

Adding a spatial element to Outbreaker

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Statement of Originality

I certify that this thesis, and the research to which it refers, are the product of my own work, conducted during the current year of the MRes in Biomedical Research at Imperial College London. Any ideas or quotations from the work of other people, published or otherwise, or from my own previous work are fully acknowledged in accordance with the standard referencing practices of the discipline. The Outbreaker model referenced in this thesis is the work of Thibaut Jombart, Anne Cori, Xavier Didelot, Simon Cauchemez, Christophe Fraser and Neil Ferguson at the Department of Infectious Disease Epidemiology at Imperial College London.

Abstract

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Acknowledgements

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Abbreviations

This is where my abbreviations go

Chapter 1

Introduction

Previous work which sought to estimate transmission rates between different groups within a population has involved using large epidemiological datasets to fit different compartmental models for different groups or more intricate modelling of a particular outbreak. Crucially these approaches seek to estimate transmission rates between groups in isolation from other epidemiological properties; this approach relegates the study of group structure to afterthought, to be performed after more pragmatic epidemic and public health properties have been understood.

In this paper we hope to add a spatial framework to an existing general Bayesian model (and corresponding R package Outbreaker) for predicting transmission routes of a pathogen during an outbreak. In the package epidemiological and genetic data collected from outbreaks is used to derive sampled from the posterior distribution of transmission trees, this method could be extended to include further data about the spatial structure of the population to see how well we can estimate parameters representing transmission rates between different groups. Additionally, this spatial structure data may also serve to improve the quality of the model output in situations where genetic data is not present; in the past genetic data has been shown to play an important role in placing constraints on potential transmission trees, making the job of finding the most likely transmission trees easier than with epidemiological data alone. By introducing group structure as part of an effective existing model it is hoped that this will allow the study of the population structure of an outbreak to begin sooner, as well as inviting in any wider benefits that this sort of analysis may bring to other areas of the model.

1.1 Aims

The aim of this project is to see if information about the spatial structure of a population can be added to the Outbreaker model of Jombart (2014),

to help us estimate information about the transmission dynamics between different groups or to further improve the process of deriving transmission tree from the posterior distribution using outbreak data. In certain outbreak scenarios it may be possible to separate the cases of infection into two or more distinct groups, the groups could be defined by what ward a patient is on in a hospital, what class a child is in at school or perhaps whether a case is a child or an adult. An interesting question in this scenario might be whether individuals in the same group are more likely to infect each other and less likely to infect individuals in the other group. We will aim to add a framework to the outbreaker model that allows further parameters to be estimated which may help us answer this question. In this first section I will introduce the Outbreaker package and go through the previous body of work which led up to the development of the Outbreaker model.

1.2 A Brief History

The Outbreaker package uses a Markov chain Monte Carlo process to try and sample from the posterior probability distribution of various parameters and pieces of augmented data. Specifically, it uses DNA sequence data and case data collected from an outbreak along with a generation time distribution and a time-to-collection distribution to infer the likely infector of each case. These likely ancestors can be combined into a transmission tree and if we are fairly confident in the truth of our assembled transmission tree then we can infer further properties about the outbreak from it such as the rate of mutation of nucleotides in the DNA sequence of the pathogen and the effective reproduction numbers of individuals through time.

The Outbreaker model builds upon previous methods that use a similar process of assigning a likelihood value to transmission trees (out of potentially thousands of tree configurations) and then searching for the tree with the maximum likelihood value or using the likelihood of a tree to sample from the posterior distribution of the trees given the data we have collected. The earliest implementation of this approach was Haydon et al, 2002, who proposed a likelihood function for transmission trees that describe the transmission of foot-and-mouth disease between farms in the UK. Their likelihood function for each transmission event is a product of two independent terms. The first term gives a likelihood value based upon whether the timings of the infection between two farms match well. We can assign a value based upon how well the period farm A was infectious during overlaps with the predicted time period that farm B was infected during. The better these time periods overlap, the more likely we think that this infection event is. The second term gives a likelihood value based on how far apart the two farms are, seeing as animals on different farms do not freely mix (especially during an outbreak) then there is only the possibility of an aerial infection

which is more plausible the closer two farms are. For each tree we can consider the likelihood of all of the separate events in the tree and come to an overall likelihood for the tree, Haydon et al proposed an algorithm which would work towards producing the transmission tree with the highest overall likelihood.

As genetic sequencing became faster and cheaper, Cottam et al could expand this model by including a genetic likelihood term. Now that most infected cases could also provide a DNA sequence of the pathogen then the DNA sequences could be compared to see if they can help figure out the ancestor of each case. Infectious diseases mutate quickly and therefore mutations in the DNA sequences can occur during one generation. We can compare the DNA sequences and produce a likelihood that one case is the ancestor of another case depending on how similar the two sampled DNA sequences are, the more similar two sequences are the more likely that one is an ancestor of the other. Cottam et al proceeded by selecting the transmission tree configurations which had the highest genetic likelihoods and then using the previous epidemiological likelihood (based on infection and collection times) to choose 4 final trees which accounted for 95% of the sum of the likelihood for every possible tree. Further alterations to the approach were made by Ypma et al ,2012, who combined the genetic and epidemiological likelihoods into a single term, therefore removing the assumption that the two likelihoods are independent. This is an important assumption to consider because more mutations will occur in a DNA sequence over longer periods of time so we expect that there will be some correlation between the generation times and the number of mutations that we find.

In the same year Morelli et al (2012) used a Markov Chain Monte Carlo (MCMC) approach to sample from the posterior distribution of transmission trees given the collected data. This technique begins with a tree and then moves the suspected ancestors of each case around according to some rules to form a new tree. The likelihood of both of these trees are calculated and the new tree is accepted a sample with a probability based on the ratio of the two likelihoods. The chain and the movement rules are constructed so that the probability of accepting a tree as a sample is equal to the posterior probability of the tree given the data. We can then look at the trees with the highest posterior probabilities or consider the posterior probability that one case is an ancestor of another.

The Outbreaker model is a combination of these approaches, it uses an MCMC approach with independent genetic and epidemiological likelihoods. It also allows for unsampled cases to occur between two cases and a more complex account of the DNA sequence mutations. Unlike the previous approaches it can also be generalised into a package for the programming language R which means it can be run on personal computers by people with less technical computing skills within a reasonable amount of time. In the next section I will briefly introduce Markov Chain Monte Carlo processes

before describing the Outbreaker process in more detail.

1.3 The Outbreaker Model

1.3.1 Markov Chain Monte Carlo Processes

Markov Chain Monte Carlo processes are a combination of two statistical tools, the easiest of the two is Monte Carlo methods. Monte Carlo methods aim to approximate values such as the expected value of a probability distribution by using a large number of samples from that distribution. To work out the expected value of a probability distribution analytically we would integrate over every possible value in the distribution multiplied by the probability of it occurring. Using Monte Carlo methods we would approximate this integration by sampling from the probability distribution thousands of times and taking the mean average of the results. Put simply, Monte Carlo is a way of approximating values of interest given lots of the right samples.

Markov Chains play the role of providing these samples, a Markov Chain is a chain of subsequent states where the next state in the chain is decided by probabilities which are only determined by the current state. A simple discrete Markov Chain may have 3 states called A, B and C, if we are currently in state A then whatever state we move to next only depends on the probability of moving from state A to states B or C (or back to A). If I then move to state B then the fact that I was just previously in state A does not play a role in my decision making about what state I will go to next. If we run certain Markov Chains for long periods of time we will find that they settle into a stationary distribution which determines what the probability of the chain being in each state at any time is. If we have a stationary distribution of interest, such as $p(X = A) = p(X = B) = p(X = C) = \frac{1}{3}$ then we can devise a Markov Chain that will have states A, B and C and this distribution as its stationary distribution, run it for a while until it converges upon this stationary distribution, and then use the values in the Markov Chain as samples from this distribution of interest.

We can use the Metropolis-Hastings algorithm to easily find Markov Chains that have a specified stationary distribution, therefore our stationary distribution could be very complex and we could still use a fairly simple Markov Chain to sample from it. We can then use these stationary distribution samples in our Monte Carlo methods to make approximations about the distribution. Metropolis-Hastings can also be used in a Bayesian setting by specifying the stationary distribution as a posterior distribution of interest. This means that instead of having to find a posterior distribution analytically we can instead use an MCMC process to sample from it and then make inferences about the distribution from our samples. This is what the Outbreaker model does in the specific context of finding the posterior distribution of transmission trees when given outbreak data. The posterior

distribution that the Outbreaker model tries to sample from is complex, yet we can use the relatively straightforward Metropolis-Hastings algorithm to construct a Markov Chain with a stationary distribution equal to our posterior distribution.

1.4 Metropolis-Hastings Algorithm

We can use the Metropolis-Hastings algorithm to sample from our target density π as follows:

- Start with a value X_0 that is from the target density, thus $\pi(X) > 0$.
- We then need a transition density $p(x, y)$ where $p(x, \cdot)$ is the probability density of the next possible states of the Markov chain given that the previous state was x . We then sample a value X_1 from the distribution $p(X_0, \cdot)$.
- We then calculate

$$\alpha(X_0, X_1) = \min \left(\frac{\pi(X_1)p(X_1, X_0)}{\pi(X_0)p(X_0, X_1)}, 1 \right)$$

- We then generate a random variable $U_1 \sim U[0, 1]$, if $\alpha(X_0, X_1) > U_1$ then we accept X_1 as a sample from π . If not then we set $X_1 \leftarrow X_0$ and accept this as a sample.
- We repeat this process for thousands of iterations, saving all of the accepted values in a chain. These values are samples from our target density π .

The need to find the values $\pi(X)$ presents a problem because it requires that we know (or can at least find probability values from) the target distribution which we are trying to sample from and this might not be the case. We can get around this when looking for posterior densities by substituting in the likelihood function which is usually easier to calculate. If our target density is a posterior density of the form $\pi(X|D)$ with parameter X and observed data D then we can write this as

$$\pi(\theta|D) \propto \frac{\pi(D|\theta) \times \pi(\theta)}{\pi(D)}$$

Since D represents fixed data, $\pi(D)$ is a constant and therefore cancels out in the equation for $\alpha(x, y)$ so we are left with

$$\alpha(X_0, X_1) = \min \left(\frac{\pi(D|X_0)\pi(X_0)p(X_1, X_0)}{\pi(D|X_1)\pi(X_1)p(X_0, X_1)} \right)$$

Therefore to use Metropolis Hastings to sample from a posterior distribution we only need to be able to construct the likelihood function and calculate values from the prior densities of our parameters.

1.5 The Outbreaker MCMC Process

Outbreaker uses the Metropolis-Hastings algorithm to sample from the posterior distribution of transmission trees when we have data on an outbreak. There is a transition density that moves around parameters such as the rate of DNA mutation and then accepts or reject the candidate parameter based on the genetic likelihood defined in the outbreaker model. Additionally outbreaker uses augmented data which are pieces of data that are moved around as if they were parameters and accepted or rejected. In the context of outbreaker each case i has an ancestor α_i ; a transition density is used to suggest a new candidate ancestor, the likelihood of this potential ancestry is calculated depending on how well the infection time, spatial and DNA sequence data fit together between the cases. In the next section I will introduce the new group structure data and likelihood and describe how it fits into the current outbreaker model.

Chapter 2

Methods

2.1 Group Data and Parameters

In certain outbreak scenarios individuals might belong to two or more different groups, people in these groups could have different levels of contact between members of their own group and members of other groups. This could lead to different rates of transmission events within and between different groups as a whole. One example of this could be groups of patients on different wards of a hospital, if someone on one ward falls ill it seems plausible that they are more likely to transmit this infection to another patient on their own ward rather than a patient on a different ward. If the outbreak spreads through several wards we could potentially use our knowledge of what ward people are on to assess the probability that one patient infected another and help us construct a plausible transmission tree. Another example could be to separate cases into groups based on their age, several studies have looked into how rates of common cold transmission differ from child to child, child to adult, adult to child and adult to adult [CITE THE STUDIES PLZ].

We can represent these differing rates of transmission between l groups as parameters in an l by l transmission rate matrix where the element λ_{12} is the rate of transmission from group 1 to group 2.

$$\begin{pmatrix} \lambda_{11} & \lambda_{12} & \cdots & \lambda_{1l} \\ \lambda_{21} & \lambda_{22} & \cdots & \lambda_{2l} \\ \vdots & \vdots & \vdots & \vdots \\ \lambda_{l1} & \lambda_{l2} & \cdots & \lambda_{ll} \end{pmatrix}$$

We can then normalise these rates to give us a transmission probability matrix where

$$P_{ij} = \frac{\lambda_{ij}}{\sum_{k=1}^l \lambda_{ik}}$$

is the probability that a newly infected case is in group j given that the ancestor is in group i .

To introduce these parameters into the MCMC process we need to propose a transition density (also known as a "move") that will produce candidate transmission rates and a likelihood function that will be used to accept or reject candidate rates depending on how well they fit the data (in this case the data is a record of what group each case is in).

2.2 Group Likelihood

The existing pseudo-likelihood function of the outbreaker model is composed of the product of the genetic and epidemiological likelihoods. We need to construct a group likelihood function to multiply onto the existing likelihood function, the group likelihood function will give us a likelihood value for the probabilities in our transmission matrix given the observed and augmented data. Some of the observed and augmented data will not play a role in determining how likely the transmission probabilities are, such as the genetic sequences and timings of each case. The data that will play a role are α_i , the index of the ancestor of case i (and their corresponding group) and κ_i , the number of generations between i and α_i .

To write the group likelihood we can think of the transmission event between case i with group g_i and its immediate ancestor α_i with group g_{α_i} as a Bernoulli trial with $P_{g_i g_{\alpha_i}}$ chance of succeeding. We know the group membership of each case and the current candidate ancestor α_i , therefore the likelihood of a transmission event between i and α_i for the candidate transmission rates matrix, denoted L , is given by:

$$\Omega_i^3 = p(g_i = x | \alpha_i, \kappa_i, g_{\alpha_i} = y, L)$$

and the likelihood of a Bernoulli trial is the probability that the event takes place, which can be found by calculating the transmission probability matrix, so for this particular case the likelihood is:

$$\Omega_i^3 = P_{xy}$$

In the Outbreaker model each transmission event is assumed to be independent of other events, therefore the group likelihood for a whole transmission tree is the product of all of the individual likelihoods for each transmission event (or the sum of the group log likelihoods).

$$\Omega^3 = \prod_i \Omega_i^3 = \prod_i P_{g_i g_{\alpha_i}}$$

This likelihood term is multiplied onto the existing likelihood term to give an overall likelihood for a case: $\Omega_i^1 \times \Omega_i^2 \times \Omega_i^3$. This assumes that the group,

epidemiological and genetic likelihoods are all independent. This assumption simplifies the likelihood term but in real outbreak data we would expect to see some correlation between the likelihood terms. For example, if transmission rates really were higher within a group than between other groups we might expect that observed DNA sequences are generally more similar between cases in the same group because mutations that occur between two cases in the same group are more likely to stay within that group, therefore distinguishing the DNA sequences from these cases from those belonging to other groups.

2.3 Transmission Rate Matrix Move

The parameters in the transmission rate matrix are moved one element at a time except for one element on each row which is set to 1 and does not move. The other elements in the row should converge upon a value which is the rate of transmission relative to the constrained rate. New candidate elements are generated from a lognormal distribution:

$$X_{n+1} \sim \text{lognormal}(\log(X_n), \sigma)$$

Where σ is determined by a tuning process which increases or decreases its value based upon the proportion of moves being accepted and rejected. The lognormal distribution is not symmetrical so we need to introduce a correction factor to account for the fact that in the transition density $p(x, y) \neq p(y, x)$. We also need to include the term from our prior distribution for the rate parameter, in this circumstance an exponential prior with a mean of 1000 was chosen. This allows rates to vary considerably but remain above zero and with a decreasing probability approaching 1000, this is sensible when we consider that one element on the row has been fixed to 1 so we would think it was very unlikely that the other rates on the row are as large as 1000. This gives the following process for updating an element in the transmission rates matrix, it is the standard Metropolis-Hastings algorithm except we have taken the logarithm of values to preserve accuracy during computation:

- Using the old rate parameter, θ_n , a candidate rate parameter is chosen: $\theta_{n+1} \sim \text{lognormal}(\log(\theta_n), \sigma)$.
- Calculate the log ratio: $LR = \log(\Omega_3(\theta_{n+1})) - \log(\Omega_3(\theta_n))$
- Add the correction factor for the lognormal distribution:

$$LR + \log(\theta_{n+1}) - \log(\theta_n)$$

- Add the values of the priors for the old and candidate rates:

$$LR + \log(\exp(\theta_{n+1}, \lambda = \frac{1}{1000})) - \log(\exp(\theta_n, \lambda = \frac{1}{1000}))$$

- If $LR > 0$, we accept θ_{n+1} as a sample.
- If $LR < 0$ then we generate a random uniform number, U , then if $\log(U) \leq LR$ then we accept θ_{n+1} as a sample. Otherwise we reject θ_{n+1} and $\theta_{n+1} \leftarrow \theta_n$.

The result of this process is a number of samples of the group transmission rate parameters from the posterior distribution, in the next section we will discuss how we can analyse this output and how we can produce data to test the extended model.

2.4 Analysing the model output

2.5 Simulating Outbreaks With Group Structure

To test the new spatial framework in Outbreaker, we need to be able to fit the model to data which was generated using groups within a population that have varying transmission rates between them. The Outbreaker package also has its own outbreak simulation procedure which we can extend to generate outbreak data that has spatial structure. We can modify the formula which chooses the infector of an infected individual (in the program code this is implemented by first choosing the ancestors and then choosing who has been infected by them), currently the individual is chosen by sampling from a multinomial distribution with probabilities:

$$\frac{w(t - t_i)}{\sum_i w(t - t_i)}$$

where w is the generation time distribution. We can incorporate the probability of transmission within and between members of different groups into these probabilities by supplying a transmission probability matrix. If we continue with the notation g_i as the group of case i and g_{α_i} as the group of the immediate ancestor of case i then we can introduce the group transmission probabilities into the multinomial distribution as follows:

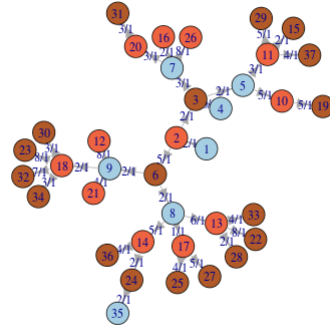
$$\frac{P_{g_i g_{\alpha_i}} \cdot w(t - t_i)}{\sum_i P_{g_i g_{\alpha_i}} \cdot w(t - t_i)}$$

At the start of the outbreak we would have n individuals, n_1 of whom are in group 1, n_2 of whom are in group 2 and so on up to group l . We can then specify the exact numbers in each group (perhaps indirectly through proportions of the population in each group) when the simulation begins. We would also specify the $l \times l$ matrix of transmission probabilities and perhaps we would choose a group which the infection will begin from. Then the procedure takes place just as before but now new cases have different

probabilities of being infected by the existing cases depending on the within and between group transmission probabilities. Finally we can then modify the output of `simOutbreak` to colour the nodes of the transmission tree depending on group so it is easy to see how the outbreak has moved around the group structure. We would also need to come up with a rule for the group membership of imported cases, they could either be assigned to the existing groups at some specified frequency or marked as group unknown which would bring up questions about how to treat these cases in terms of transmission probabilities. In some situations such as hospital wards it might be sensible to take the first approach, our groups might be in one large ward and one small ward so we would expect imported cases to have joined one of the wards and although their ancestors are not present in our transmission tree we expect them to inherit the transmission dynamics of their group once they join one. For the second scenario we would have to decide what would be a sensible transmission probability between each group and a case where the group is unknown, we might assign a "baseline" transmission probability that we use for any cases where one or both of the groups are unknown during a transmission event. This is a better approach if our groups are set within a larger community that has some probability of transmission between the members (this is equivalent to assigning all imported cases to an extra group with equal within and between group transmission). Another benefit of this second approach is that it also provides a way of dealing with cases where group membership data is missing.

Having implemented this method in `simOutbreak`, the user can now pass a matrix to the `simOutbreak` function giving the true values of the transmission probabilities within and between groups, the user must also specify the number of individuals within each group. The number of individuals in each of the groups must sum to the overall number of individuals in the simulation, individuals are then assigned to groups randomly. Imported cases are assigned a group based on the relative sizes of the groups defined by the user. Users can now also colour nodes on the plotted transmission trees by their group membership, this allows us to see how the transmission tree is affected by different group sizes and transmission probabilities. For example, the tree below was created and coloured using three groups with the transmission probability matrix

$$\begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{pmatrix}$$



We can now go on to generate some data to see how the method performs on generated data and data from a real outbreak with spatial structure.

Chapter 3

Results

Chapter 4

Discussion

4.1 Discuss Results

4.2 Modelling Assumptions

This way of modelling group structure makes some simplifying assumptions, it is important to recognise these assumptions and consider how they may effect the interpretation of the model output. The first and main assumption is that the likelihood terms for the genetic, epidemiological and spatial data are independent, this would imply that we expect no correlation between the likelihoods for our data, yet we would actually expect there to be some correlation. We would expect cases which occur around a similar time to have a high epidemiological likelihood of transmission between each other, but this short time frame means that there has not been much time for the pathogen DNA sequences to diverge, therefore we would also see that some of these cases have similar pathogen DNA sequences and a high genetic likelihood between them. As the Markov Chain approaches true transmission events we would see that the likelihoods rise and fall together, rather than being independent of each other. However, combining these likelihoods would be a very tricky process and would inevitably produce a more complex likelihood function, this having consequences in terms of computational effort when we attempt to compute the likelihood function for thousands of moves. It is also hard to gauge what sort of effect this assumption will have on the output of the model without computing a combined likelihood and comparing the results. One possibility is that having separate likelihoods which are correlated could inflate the overall likelihood value for a tree in places where the individual likelihoods are high. This could lead to a likelihood landscape with more drastic peaks and troughs, making it harder for the Markov Chain to jump between these areas of high likelihood.

A second, less worrying assumption is that transmission probabilities between groups remain constant over time. This assumption serves to con-

straint the situations to which this model could be fit, depending on whether the assumption would be violated. In most of the scenarios envisioned such as an outbreak in a hospital ward it is probably safe to assume that the transmission rate between groups stays fairly constant over the period of the outbreak. However, this does rule out the model being used to assess the effectiveness of an intervention on reducing the transmission rates between groups where all of the data comes from the same outbreak. Although data from two outbreaks that are similar in every other respect apart from the presence of an intervention strategy during one of the outbreaks could be used to compare the effectiveness of the intervention strategy at preventing between group transmissions.

4.3 Modelling Limitations

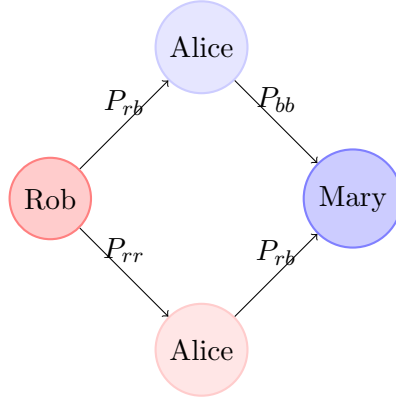
In this section I will discuss constraints placed upon the model by adding the group structure framework and vice versa. The new parameters in the model cannot be considered too helpful if they unduly restrict other parts of the model. In this case the significant restraint place on the rest of the model by the group transmission parameters is that we must assume that there are no unsampled cases between infected individuals, thus limiting the situations in which we can use the extended model to those where we can be sure that we have collected data on every case in an outbreak. These sorts of outbreak would be relatively small and in places where data can easily be collected, thankfully the imagined scenario of different wards in a hospital matches this description.

When we are dealing with transmission between two cases where there are unsampled generation between them we do not know the group membership of the unsampled cases which causes problems when we come to assess the likelihood of this transmission event. For example if Rob is in red ward and Mary is in blue ward and we are considering the group likelihood of a transmission event between them with one unsampled generation, Alice say, then the group likelihood would be the product of two probabilities, that Rob gave the infection to Alice and then that Alice gave the infection to Mary. The problem is that we don't know what group Alice belongs to so we don't know what the relevant group transmission probabilities are.

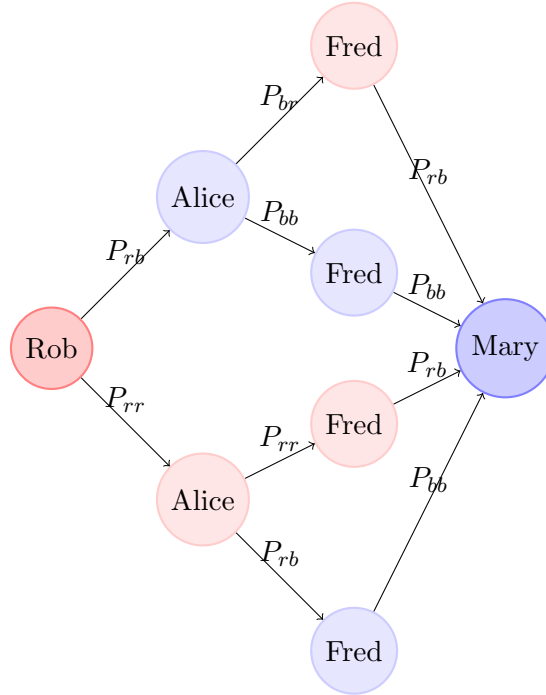
would sum the likelihoods that Rob infected Alice who then infected Mary for the case that Alice is a member of any possible group - in this case red or blue ward.

For small values of κ we can easily calculate the sum of these likelihoods, in the image below the group likelihood that Rob infected Mary would be

$$(P_{rb} \cdot P_{bb}) + (P_{rr} \cdot P_{rb})$$



I have called the unsampled case Alice but in reality we would know nothing about them apart from the fact that we must assume that they belong to one of the groups that we are looking at. For a given value of κ we have to consider 2^κ different potential group combinations so for cases where κ is large we will have to perform a lot of computations. Below is an example for when $\kappa = 2$ by adding Fred to the transmission path.



If we have n groups then calculating the group likelihood for a transmission event with κ unsampled cases between them will require n^κ individual calculations for each possible permutation of the different groups that the unsampled cases might belong to.

Kappa 1 Cartesian co-ordinates Jombart (2014)

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