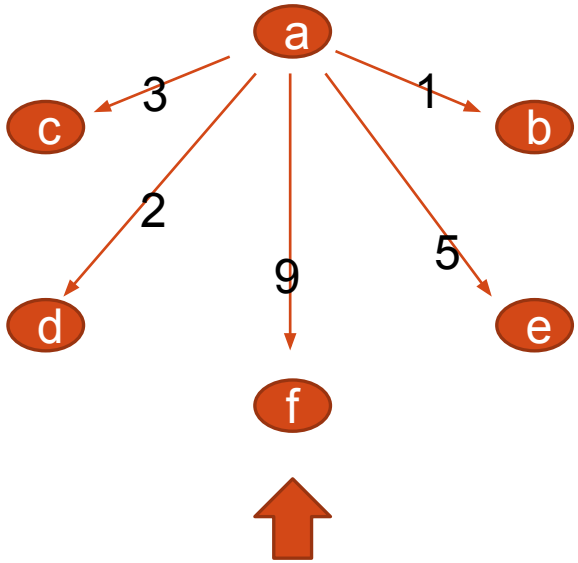
(i) Create a connected, directed graph with weights w_{ij} equal to the genetic distance



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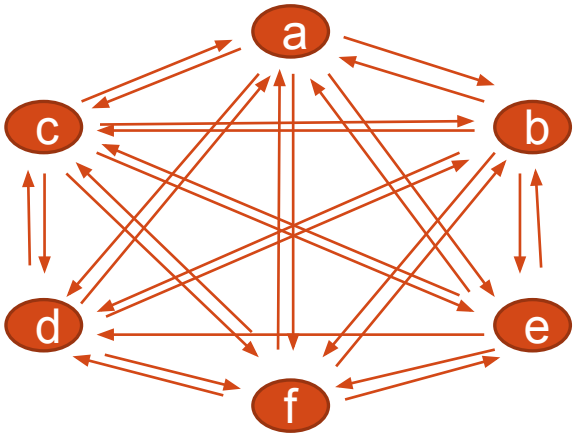

(i) Create a connected, directed graph with weights w_{ij} equal to the genetic distance

We do this every case/node, but lets restrict to (a) for simplicity...

Sample collection dates:

a: t=3 d: t=5
b: t=1 e: t=4
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Imagine we have an outbreak with 6 cases, a:f

Genomic distance matrix

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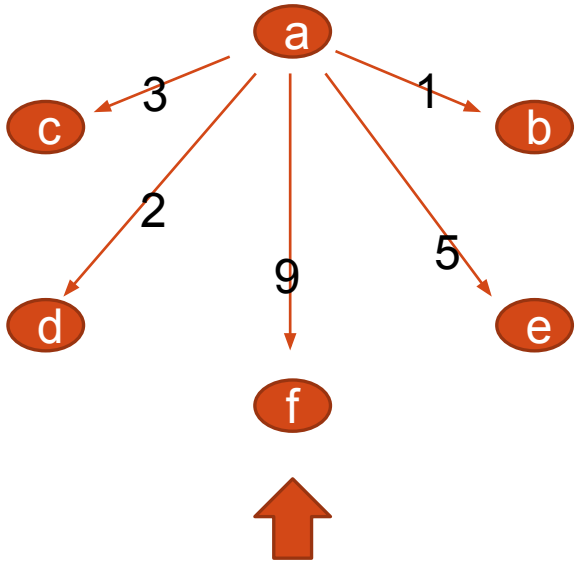

(i) Create a connected, directed graph with weights w_{ij} equal to the genetic distance
(ii) Remove edge ij if $t_j < t_i$

Sample collection dates:

a: t=3 d: t=5
b: t=1 e: t=4
c: t=2 f: t=7

Imagine we have an outbreak with 6 cases, a:f

Genomic distance matrix

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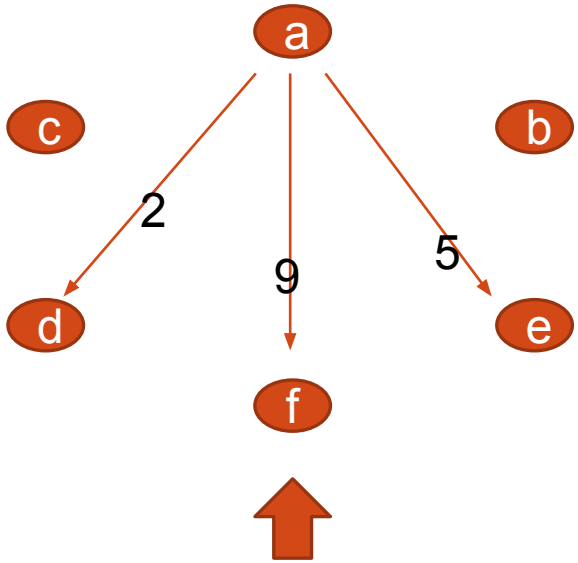

(i) Create a connected, directed graph with weights w_{ij} equal to the genetic distance
(ii) Remove edge ij if $t_j < t_i$

ASSUMPTION: sample collection must be chronological in the transmission tree

Sample collection dates:

a: t=3 d: t=5
b: t=1 e: t=4
c: t=2 f: t=7

Imagine we have an outbreak with 6 cases, a:f

Genomic distance matrix

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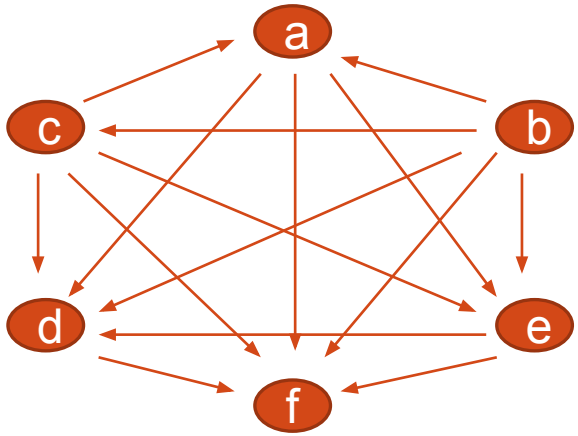

(i) Create a connected, directed graph with weights w_{ij} equal to the genetic distance
(ii) Remove edge ij if $t_j < t_i$

Repeat for every node in the graph

Sample collection dates:

a: t=3 d: t=5
b: t=1 e: t=4
c: t=2 f: t=7

Imagine we have an outbreak with 6 cases, a:f

Genomic distance matrix

	a	b	c	d	e	f
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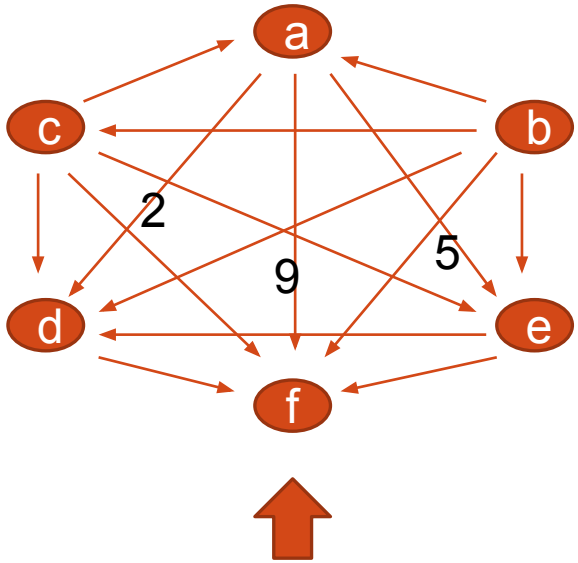

(i) Create a connected, directed graph with weights w_{ij} equal to the genetic distance
(ii) Remove edge ij if $t_j < t_i$
(iii) Find the spanning directed tree optimizing (i.e. minimizing) $\sum w_{ij}$

Sample collection dates:

a: t=3 d: t=5
b: t=1 e: t=4
c: t=2 f: t=7

'This problem has been solved by Edmonds (1967) and Chu and Liu (1965), ...The algorithm proceeds by identifying optimum ancestors for each node at the exception of the root (the oldest isolate), and then recursively removes possible cycles. However, in our case, cycles are impossible as ancestries cannot go back in time, which greatly simplifies computations.'

	a	b	c	d	e	f
a	0	1	3	2	5	9
b		0	2	4	7	5
c			0	1	4	12
d				0	1	3
e					0	8
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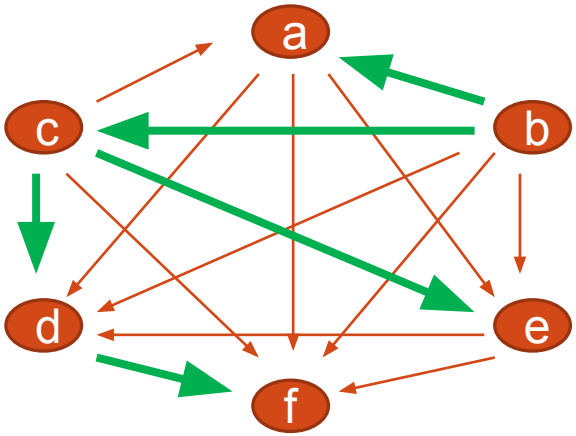


Sample collection dates:

a: t=3 d: t=5
b: t=1 e: t=4
c: t=2 f: t=7

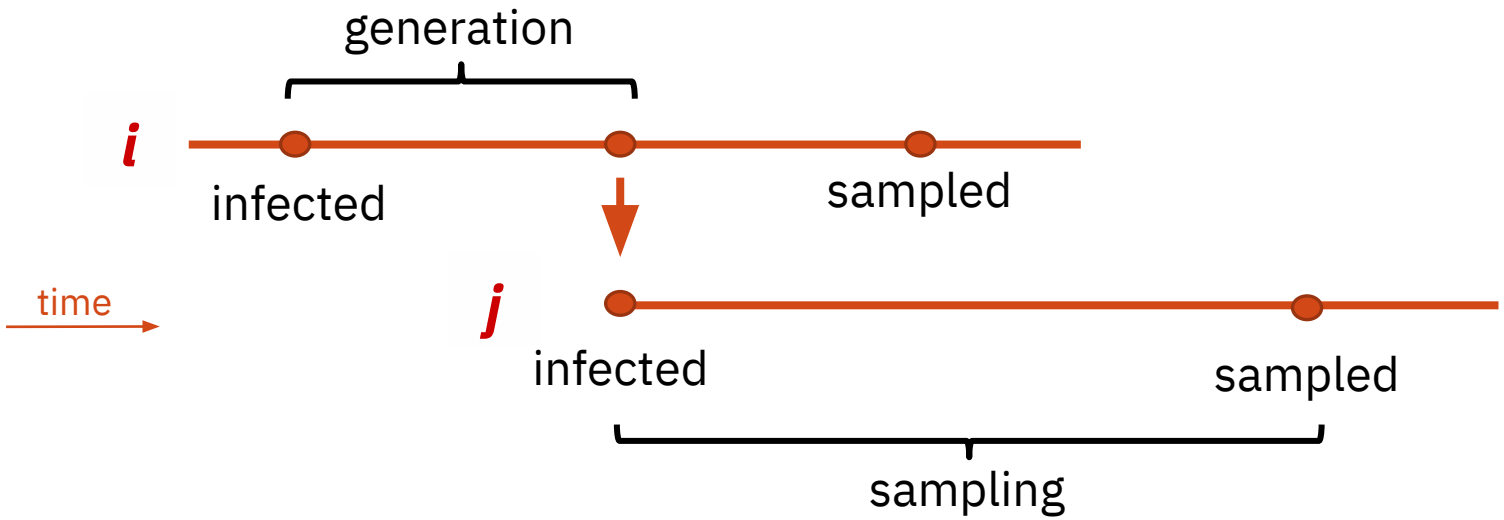
Some limitations:
- All cases come from a single index case i.e. a single sampled ancestor
- All cases are known and sampled
- Sampling times not used in weighting

SeqTrack also:
- Assumes that individuals became infectious in the order they are sampled
- Has no uncertainty in the output transmission tree

But
- Fast, simple, explore all the possibilities
- Easily adaptable to add rules about e.g. end of infectiousness

2 short primers for lecture 2

A quick primer 1: generation time and sampling time



Generation time = the time interval between the infection of an individual and their seeding of new secondary cases.

Sampling time = the time interval between infection and collection of an isolate.

A quick primer 2: Markov Chain Monte Carlo (MCMC)

A popular computational method for exploring complex and/or high-dimensional spaces – e.g. transmission trees

The main idea, from Bayes theorem:

likelihood

$$p(\theta|y) \propto p(y|\theta)p(\theta)$$

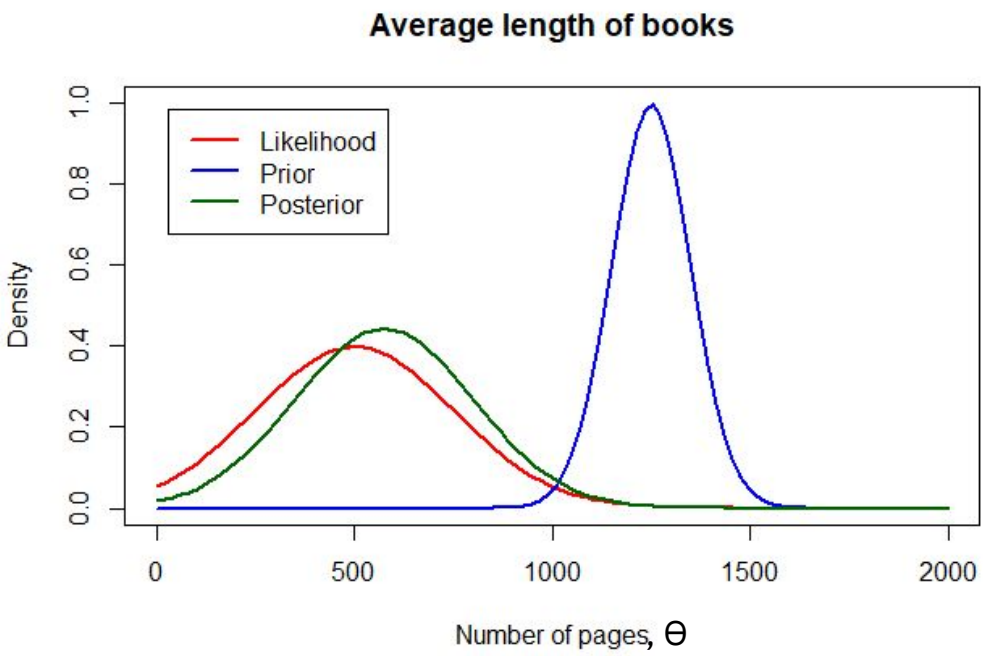
Posterior distribution– the probability of our model parameters Θ given the data *y*

prior

For us, we may have e.g.
Θ = transmission tree and parameters controlling it
y = sequences and epi data

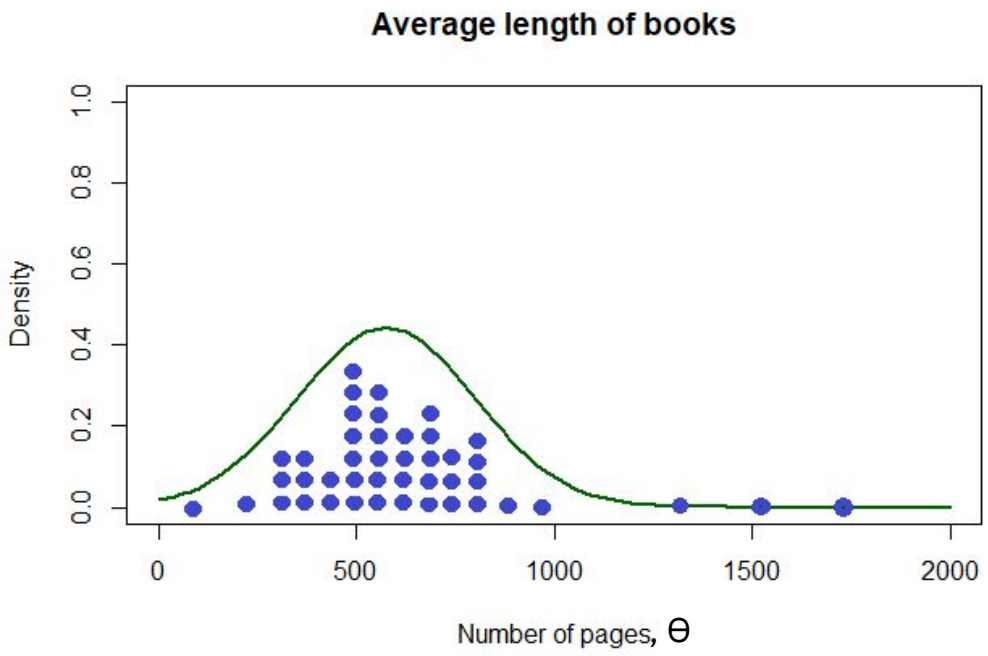
When this quantity (the posterior) is hard to maximise directly, we instead form a Markov chain with equilibrium distribution equal to the posterior distribution, and take many samples from this chain.

A quick primer 2: Markov Chain Monte Carlo (MCMC)



A (not quite correct) intuitive explanation

A quick primer 2: Markov Chain Monte Carlo (MCMC)



Essentially, we approximate the posterior distribution by random sampling from a probabilistic space (of all possible books or all possible transmission trees).

A quick primer 2: Markov Chain Monte Carlo (MCMC)

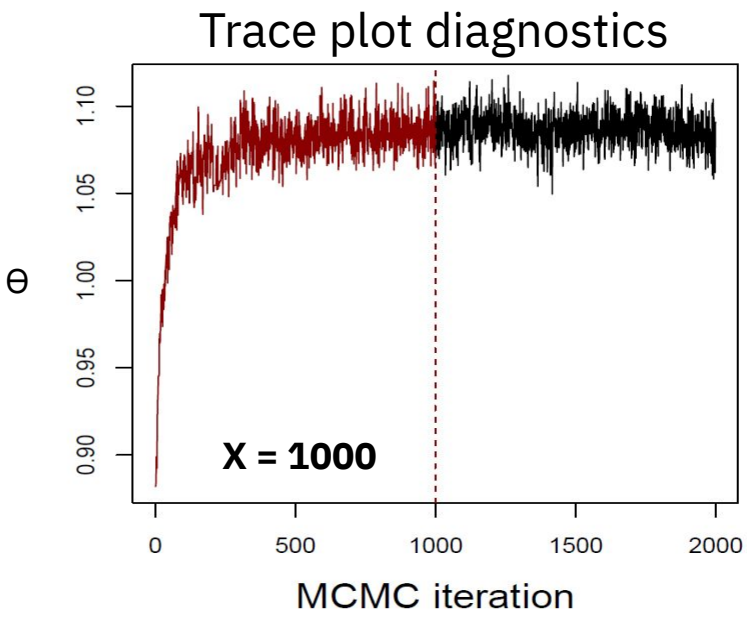
Data-augmented MCMC is a method for dealing with missing data within an MCMC algorithm. As well as sampling from the parameter space at each step of the Markov chain, we also sample values for the missing data.

In transmission inference, missing data might be the time of infection of the cases (since typically we only know sampling times) or the number of unsampled cases, for example.

A quick primer 2: Markov Chain Monte Carlo (MCMC)

In actuality, the ‘random’ samples we collect in MCMC are not independent draws – they form a chain with *equilibrium* distribution equal to the target posterior distribution.

The set of **X** samples at the start of the MCMC run are often discarded – it takes some time to reach an area of the state space with good posterior support. We call this initial set **X** the **burn-in.**



Transmission reconstruction with *outbreaker(2)*

outbreaker and outbreaker2

We're going to look at these methods in detail – and will be using them in the next exercise

These create a unified likelihood for genetic & epidemiological data, but within a Bayesian framework, that allows more estimation and greater flexibility.

outbreaker vs outbreaker2

outbreaker2 is a more customisable version of outbreaker

We're mainly going to focus on the core outbreaker model...

OPEN ACCESS Freely available online

PLOS | COMPUTATIONAL BIOLOGY

Bayesian Reconstruction of Disease Outbreaks by Combining Epidemiologic and Genomic Data

Thibaut Jombart*, Anne Cori, Xavier Didelot, Simon Cauchemez, Christophe Fraser*, Neil Ferguson

MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, United Kingdom

Data:

N sampled cases, each with genetic sequence s_i and time of sampling t_i

Quantities:

$\mathrm{d}(s_i, s_j)$ = number of mutations (distance) between sequences i and j
$\mathrm{l}(s_i, s_j)$ = number of nucleotide positions which can be compared i and j
w = distribution of the generation time
f = distribution of the sampling time

```
> 1:1999-08-01
GCACCCATTCCCGCCTGGAGAT
> 2:2007-11-01
GCACCCATTCCCGCCTAGAGAT
```

outbreaker: the data

Data:

N sampled cases, each with genetic sequence s_i and time of sampling t_i

Quantities:

$\mathrm{d}(s_i, s_j)$ = number of mutations (distance) between sequences i and j
$\mathrm{l}(s_i, s_j)$ = number of nucleotide positions which can be compared i and j
} Derived

w = distribution of the generation time
f = distribution of the sampling time
} Assumed

```
> 1:1999-08-01
GCACCCATTCCCGCCTGGAGAT
> 2:2007-11-01
GCACCCATTCCCGCCTAGAGAT
```

Goal: find the most likely transmission tree

outbreaker: the data

Data:

N sampled cases, each with genetic sequence s_i and time of sampling t_i

Quantities:

$\mathrm{d}(s_i, s_j)$ = number of mutations (distance) between sequences i and j
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f = distribution of the sampling time

Augmented data:

α_i = index of the most recent sampled ancestor of i
κ_i = number of (Sampled and unsampled) generations between i and α_i
T_i^{inf} = date of infection of i

outbreaker: the data

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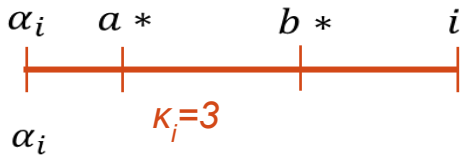
Augmented data:



α_i = index of the most recent sampled ancestor of i
κ_i = number of (Sampled and unsampled) generations between i and α_i
T_i^{inf} = date of infection of i

In addition to obtaining MCMC samples of the augmented data, we estimate 2 parameters

Parameters:

μ = mutation rate, per site per generation of infection
π = proportion of unsampled cases
are estimated as well as the transmission tree

outbreaker: the parameters

In addition to obtaining MCMC samples of the augmented data, we estimate 2 parameters

Parameters:

μ = mutation rate, per site per generation of infection
π = proportion of unsampled cases
are estimated as well as the transmission tree

Posterior distribution:

$$P(A, \theta \mid D) = \frac{P(D, A \mid \theta) P(\theta)}{P(D)} \propto p\left(\left\{s_i, t_i, \alpha_i, \kappa_i, T_i^{\inf}\right\}_{i=1,\ldots,N} \,\middle|\, \mu, \pi\right) \times p(\mu, \pi).$$

D = Data
A = Augmented data
Θ = Parameters

outbreaker: the model

In addition to obtaining MCMC samples of the augmented data, we estimate 2 parameters

Parameters:

μ = mutation rate, per site per generation of infection
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are estimated as well as the transmission tree

Posterior distribution:

$$P(A,\theta\,|D) = \frac{P(D,A\,|\theta)P(\theta)}{P(D)} \propto \underbrace{p}_{\text{likelihood}}\Big(\underbrace{\{\underbrace{s_i, t_i}_{\text{data}}, \underbrace{\alpha_i, \kappa_i, T_i^{\text{inf}}}_{\text{augmented data}}\}_{i=1,\ldots,N}}\,\Big|\,\underbrace{\mu,\pi}_{\text{given the param.s}}\Big) \times \underbrace{p(\mu,\pi)}_{\text{prior on param.s}}.$$

In addition to obtaining MCMC samples of the augmented data, we estimate 2 parameters

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Posterior distribution:

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All cases are assumed to be conditionally independent, given the identity of their most recent sampled ancestor, so the likelihood decomposes to:

$$p\left(\left\{s_i, t_i, \alpha_i, \kappa_i, T_i^{\inf}\right\}_{i=1,\ldots,N} \middle|\, \mu, \pi\right) = \prod_{i=2}^{N} p\left(s_i, t_i, \alpha_i, \kappa_i, T_i^{\inf}\,|s_{\alpha_i}, t_{\alpha_i}, T_{\alpha_i}^{\inf}, \mu, \pi\right) \times$$
$$p(t_1\,|T_1^{\inf})p(s_1)p\left(T_1^{\inf}\right)p(\alpha_1)p(\kappa_1)$$

In addition to obtaining MCMC samples of the augmented data, we estimate 2 parameters

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$$p(t_1\,|T_1^{\inf})p(s_1)p\left(T_1^{\inf}\right)p(\alpha_1)p(\kappa_1)$$

These terms relate only to initial case

This is actually an *approximate* likelihood

One point to note: since cases may share a common unsampled ancestry, this is technically a composite (approximate/pseudo) likelihood

$$p\left(\left\{s_i, t_i, \alpha_i, \kappa_i, T_i^{\text{inf}}\right\}_{i=1,\ldots,N} \,\middle|\, \mu, \pi\right) = \prod_{i=2}^{N} p\left(s_i, t_i, \alpha_i, \kappa_i, T_i^{\text{inf}} \,|s_{\alpha_i}, t_{\alpha_i}, T_{\alpha_i}^{\text{inf}}, \mu, \pi\right) \times$$
$$p(t_1 \,|T_1^{\text{inf}}) p(s_1) p\left(T_1^{\text{inf}}\right) p(\alpha_1) p(\kappa_1)$$

A genetic part and an epidemiological part

The pseudo-likelihood is further decomposed into genetic and epidemiological components. For each case $i = 1, \ldots, \mathrm{N}$:

$$p\left(s_i, t_i, \alpha_i, \kappa_i, T_i^{\inf} \,|s_{\alpha_i}, t_{\alpha_i}, T_{\alpha_i}^{\inf}, \mu, \pi\right)$$
$$= \underbrace{p\left(s_i \,|\alpha_i, s_{\alpha_i}, \kappa_i, \mu\right)}_{\text{Genetic part}} \times \underbrace{p\left(t_i \,|T_i^{\inf}\right) p\left(T_i^{\inf} \,\middle|\, \alpha_i, T_{\alpha_i}^{\inf}, \kappa_i\right) p(\kappa_i \,|\pi)}_{\text{Epidemiological part}} \underbrace{p(\alpha_i)}_{\text{Constant}}$$

A genetic part and an epidemiological part

The pseudo-likelihood is further decomposed into genetic and epidemiological components. For each case $i = 1, \ldots, \mathrm{N}$:

$$p\left(s_i, t_i, \alpha_i, \kappa_i, T_i^{\inf} \,|s_{\alpha_i}, t_{\alpha_i}, T_{\alpha_i}^{\inf}, \mu, \pi\right)$$
$$= \underbrace{p\left(s_i \,|\alpha_i, s_{\alpha_i}, \kappa_i, \mu\right)}_{\text{Genetic part}} \times \underbrace{p\left(t_i \,|T_i^{\inf}\right) p\left(T_i^{\inf} \,\middle|\, \alpha_i, T_{\alpha_i}^{\inf}, \kappa_i\right) p(\kappa_i \,|\pi)}_{\text{Epidemiological part}} \underbrace{p(\alpha_i)}_{\text{Constant}}$$

Probability of their sequence arising, given their infector, their infector's sequence, any unsampled cases and the mutation rate

A genetic part and an epidemiological part

The pseudo-likelihood is further decomposed into genetic and epidemiological components. For each case $i = 1, \ldots, \mathrm{N}$:

$$p\left(s_i, t_i, \alpha_i, \kappa_i, T_i^{\inf} \,|s_{\alpha_i}, t_{\alpha_i}, T_{\alpha_i}^{\inf}, \mu, \pi\right)$$
$$= \underbrace{p\left(s_i \,|\alpha_i, s_{\alpha_i}, \kappa_i, \mu\right)}_{\text{Genetic part}} \times \underbrace{p\left(t_i \,|T_i^{\inf}\right) p\left(T_i^{\inf} \,\middle|\, \alpha_i, T_{\alpha_i}^{\inf}, \kappa_i\right) p(\kappa_i \,|\pi)}_{\text{Epidemiological part}} \underbrace{p(\alpha_i)}_{\text{Constant}}$$

Probability they were sampled at t_i given their time of infection.
Probability they were infected when they were, given ancestor and unsampled intermediates.
Probability of their unsampled intermediates given sampling rate

A genetic part and an epidemiological part

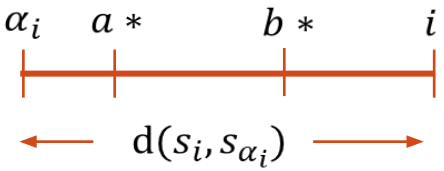
The pseudo-likelihood is further decomposed into genetic and epidemiological components. For each case $i = 1, \ldots, \mathrm{N}$:

$$p\left(s_i, t_i, \alpha_i, \kappa_i, T_i^{\inf} \,|s_{\alpha_i}, t_{\alpha_i}, T_{\alpha_i}^{\inf}, \mu, \pi\right)$$
$$= \underbrace{p\left(s_i \,|\alpha_i, s_{\alpha_i}, \kappa_i, \mu\right)}_{\text{Genetic part}} \times \underbrace{p\left(t_i \,|T_i^{\inf}\right) p\left(T_i^{\inf} \,\middle|\, \alpha_i, T_{\alpha_i}^{\inf}, \kappa_i\right) p(\kappa_i \,|\pi)}_{\text{Epidemiological part}} \underbrace{p(\alpha_i)}_{\text{Constant}}$$

Genetic part

The outbreaker genetic model assumes no within-host genetic diversity, and so mutations are direct features of transmission events. All transmission events are assumed independent, and the genetic pseudo-likelihood is very fast to compute.

Genetic pseudo-likelihood of case i = the probability of observing genetic distance $\mathrm{d}(s_i, s_{\alpha_i})$ between sequence s_i and the ancestral sequence s_{α_i} with i and α_i separated by κ_i generations.



As a method designed for shorter timescale outbreaks, reverse mutations are considered negligible.

Genetic pseudolikelihood = $\boxed{\mu^{\mathrm{d}(s_i, s_{\alpha_i})} (1-\mu)^{\kappa_i \times \mathrm{l}(s_i, s_{\alpha_i}) - \mathrm{d}(s_i, s_{\alpha_i})}}$

Epidemiological part

Remember:
w = distribution of the generation time
f = distribution of the sampling time

Describes the probability of…

Time of sampling given time of infection

Time of infection given knowledge of infector

Number of missing cases given rate of missing cases

$$p\left(t_i \mid T_i^{\text{inf}}\right) p\left(T_i^{\text{inf}} \,\middle|\, \alpha_i, T_{\alpha_i}^{\text{inf}}, \kappa_i\right) p(\kappa_i \mid \pi)$$

$$=$$

$$f\left(t_i - T_i^{\text{inf}}\right) \times w^{\kappa_i}\left(T_i^{\text{inf}} - T_{\alpha_i}^{\text{inf}}\right) \times \text{NB}(1 \mid \kappa_i\text{-}1, \pi)$$

probability of obtaining one 'success' (sampling a case) after $\kappa_i - 1$ 'failures' (unobserved cases), with probability of success π.

Combine genomic & epi parts for each case in the outbreak

$$p\left(s_i, t_i, \alpha_i, \kappa_i, T_i^{\text{inf}} \,|s_{\alpha_i}, t_{\alpha_i}, T_{\alpha_i}^{\text{inf}}, \mu, \pi\right)$$
$$= \underbrace{p\left(s_i \,|\alpha_i, s_{\alpha_i}, \kappa_i, \mu\right)}_{\text{Genetic part}} \times \underbrace{p\left(t_i \,|T_i^{\text{inf}}\right) p\left(T_i^{\text{inf}} \,\middle|\, \alpha_i, T_{\alpha_i}^{\text{inf}}, \kappa_i\right) p(\kappa_i \,|\pi)}_{\text{Epidemiological part}} p(\alpha_i)$$

Constant

That forms the core of the outbreaker model.

The likelihood expressions introduced in the previous slides are combined with priors for the mutation rate μ and proportion of unsampled cases π.

In outbreaker 1:

μ is given a uniform prior on [0,1] – corresponding to an assumption of scarce prior information on this
π is given a beta distributed prior with parameters controlled by the user of outbreaker. This is a flexible prior which can reflect different levels of prior knowledge for different datasets.

Option to detect imported cases

The authors also introduce a method for detecting imported cases – i.e. cases that are not descended from another case in the outbreak.

In an initial step of the model, genetic outliers are detected, relative to the other samples in the dataset. A 'global influence' GI_i is calculated for each sampled case, defined as

$$GI_i = \mathbb{E}\left(\sum_{j=1, j\neq i}^{n} GPL_J\right) - \mathbb{E}\left(\sum_{i=1}^{n} GPL_i\right)$$

Describes what proportion i's GPL is of the total GPL

where GPL is the genetic pseudo-likelihood. This is calculated over the first few samples of the MCMC, say 50.

A large value of the GI_i implies unlikely numbers of mutations i.e. a 'distant' sequence. Cases with a global influence more than 5 times the average across all cases are considered outliers.

An application from

Data from 2003 Singaporean Severe Acute Respiratory Syndrome (SARS) outbreak.
13 genomes with <15 mutations between all pairs.

Generation time = Γ(mean 8.4, SD 3.8)
Same sampling time

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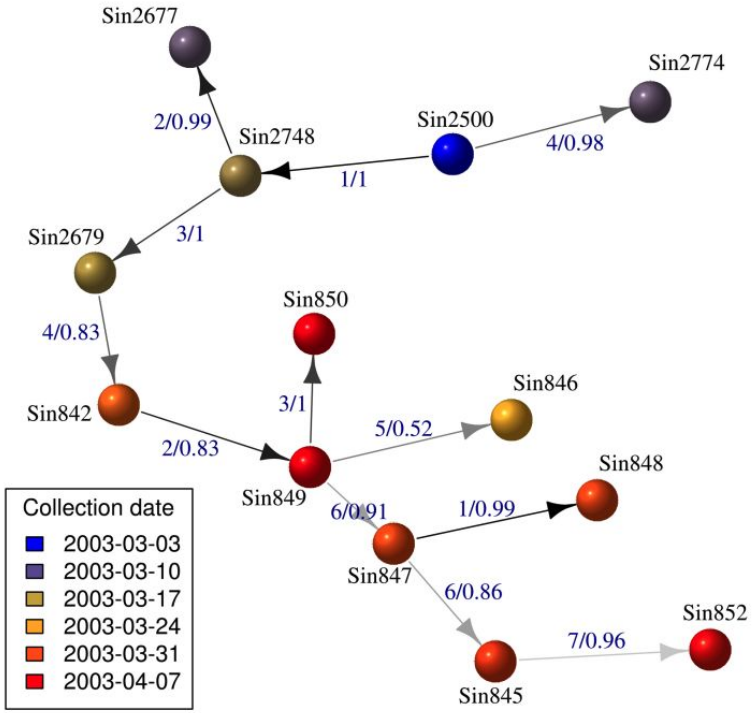
Bayesian Reconstruction of Disease Outbreaks by Combining Epidemiologic and Genomic Data

Thibaut Jombart*, Anne Cori, Xavier Didelot, Simon Cauchemez, Christophe Fraser*, Neil Ferguson

MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, School of Public Health, Imperial College London, London, United Kingdom



An application from

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13 genomes with <15 mutations between all pairs.

Generation time = Γ(mean 8.4, SD 3.8)
Same sampling time

How to get here from the posterior expression?

1. Run MCMC to sample many trees (and many μ, π, … values)
2. Discard burn-in
3. Pick a consensus tree that best represents the remaining trees

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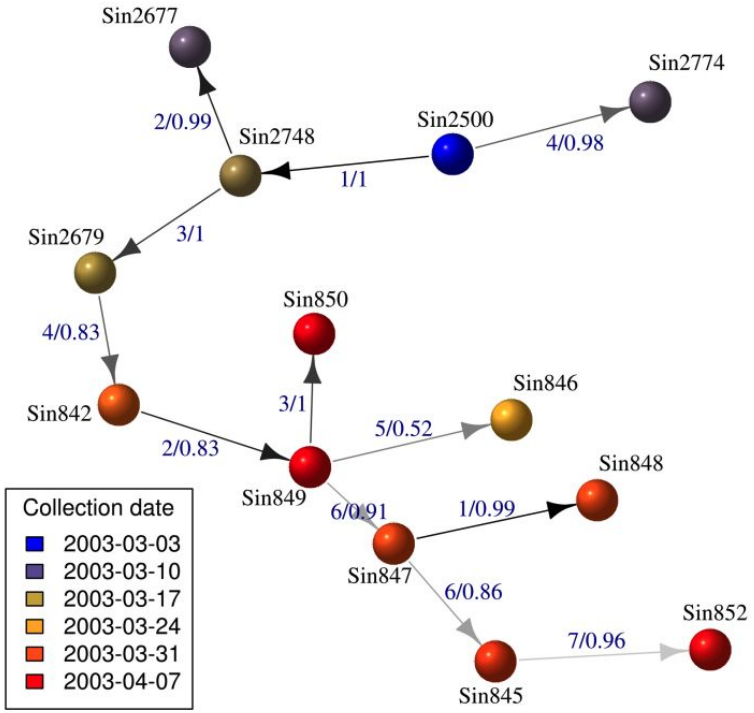
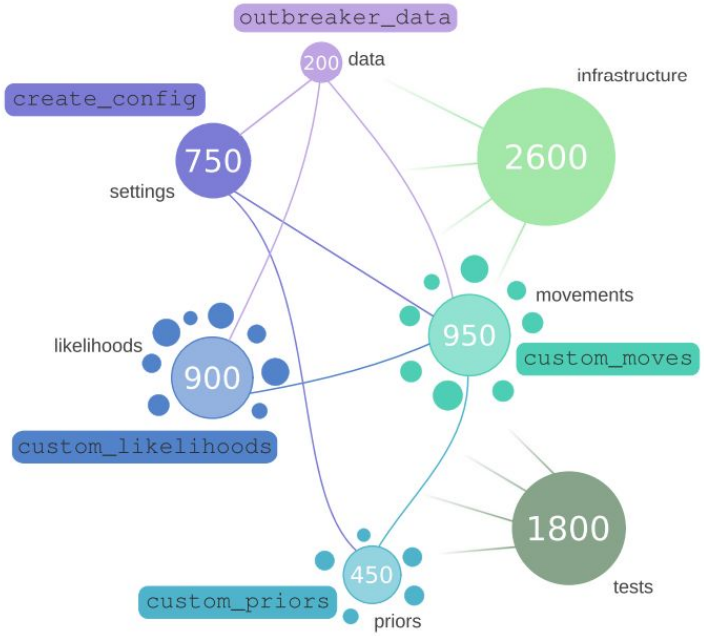


outbreaker2: extensions



numbers = lines of code

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SOFTWARE Open Access

outbreaker2: a modular platform for outbreak reconstruction

Finlay Campbell, Xavier Didelot, Rich Fitzjohn, Neil Ferguson, Anne Cori and Thibaut Jombart*

From the 6th Workshop on Computational Advances in Molecular Epidemiology (CAME 2017)
Boston, MA, USA. 20 August 2017

- Combines an R package with C++ code for efficiency, through Rcpp
- Can customise all these facets of the package
- For example, they implemented the TransPhylo methodology, which we will work with tomorrow, in outbreaker2.

After the break

We’ll explore outbreaker for some TB and SARS-CoV-2 data

Any questions?