

Adding a spatial element to Outbreaker

February 24, 2015

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 MCMC - Markov chain Monte Carlo

Chapter 1

Introduction

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. Previous work which has sought to estimate transmission rates between different groups within a population has involved using large epidemiological datasets to fit a different compartmental model for each group, or the creation of bespoke models for specific outbreak scenarios. Crucially these approaches seek to estimate transmission rates between groups in isolation from other epidemiological properties; this approach relegates the study of the spatial structure of an outbreak to an afterthought, to be performed after more pragmatic epidemiological analyses have been undertaken.

In this paper we will 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 samples from the posterior distribution of transmission trees. We will show how this method can be extended to include further data about the spatial structure of the population and see how well we can estimate parameters representing transmission rates between different groups. Additionally, this spatial 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 spatial structure of the population during an outbreak to begin sooner, as well as inviting in any wider benefits that introducing this

spatial framework 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 et al. (2014), to estimate information about the rates of transmission between different groups or to further improve the process of deriving transmission tree samples from the posterior distribution using outbreak data. By adding this framework we will introduce parameters that will estimate these group transmission rates. In this first section we go through the previous body of work which led up to the development of the Outbreaker model before introducing the modelling techniques which are utilised in 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 immediate ancestor 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. These properties include the rate of mutation of nucleotides in the DNA sequence of the pathogen and the effective reproduction numbers of individuals through time (which has important properties concerning the potential of an outbreak to become an epidemic [CITATION HERE Christophe’s review paper?]).

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 over all possible trees given the data we have collected. The earliest implementation of this approach was Haydon et al. (2003), who proposed a likelihood function for transmission trees which might define the spread 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. Haydon et al. (2003) assigned a value based upon how well the period during which farm A was infectious overlaps with the predicted time period during which farm B was infected. The better these time periods overlap, the more likely this

transmission event was. 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, this is more plausible the closer the two farms are. For each tree they considered the likelihood of all of the separate events in the tree and came to an overall likelihood for the tree. Finally, Haydon et al. (2003) proposed an algorithm which would work towards finding the transmission tree with the highest overall likelihood.

As genetic sequencing became faster and cheaper [IS THIS ASSUMED KNOWLEDGE?], Cottam et al [REFERENCE PROCEEDINGS] could expand upon this previous model by including a genetic likelihood term. Now that most case data also included a DNA sequence of the pathogen then the DNA sequences could be compared to see if they could help figure out the immediate ancestor of each case. Infectious diseases mutate quickly, therefore mutations in the DNA sequences can occur between each generation of cases in an outbreak. 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 [ANOTHER CITATION] 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 by Haydon et al. (2003)) to choose 4 final trees which accounted for 95% of the sum total of the likelihood for every possible tree. Further alterations to the model were made by Ypma et al. (2013), 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 certain probability rules to form a new tree. The likelihood of both of these trees are calculated and the new tree is accepted as a sample with a probability calculated from 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 likeli-

hoods. 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 [CITE R PROPERLY] which means it can be run on personal computers by people with less technical computing skills within a reasonable amount of time. To understand the Outbreaker model we must first look at MCMC methods in general and understand how we can use an MCMC method to sample from a specified distribution.

1.3 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:

$$E(X) = \int_{-\infty}^{\infty} x \cdot p(x) dx$$

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:

$$E(X) \approx \frac{1}{N} \sum_{i=1}^N X_i$$

Put simply, Monte Carlo methods are 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 determined only 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, 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 that has this distribution as its stationary distribution. We can run this Markov

chain for a while until it converges upon its stationary distribution and use the values in the Markov Chain as samples from this distribution of interest. MCMC methods combine the two methods by sampling from a Markov chain and then using these samples to estimate properties of their distribution.

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 with 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 The Metropolis-Hastings Algorithm

Voss (2014) describes how 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 $\pi(\theta|D)$ with parameter θ 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. We can now go on to discuss how the new group structure data and group likelihood fit into the current Outbreaker model.

Chapter 2

Methods

2.1 Group Data and Parameters

As previously mentioned, certain outbreak scenarios lend themselves to a model whereby the population is separated into distinct groups, people in these groups could have different levels of contact between members of their own group and members of other groups. This could potentially lead to different rates of transmission within and between different groups. 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 use our knowledge of what ward cases are on to assess the probability that one case infected another and help us construct a transmission tree. Another example could be to separate cases into groups based on their age, several studies have looked into how the probability of common cold transmission differs from child to child, child to adult, adult to child and adult to adult [CITE THE STUDIES PLZ].

We represent these differing rates of transmission between l groups as parameters in an $l \times l$ transmission probability matrix where the element p_{12} is the probability that a case's immediate ancestor is in group 2 given that the case is in group 1.

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

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 probabilities and a likelihood function that will be used

to accept or reject candidate probabilities depending on how well they fit the data on 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. Having defined our group likelihood term we must now decide upon the way in which the Metropolis-Hastings algorithm will move the parameters in the transmission rate matrix to produce new candidate rates.

2.3 Transmission Rate Matrix Move

We implemented a move for the transmission probabilities matrix in the MCMC algorithm which proposes new probabilities for each row of the matrix at a time, l candidate probabilities are sampled from the Dirichlet distribution with concentration parameters equal to the old probability values in the chain multiplied by a constant value. This constant value is increased or decreased to keep the rate of acceptance of the move between 25 and 50% for each row. The Dirichlet distribution is not symmetrical so we need to introduce a correction factor to account for the fact that in the transition density $p(x, y) \neq p(y, x)$. The prior distribution for each row is a symmetric Dirichlet distribution where all concentration parameters are equal and multiplied by a constant provided by the user. The multiplication constant reflects how confident the user is that the probabilities in the matrix are equal, larger values reflect a belief that the transmission probabilities are not equal between groups. 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:

- For row i we take the current probabilities, $\mathbf{p}_n = \{p_{i1}, p_{i2}, \dots, p_{il}\}$ and sample candidate probabilities: $\mathbf{p}_{n+1} \sim \text{Dir}(m\mathbf{p})$ where m is the multiplying constant.
- Calculate the log ratio: $LR = \log(\Omega_3(\mathbf{p}_{n+1})) - \log(\Omega_3(\mathbf{p}_n))$
- Add the correction factor for the Dirichlet distribution, if we define $\text{Dir}(\alpha, \mathbf{x})$ as the probability distribution function of the Dirichlet distribution with concentration parameters α evaluated at the values \mathbf{x} then the correction factor is given by:

$$LR + \log(\text{Dir}(\mathbf{p}_{n+1}, \mathbf{p}_n)) - \log(\text{Dir}(\mathbf{p}_n, \mathbf{p}_{n+1}))$$

- Add the values of the priors for the old and candidate rates, with the user specified constant c and concentration parameter α with elements

α_i all equal this is given by:

$$LR + \log(\text{Dir}(\alpha, \mathbf{p}_{n+1})) - \log(\text{Dir}(\alpha, \mathbf{p}_n))$$

- If $LR > 0$, we accept \mathbf{p}_{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 \mathbf{p}_{n+1} as a sample. Otherwise we reject \mathbf{p}_{n+1} and $\mathbf{p}_{n+1} \leftarrow \mathbf{p}_n$.

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

2.4 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 a population that has groups which have varying transmission rates between them. The Outbreaker package has its own outbreak simulation procedure, `simOutbreak`, which we can extend to generate outbreak data that has the desired 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:

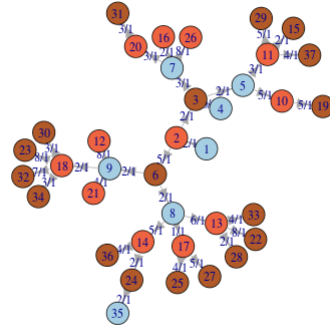
$$\frac{P_{g_i g_{\alpha_i}} \cdot w(t - t_i)}{\sum_i P_{g_i g_{\alpha_i}} \cdot w(t - t_i)}$$

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 which would be

the true, unknown parameters in our model tests. 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. 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 further 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

3.1 Testing Procedures

We tested the extended method on simulated data with a spatial structure generated by the new `simOutbreak` function. The efficacy of outbreaker for reconstructing transmission trees in different situations has been researched before [cite outbreaker paper]. Therefore when testing the extended model we focused on the how well the method detected (inferred?) the spatial structure of the data and whether adding the spatial structure to the model improves transmission tree reconstruction when DNA sequence data is or is not available. In addition to this we tested outbreakers ability to determine the spatial structure of an outbreak in two different situations an outbreak of a rapidly evolving viral infection with a short generation time and an outbreak of a bacterial infection with a longer generation time and slower rate of mutation.

3.2 Simulating an Ebola Outbreak

We tested the method using the imagined scenario of four districts in fairly close proximity in West Africa during the 2014 Ebola Virus Disease (EVD) outbreak. The study of the outbreak led the Team (2014) to hypothesise that the spread of EVD was in part due to a large amount of population movement between cities in bordering countries. In this scenario infected individuals are divided into groups based upon their city of residence and the probabilities of transmission between groups is dependent on the amount people travelling between the two cities. If many people commute between two cities regularly then it is more likely that an individual unknowingly infected with EVD will travel to the other city and transmit EVD to the people who live there during their trip. To make the scenario as realistic as possible the simulated data was created using the properties estimated during the recent analysis by Team (2014).

Parameter	Value	Source
Serial Interval	Gamma distribution with mean = 13.5, s.d. = 9.2	Team (2014)
R_0	1.9	Team (2014)
Mutation Rates	Substitution rate (transversions) per site per day = 5.479452e-06	?

The spatial structure of the data was created by providing a transmission matrix and vector of varying group sizes to the `simOutbreak` function. For the first simulation we used [PARAMETER VALUES HERE] and assessed the proportion of ancestries that were correctly inferred for each dataset when `outbreaker` was run using DNA and spatial data, DNA data alone, spatial data alone and neither of the two types of data. Using the parameters specified in the table above we saw that including spatial data resulted in a modest improvement in the proportion of ancestries correctly reconstructed whether DNA sequences were included or not (and, as seen by Jombart et al. (2014), the proportion of correctly inferred ancestors was much higher when DNA sequence data was included).

VIOLIN PLOT GOES HERE

We also ran `outbreaker` on simulated datasets with different parameters to see if including spatial data was more beneficial to inferring correct ancestries under different conditions such as pathogens with shorter genomes, slower mutations or faster generation times - all of which mean that there will be less mutations observed between cases and therefore DNA sequence data will not be as effective in determining transmission events.

3.3 Equine Flu Data

To test the method on real outbreak data we used some of the dataset of the 2003 equine influenza outbreak in Newmarket provided with the R package `OutbreakTools`, the dataset contains pathogen DNA sequence data and sequence collection dates for 121 individuals in 25 different paddocks. We chose to define the group of each case to be their corresponding paddock number and took a subset of the data from the beginning of the outbreak (to keep group numbers small and the number of individuals in each group reasonable) and tried to reproduce the transmission tree inferred by [Josephs Equine Flu paper].

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 and usefulness 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 therefore 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 has 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 constrain the situations in which this model would be appropriate, 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 placed 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 cases 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.

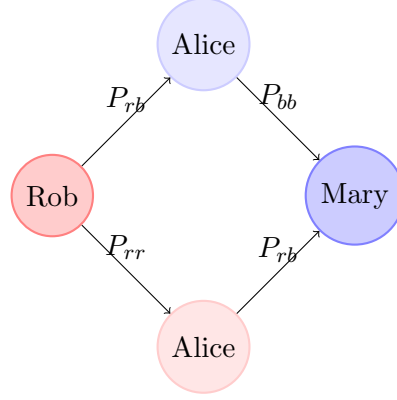
4.4 Not finished yet

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.

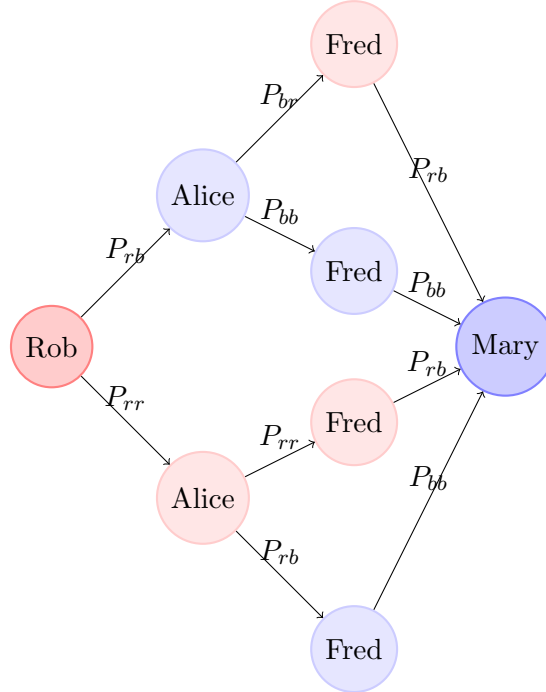
For small values of κ we can easily calculate the sum of these likelihoods, in

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 et al. (2014)

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