Imperial College London

MRC Centre for Outbreak Analysis and Modelling

outbreakeR

disease outbreak recontruction using genetic data

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GenEpi — LSHTM, London
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Investigating disease outbreaks using genetic data

Background

- here, "*outbreak*" = small, localised epidemic
- **small-scale** → **dense sampling** possible
- **pathogen genomes sequences increasingly available**

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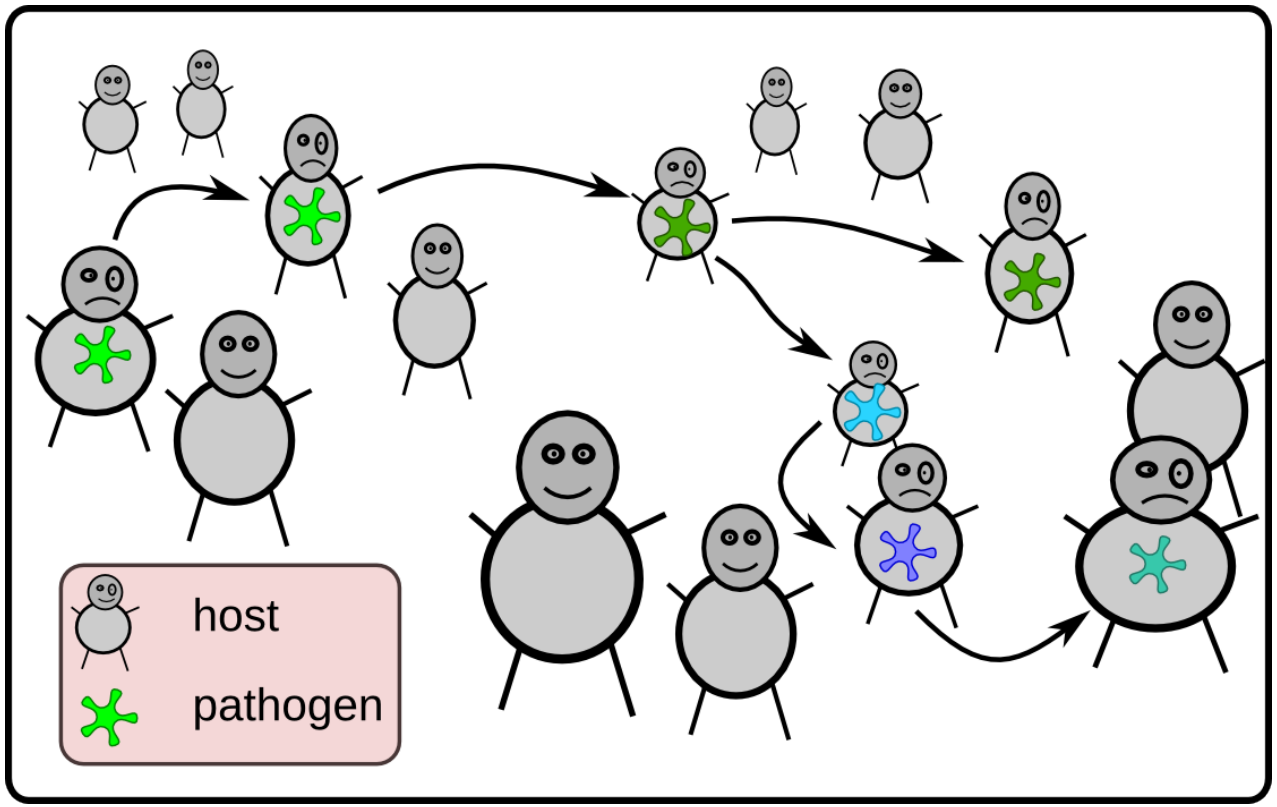
Objectives

- exploit genetic information to reconstruct outbreaks
- infer **transmission trees**, dates of infection, R, ...
- design a tool for **retrospective** or **near real-time** analysis

The data



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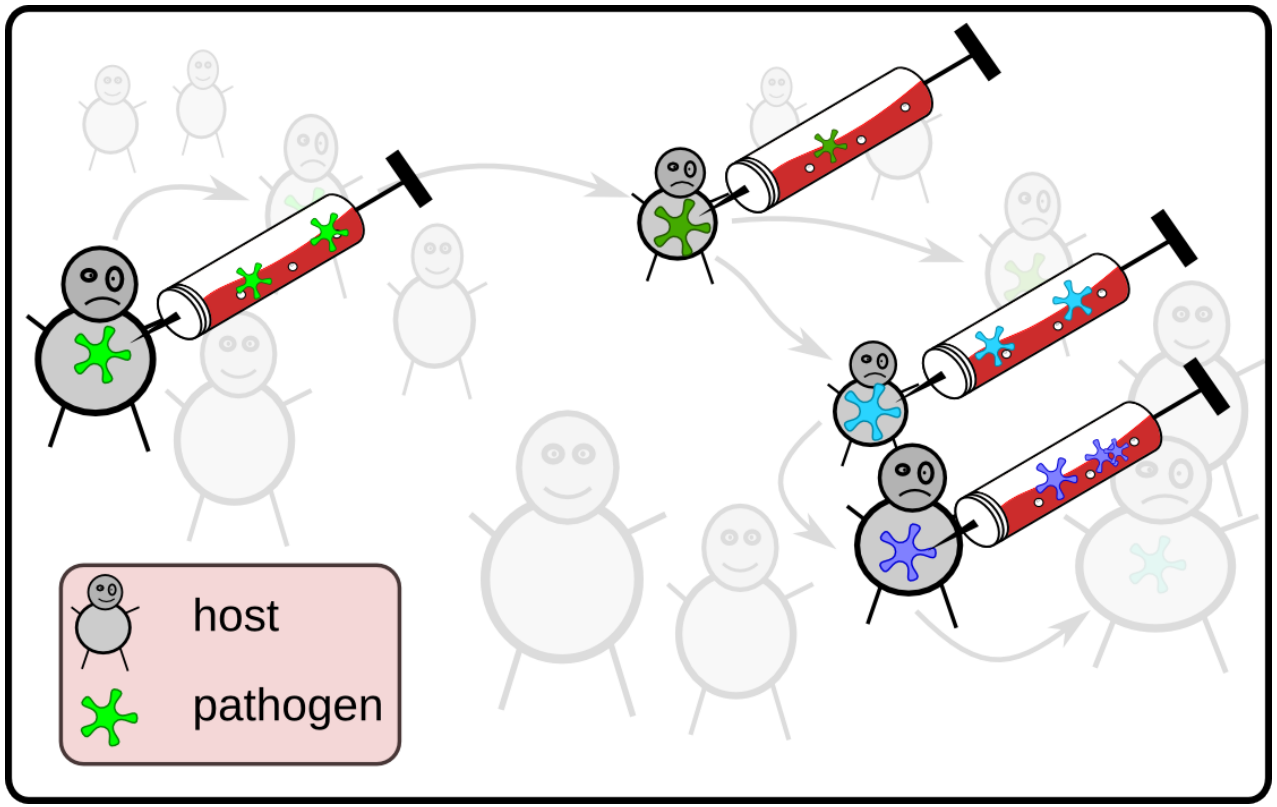

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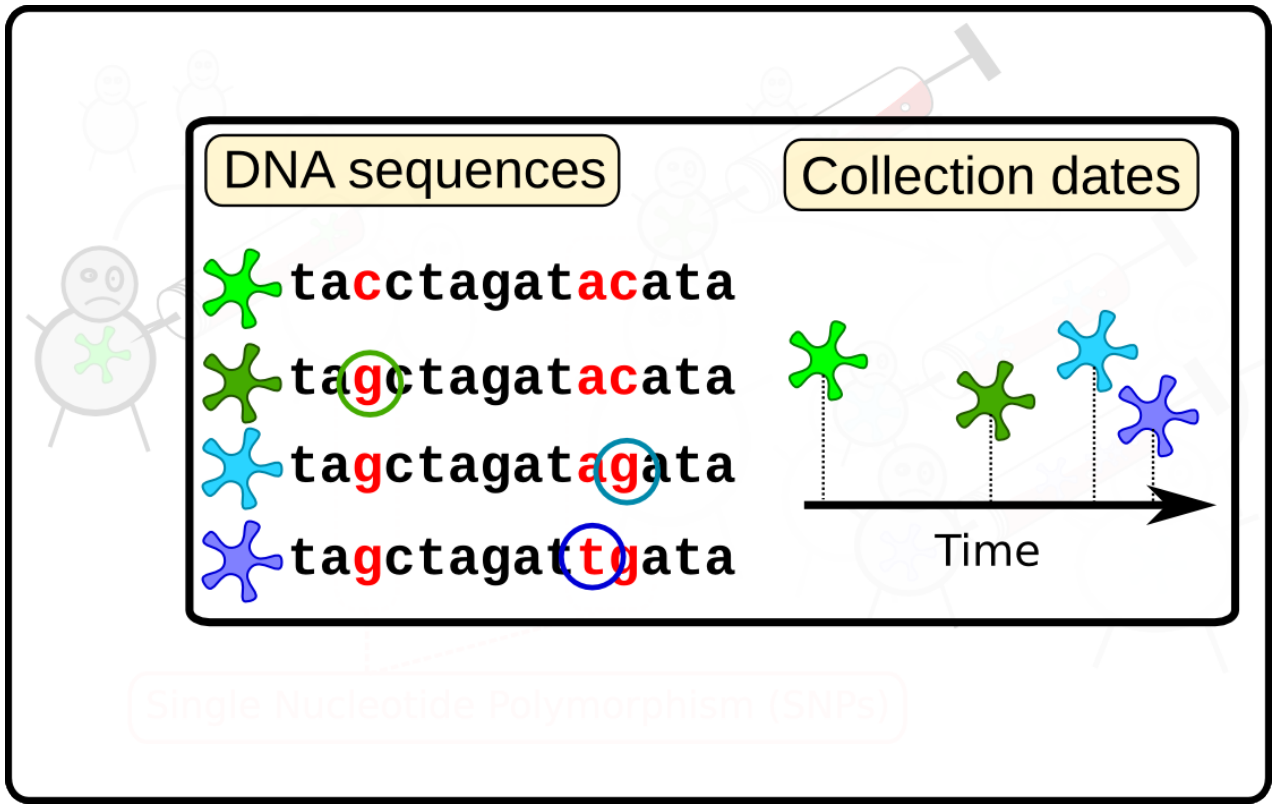
DNA sequences
Collection dates
tacctagatacata
tagctagatacata
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Time

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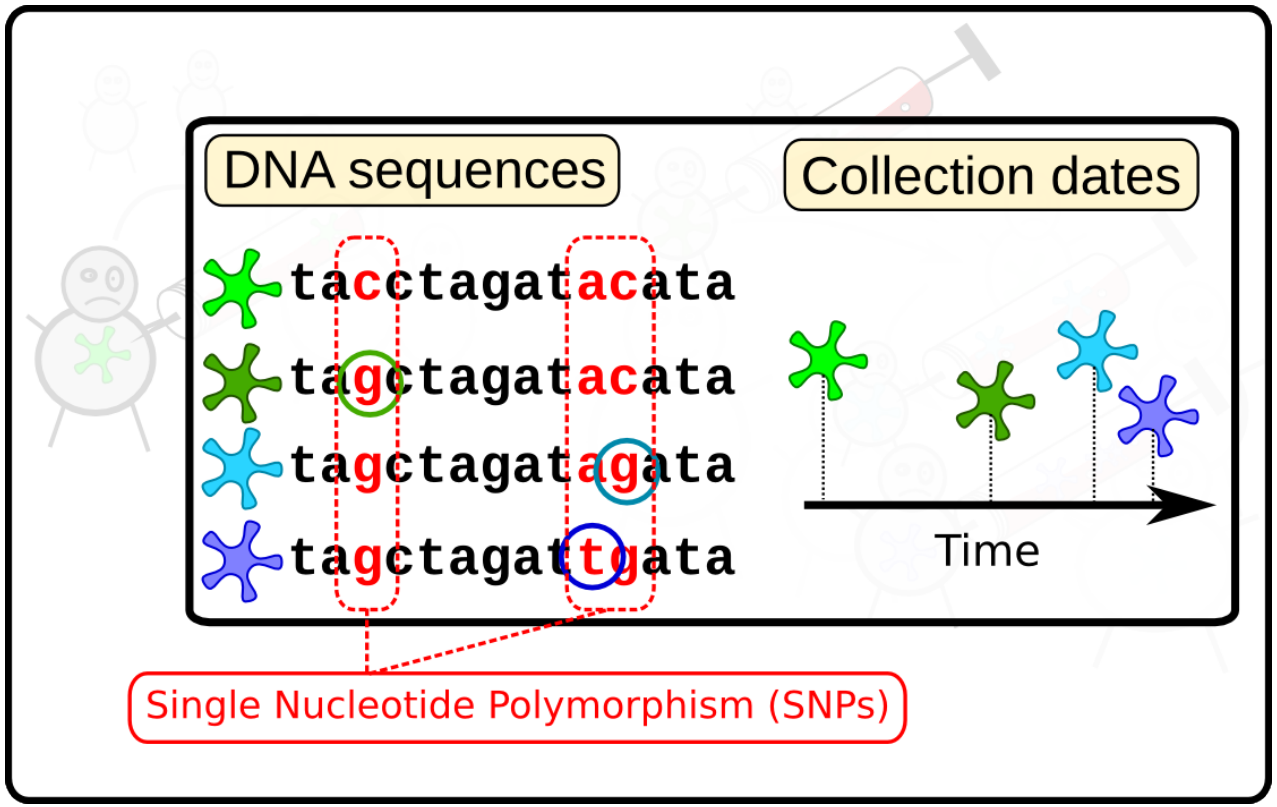
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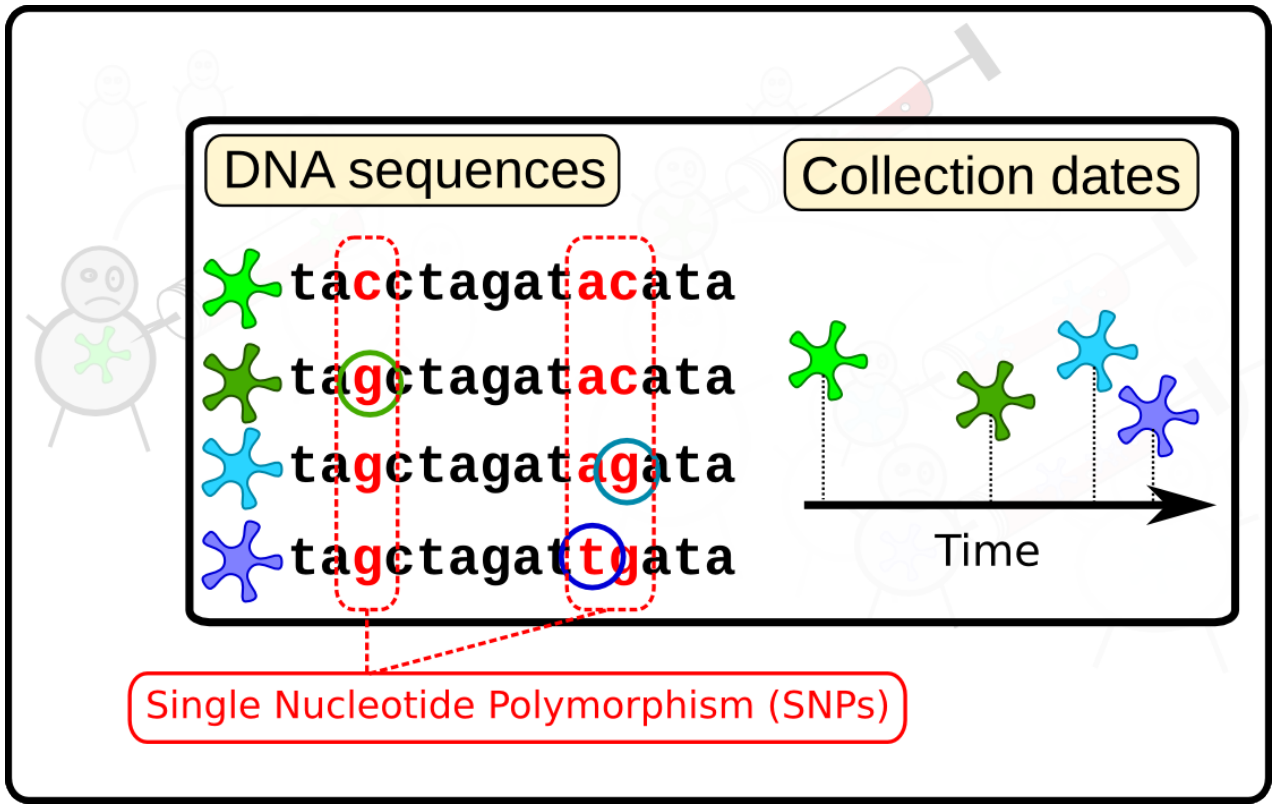
Time
Single Nucleotide Polymorphism (SNPs)

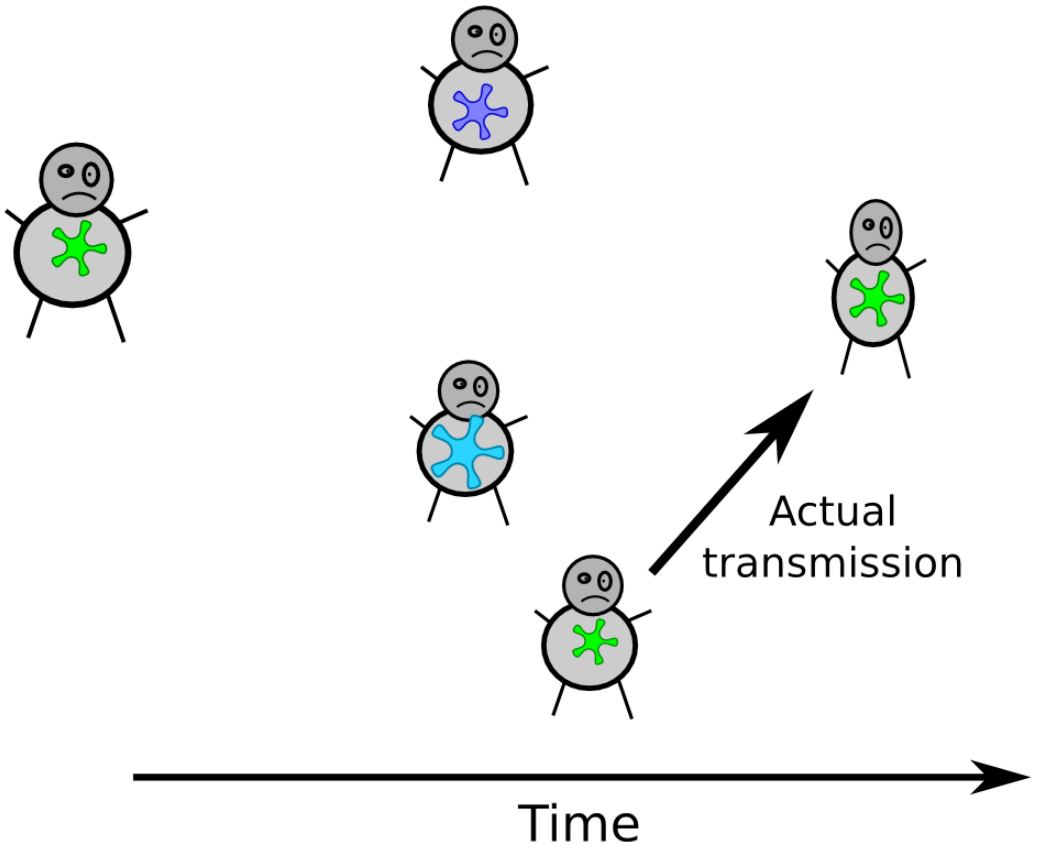
The data



Generic model integrating **genomic data** and **collection dates**

Rationale of the method

How to infer the infector of a given individual?



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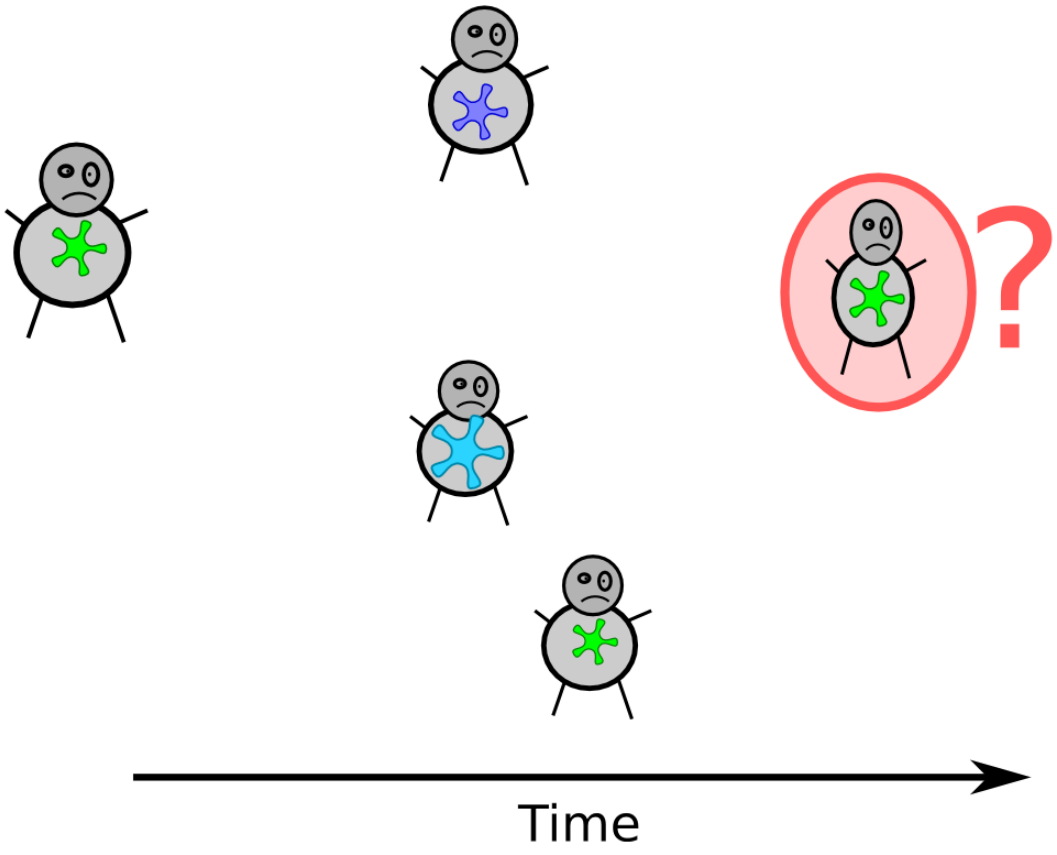
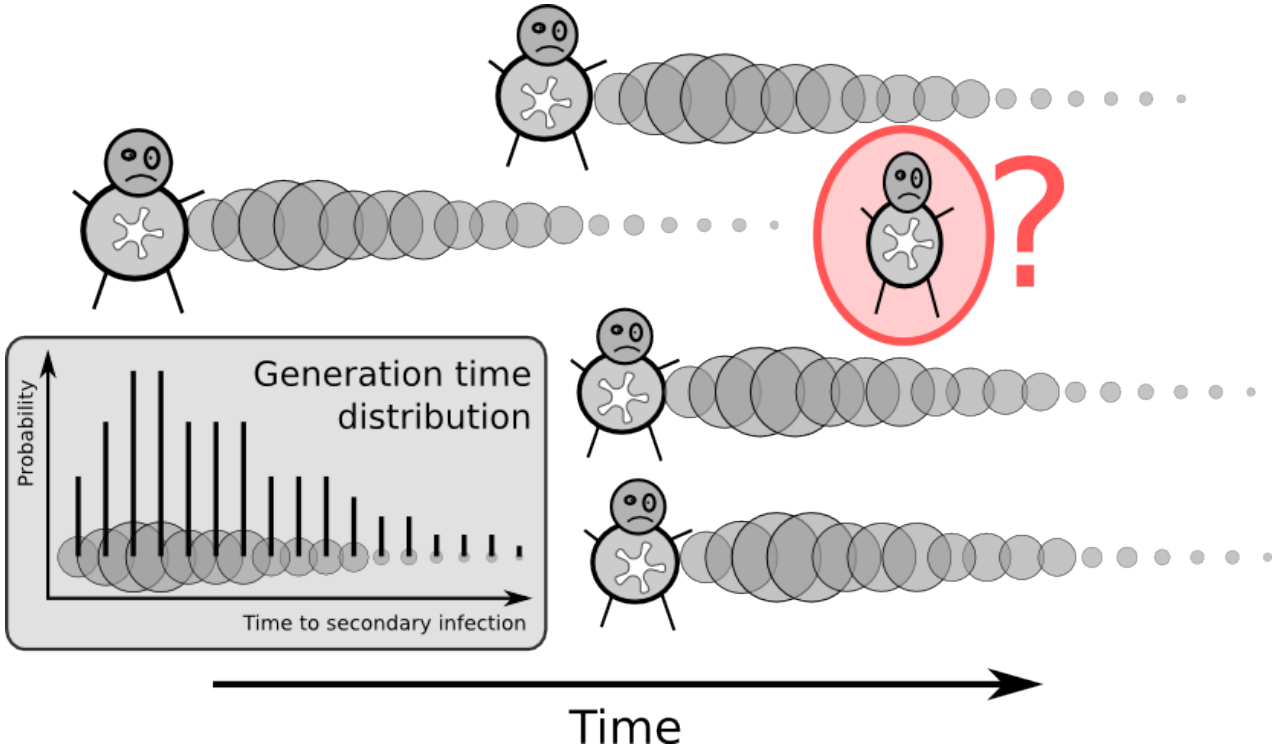


Rationale of the method

Approach based on generation time distribution

(Ferguson *et al.* 2001, Nature; Wallinga & Teunis 2004, Am. J. Epidemiol.)



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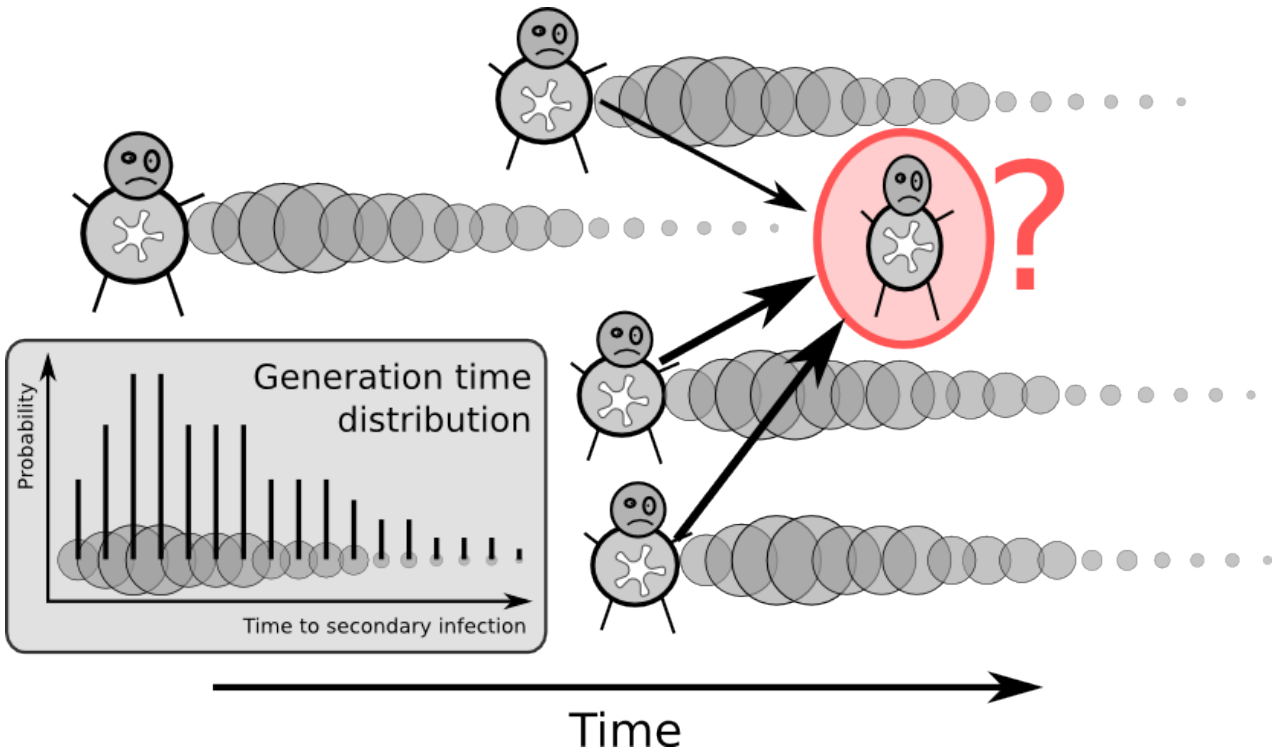

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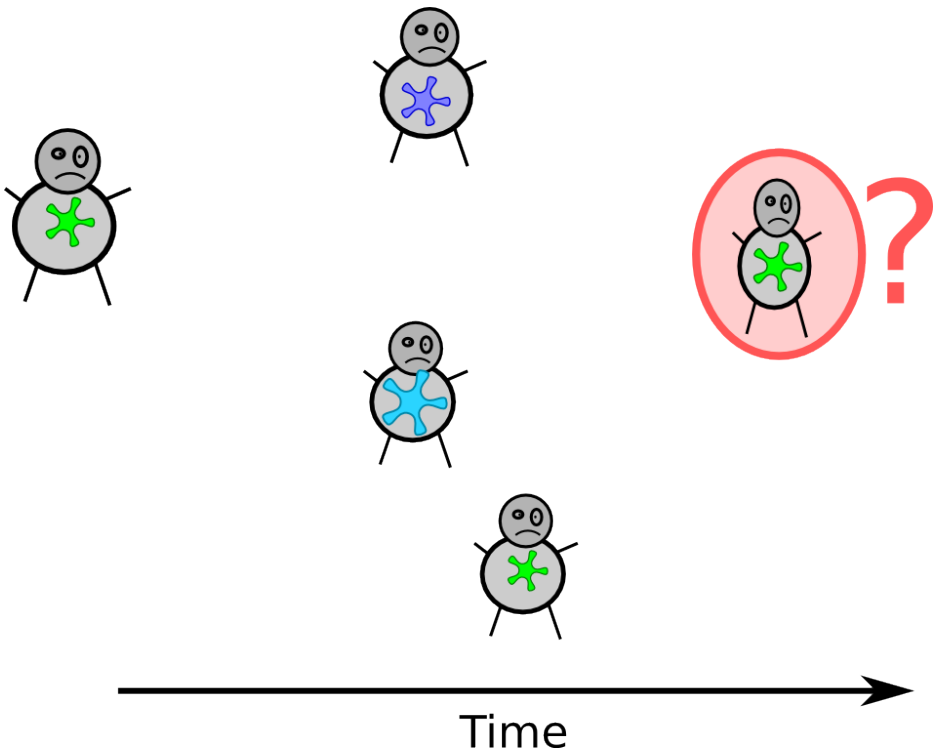
Approach based on genetic data (*SeqTrack*)

(Jombart *et al.* 2010, Heredity.)



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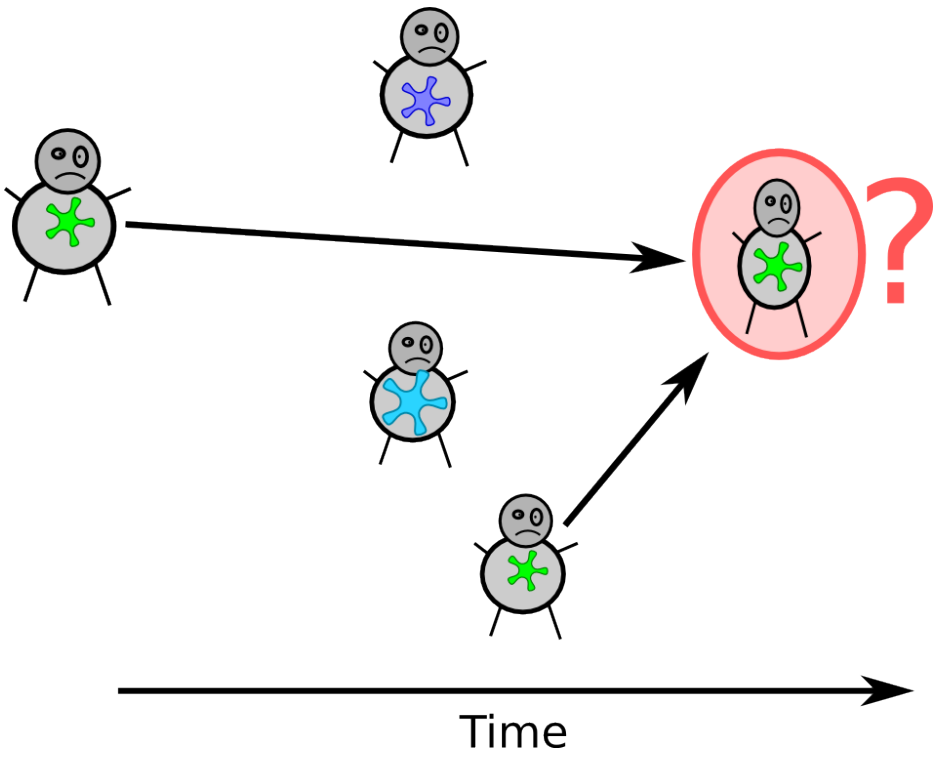
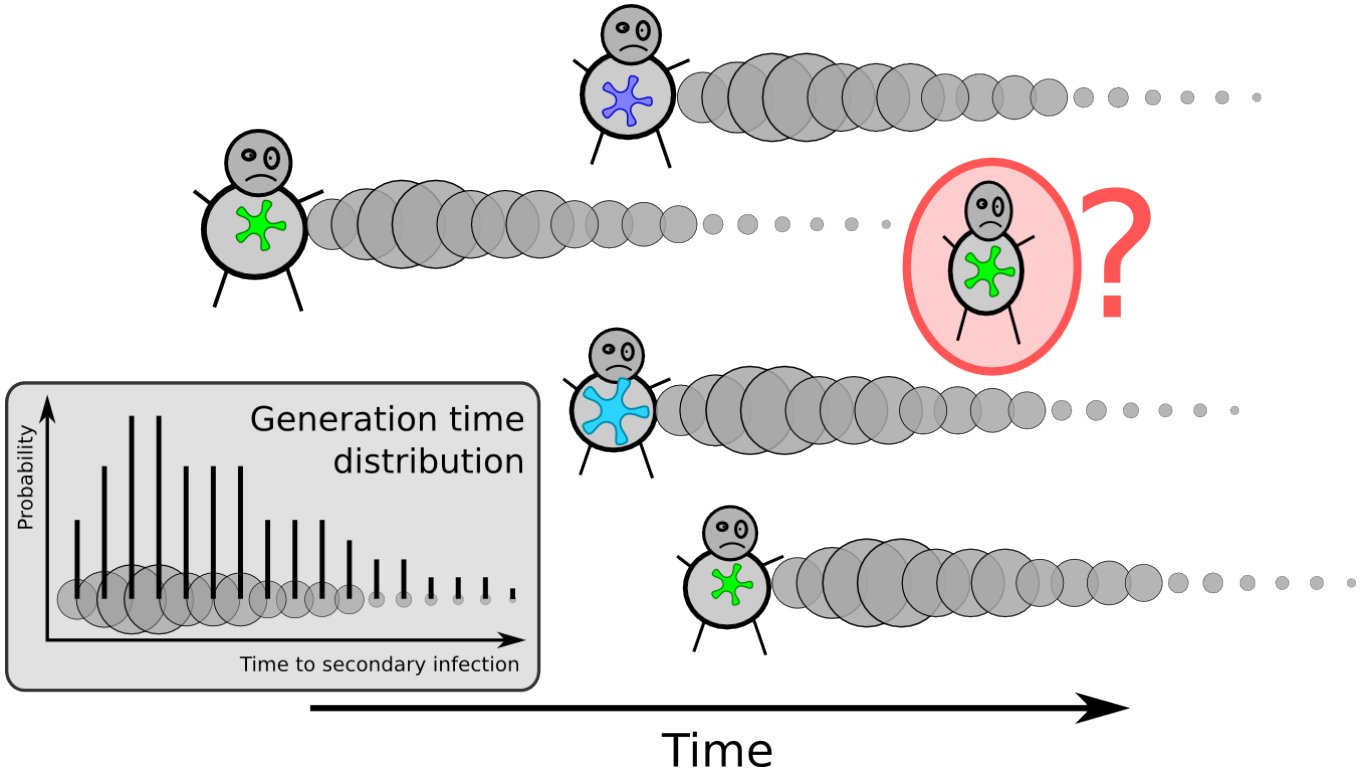


Rationale of the method

outbreaker: use generation time distribution and genetic data:



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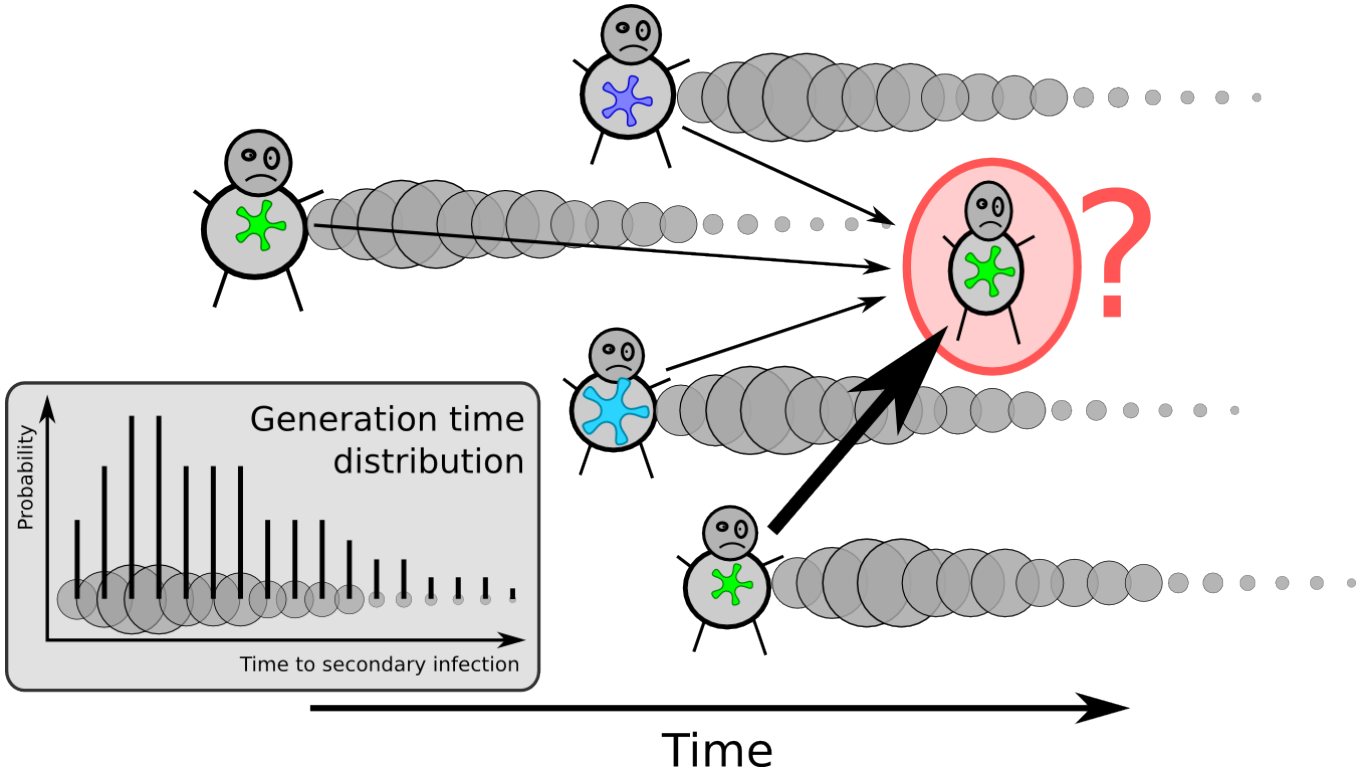

Outline of the model

Likelihood

- branching process:

$$p(\text{transmission tree}) = \prod_{\text{all branches}} p(\text{branches})$$

- $p(\text{branch}) =$
  $p(\text{infection/collection dates}) \times p(\text{genetic differences})$

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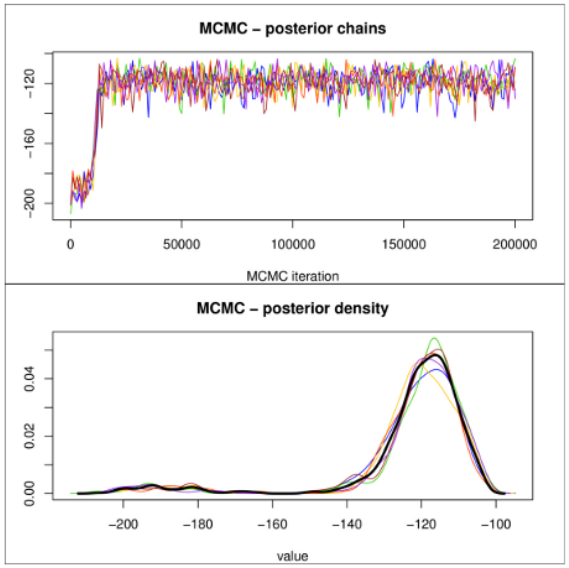
Implementation

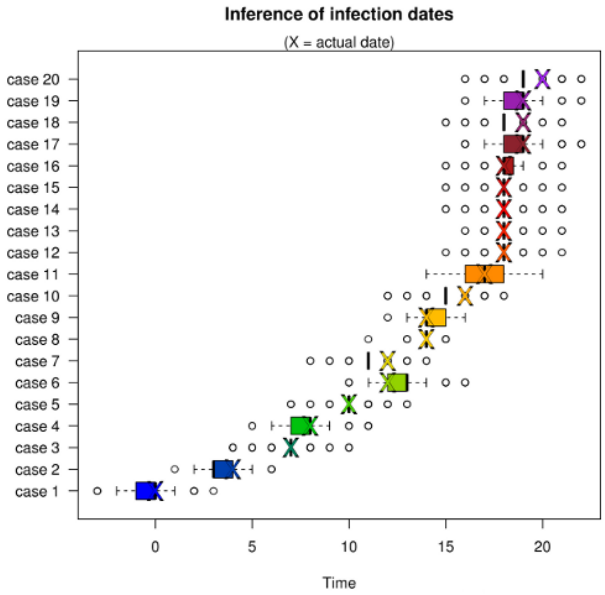
- Bayesian framework
- augmented data for ancestries and unobserved cases
- MCMC (Metropolis-Hasting) for sampling from posterior

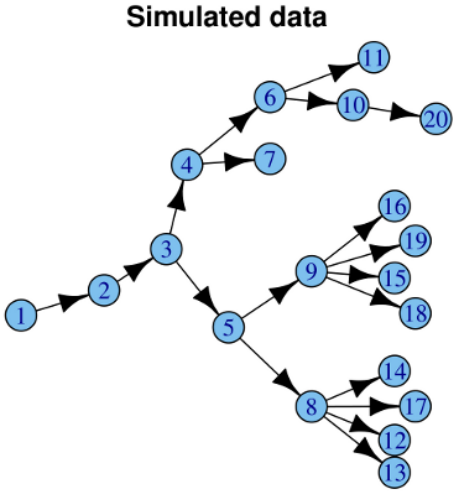
The R package outbreakeR

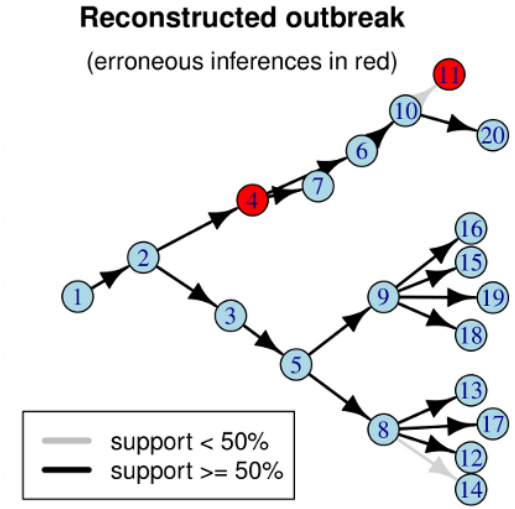
- C implementation embedded within R package
- multi-platform: linux, MacOS X, Windows, Solaris, ...
- supports parallelization
- post-processing of MCMC, simulations, graphics
- tested on wide range of simulations

outbreakeR : some examples





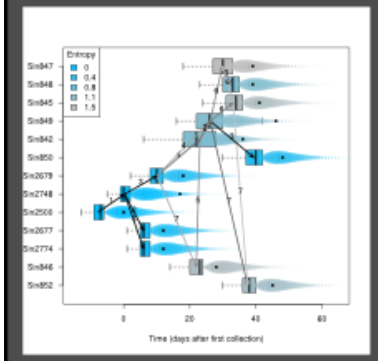




Looking ahead: applications and developments

Applications

SARS 2003 Singapore outbreak



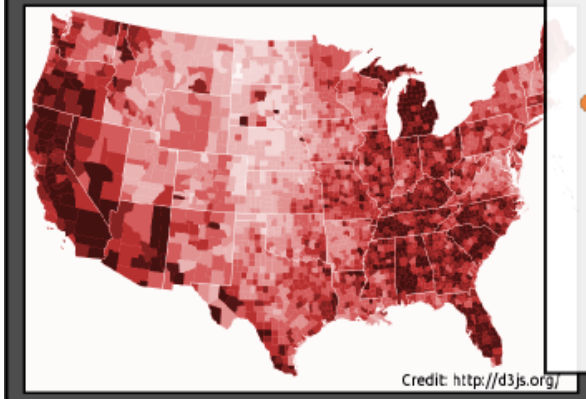
S. pneumoniae carriage
Maela camp, Thaïland

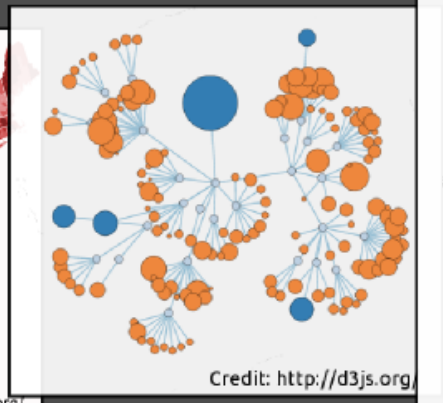
Model improvement

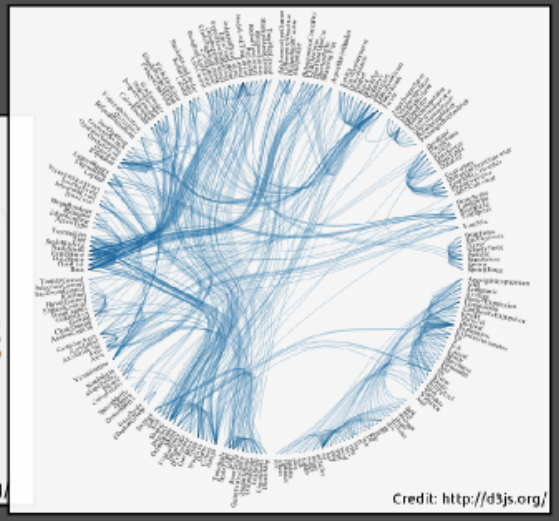
Spatial information, contact networks

New visualization tools

Web-based interactive graphics







Looking ahead: the bigger picture

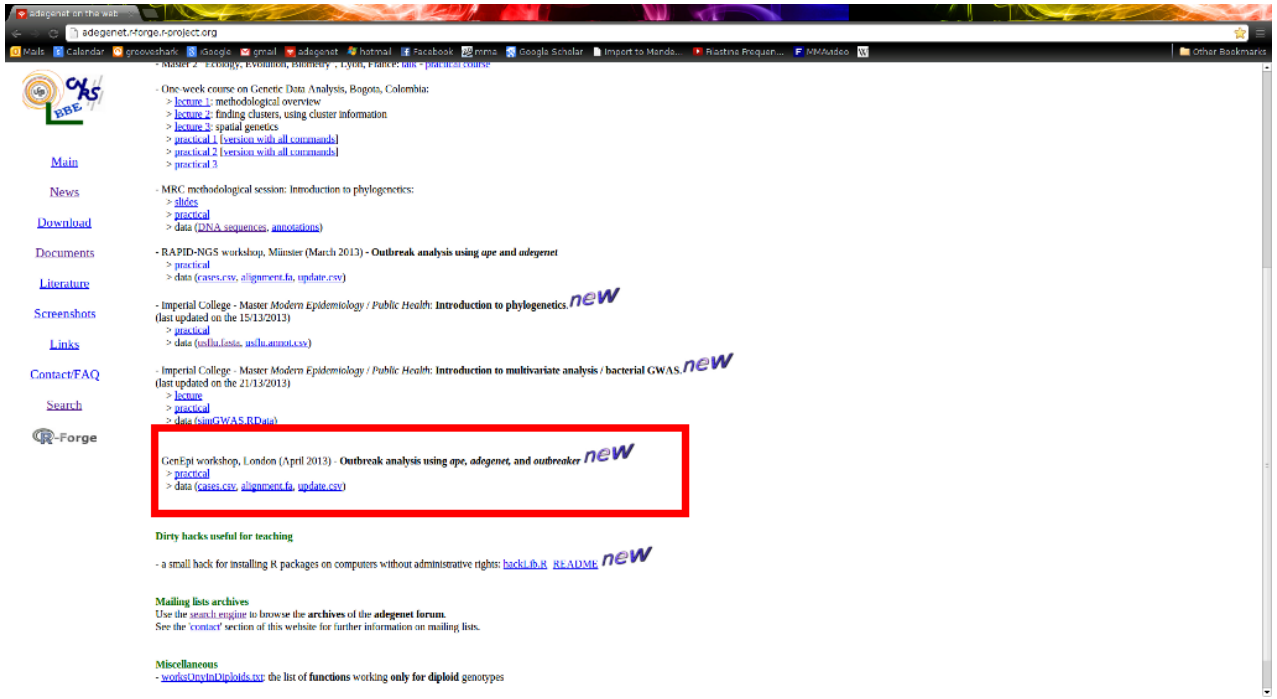
Acknowledgements

- **Organisers**: Anton Camacho & Marc Baguelin
- **Imperial College London:** Anne Cori, Simon Cauchemez, Xavier Didelot, Christophe Fraser, Neil Ferguson, David Aanensen
- **Wellcome Trust Sanger Institute:** Claire Chewapreecha, Sephen Bentley
- **Funding:** MIDAS

- **Thanks for your attention.**

Getting your hands dirty

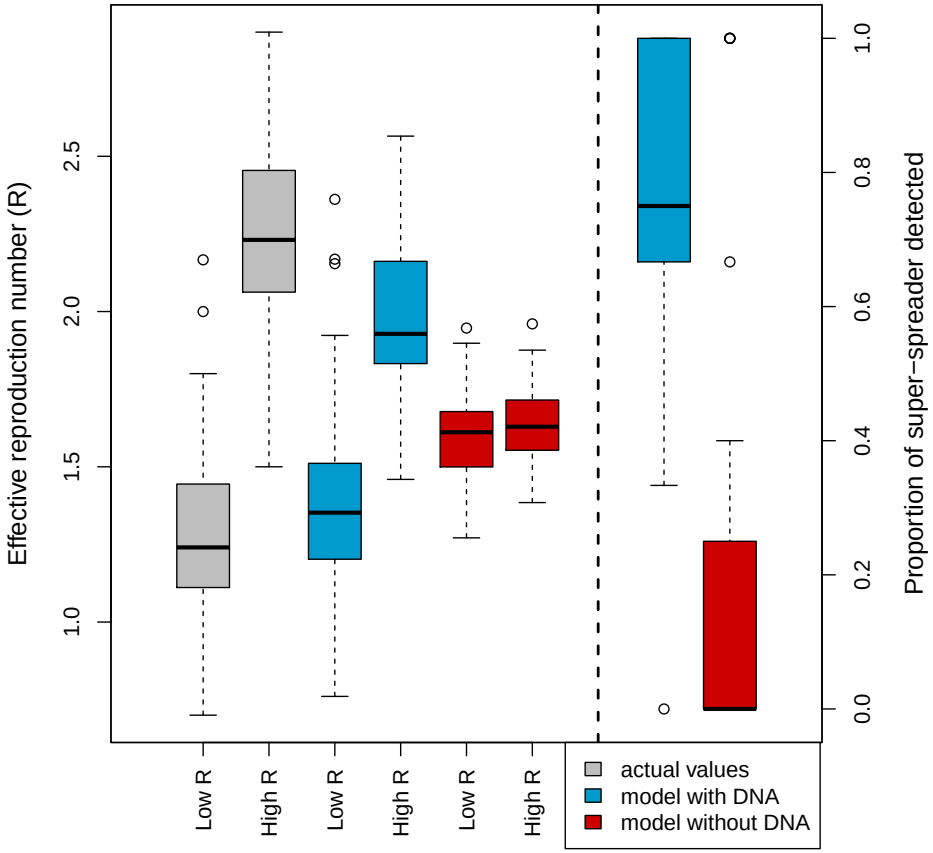
Google "adegenet" → "adegenet on the web" → "Documents" (`http://adegenet.r-forge.r-project.org/`)



Genetic data reveal heterogeneous infectivity

Simulations with structured infectivity

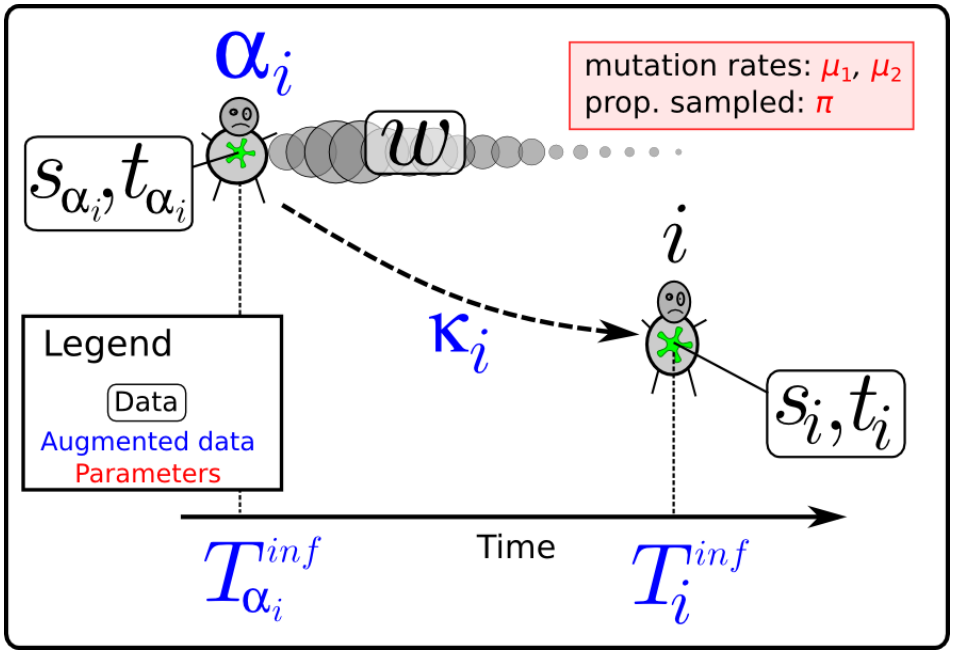
- left: 2 groups of hosts, low/high infectivity ($R_0 = 1.5/3$)
- right: rare super-spreaders ($R_0 = 1.5/20$)



outbreakeR : model notations

Data

- i: index of cases ($i = 1, \ldots, n$)
- s_i: genetic sequence of i
- t_i: collection date for s_i
- w: generation time distribution



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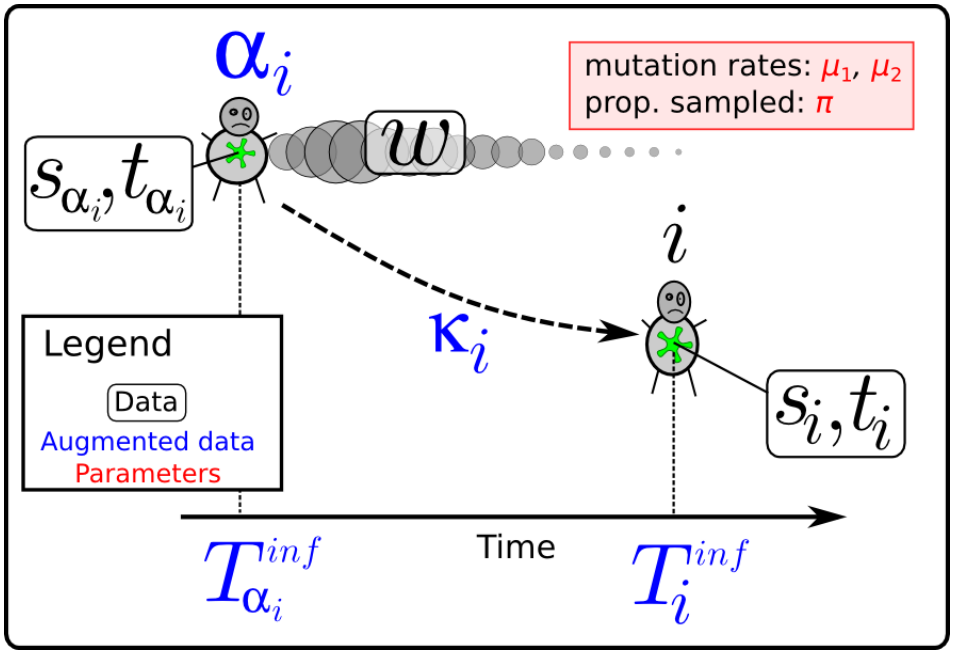

Augmented data

- T_i^{inf}: date of infection of i
- α_i: infector of i
- κ_i: number of generations between i and α_i

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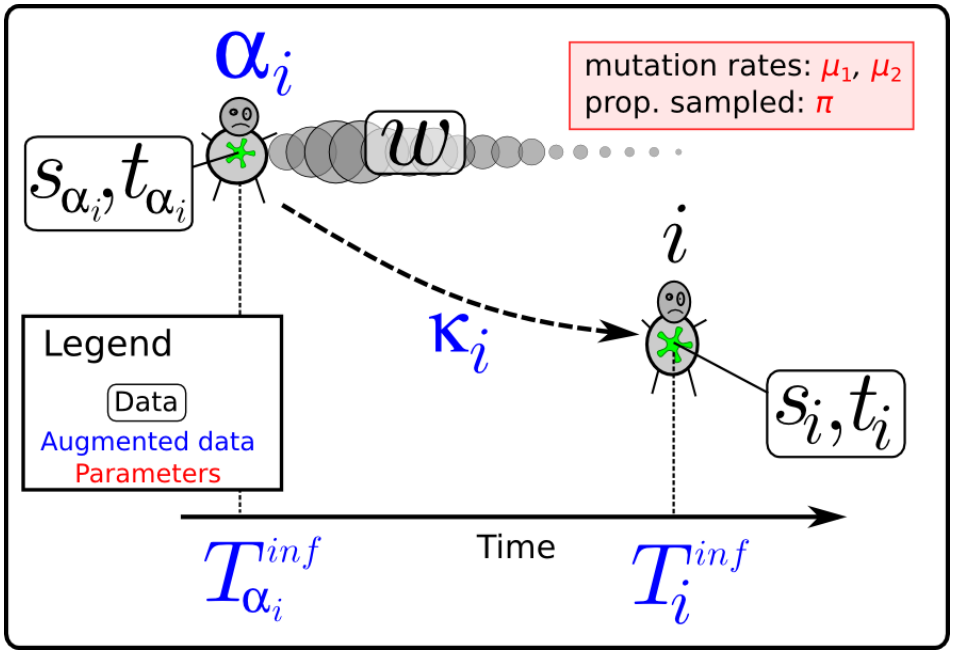

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Parameters

- μ_1, μ_2: rates of transitions and transversions ($\mu_2 = \gamma \times \mu_1$)
- π: proportion of the outbreak sampled

outbreakeR : model definition

- Posterior proportional to joint distribution:

$$
\begin{aligned}
& p(\{s_i, t_i, T_i^{inf}\}_{(i=1,\ldots,n)}, \alpha, \kappa, w, \mu_1, \gamma, \pi) \\
= \; & \underbrace{p(\{s_i, t_i, T_i^{inf}, \alpha_i, \kappa_i\}_{(i=1,\ldots,n)} | w, \mu_1, \gamma, \pi)}_{likelihood} \times \underbrace{p(w, \mu_1, \gamma, \pi)}_{prior}
\end{aligned}
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- Likelihood of case i decomposed as:

$$
\underbrace{p(s_i | \alpha_i, s_{\alpha_i}, \kappa_i, \mu_1, \gamma)}_{genetic} \times \underbrace{p(t_i | T_i^{inf}, w) p(T_i^{inf} | \alpha_i, T_{\alpha_i}^{inf}, \kappa_i, w) p(\kappa_i | \pi)}_{epidemiological}
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$$

- Sampling from posterior distribution using MCMC (Metropolis-Hasting)

Model - detail of likelihoods

- Genetic likelihood:

$$\underbrace{\mathcal{B}\left(d(s_i, s_{\alpha_i})|l(s_i, s_{\alpha_i})\kappa_i, \mu_1\right)}_{transitions} \times \underbrace{\mathcal{B}\left(g(s_i, s_{\alpha_i})|l(s_i, s_{\alpha_i})\kappa_i, \gamma\mu_1\right)}_{transversions}$$

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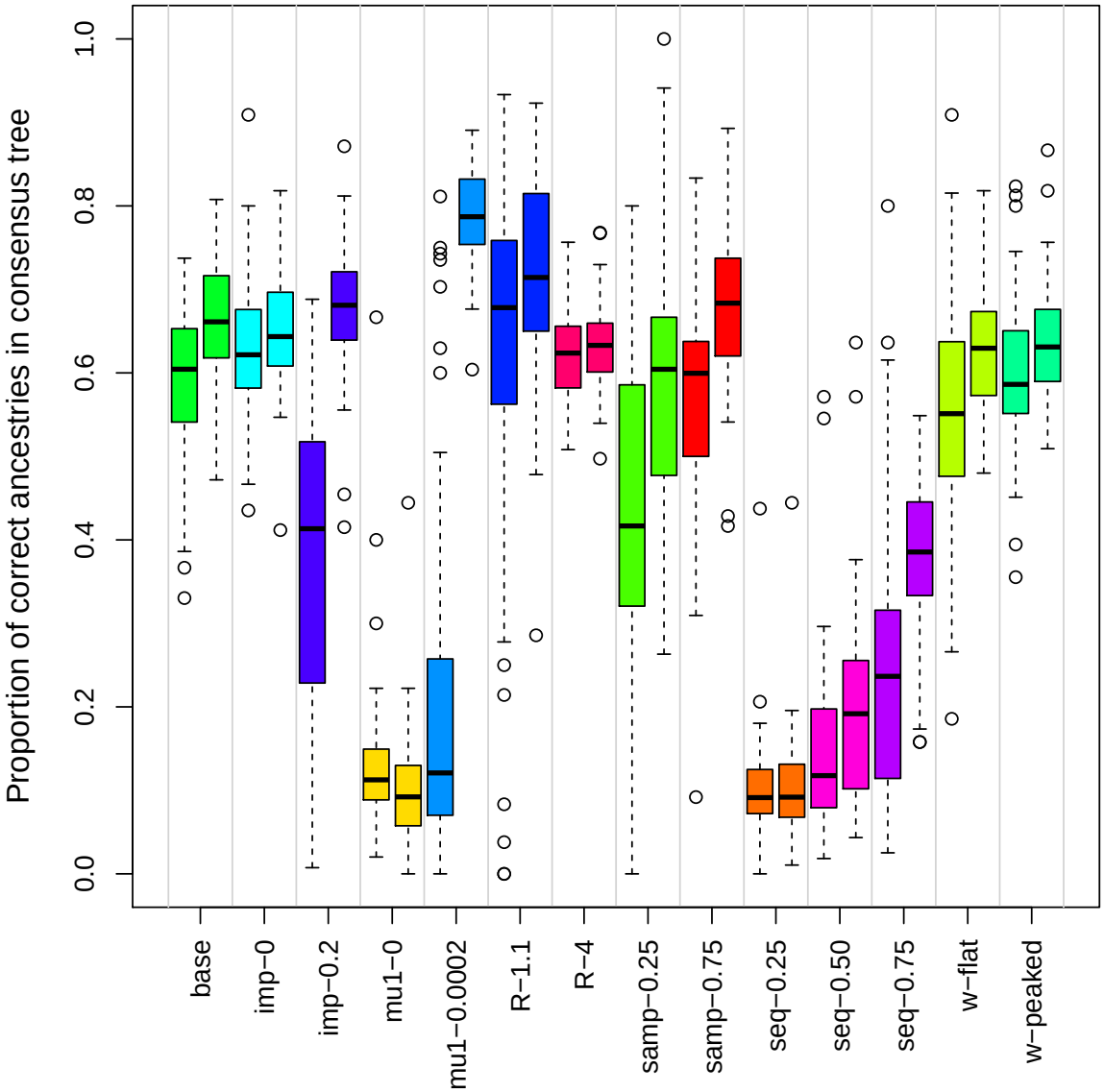
- Epidemiological likelihood:

$$p(t_i|T_i^{inf}, w) \times p(T_i^{inf}|\alpha_i, T_{\alpha_i}^{inf}, \kappa_i, w) \times p(\kappa_i|\pi)$$
$$w(t_i - T_i^{inf}) \times w^{(\kappa_i)}(T_i^{inf} - T_{\alpha_i}^{inf}) \times f_{\mathcal{NB}}(1|\kappa_i - 1, \pi)$$

with:

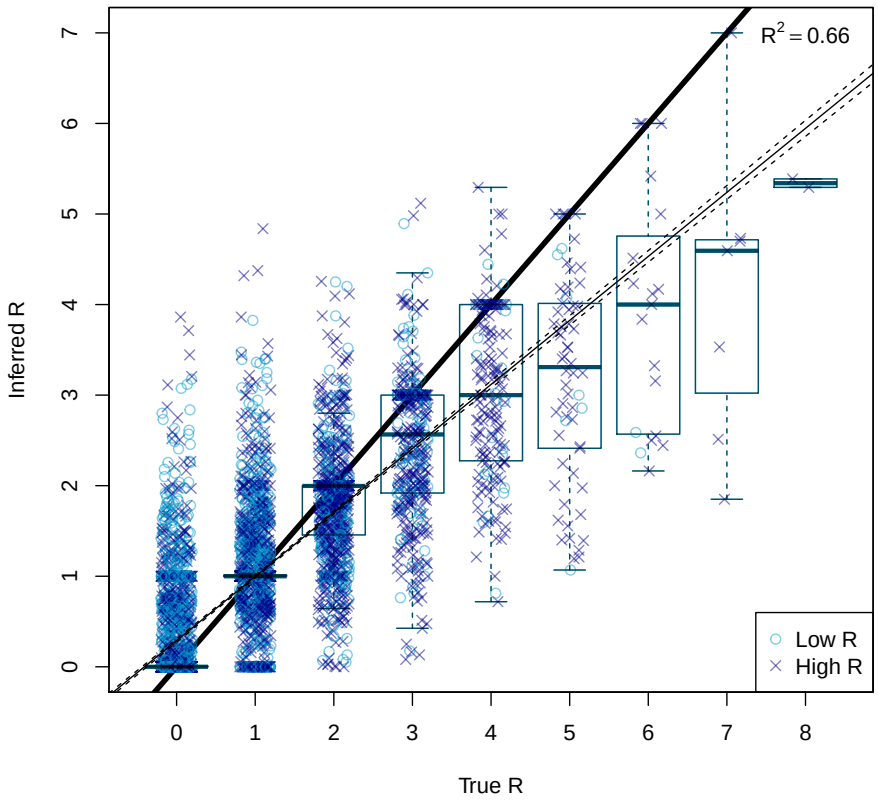
- $w(t_i - T_i^{inf})$: probability of sampling date (assumed prop. to infectiousness
- $w^{(\kappa_i)}(T_i^{inf} - T_{\alpha_i}^{inf})$: probability of infection date ($w^{(\kappa_i)}$ denotes κ_i convolutions of w)
- $f_{\mathcal{NB}}(1|\kappa_i - 1, \pi)$: probability of $\kappa_i - 1$ unsampled cases ($f_{\mathcal{NB}}$: density of the Negative Binomial distribution)

Simulation results: inferrence of correct ancestries



Inferring heterogeneous R: 2-groups simulations

With genetic data:



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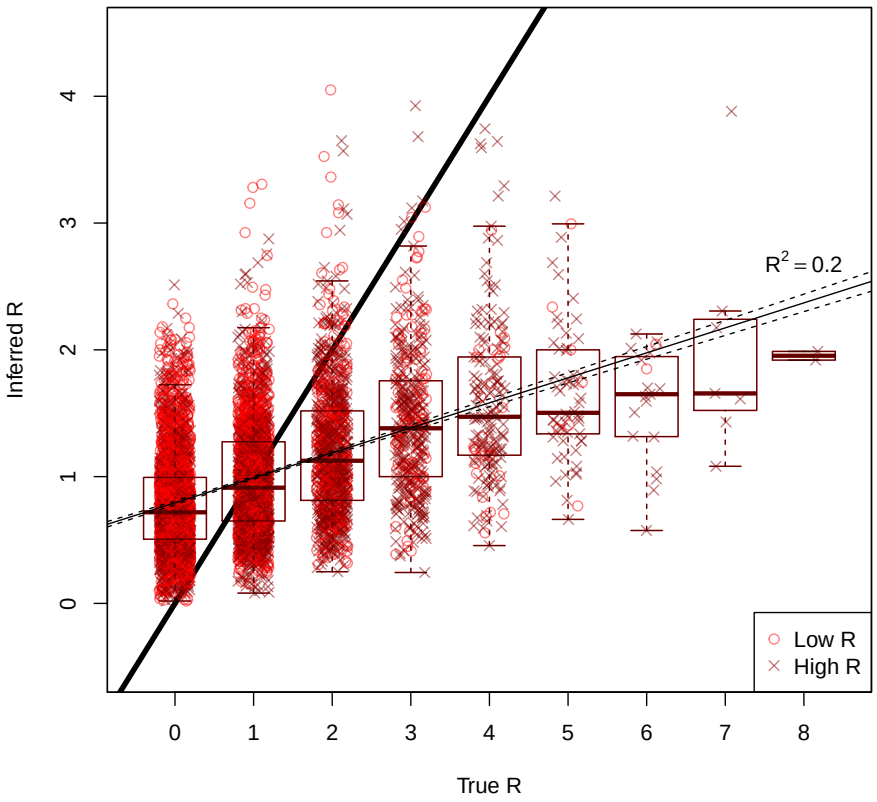

Inferring heterogeneous R: super-spreader simulations

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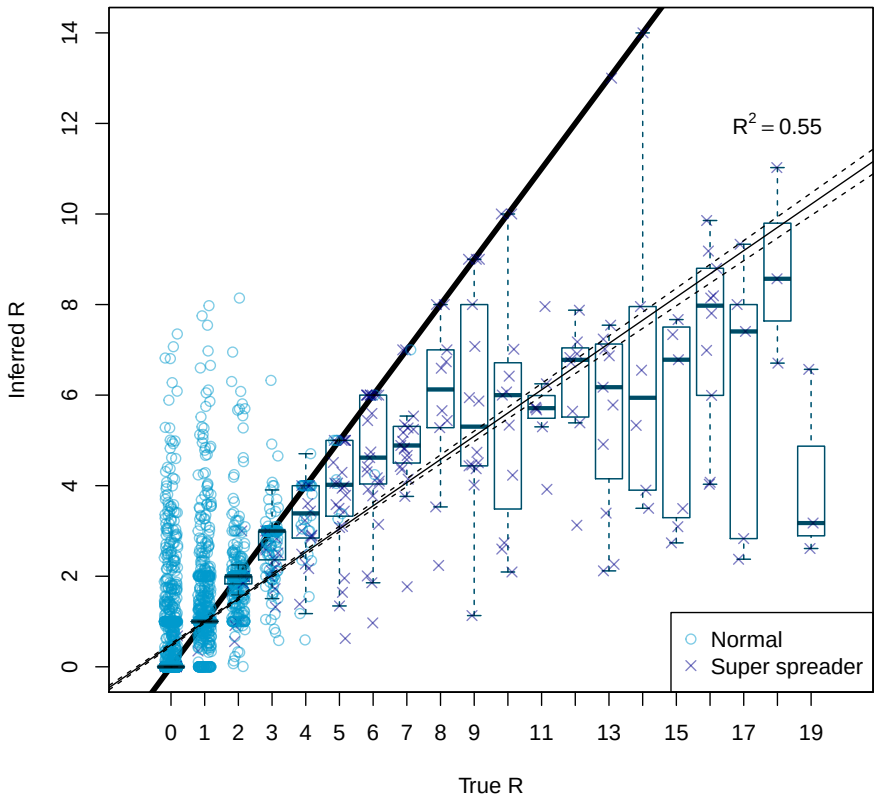

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