Adding a spatial element to Outbreaker

March 10, 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. For this thesis I conceived the new spatial likelihood, programmed this likelihood into the existing code, created all simulations and performed all resulting analysis myself.

Abstract

This is where my abstract goes

Acknowledgements

This is where my acknowledgements go

Contents

Abbreviations

This is where my abbreviations go MCMC - Markov chain Monte Carlo

Chapter 1

Introduction

In recent years new technological advances have made the collection of DNA sequence data fast and cost effective [source - find from other paper claiming same thing]. At the same time new statistical techniques have risen to popularity which take advantage of these new gains in computational power[mcmc for outbreaks paper]. For researchers modelling infectious diseases this has meant a move away from modelling the incidence of a disease in a population to reconstructing specific outbreak scenarios[source]. The aim of this work has been to infer who infected whom from data on cases during an outbreak, this can then tell us other information about the transmission methods of the pathogen. To reconstruct an outbreak, past authors such as [Haydon] have built transmission trees using the locations and infection dates of cases, others such as [Cottam] have used phylogenetic approaches. Further work by [Ypma] and [Jombart] has combined the use of both of these types of data in the same model. When reconstructing outbreaks, one area which has not been investigated is the role in which different groups within a population may effect the transmission dynamics of the outbreak.

In certain outbreak scenarios it may be possible to separate the cases

of infection into two or more distinct groups. For instance [source] investigated [WHATEVER THEY INVESTIGATED]. 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 [source, Cauchemez schools paper?], or the creation of bespoke models for specific outbreak scenarios [Cottam,Ypma etc]. The earliest attempt to infer who infected whom began with Haydon et al. (2003) who devised a technique to reconstruct a foot-and-mouth outbreak in the UK. The cases in this model were animals on farms which meant that it was easy to track which animals had come into contact with one another and when each animal had fallen ill. Later work by Cottam et al. (2008) and Ypma et al. (2013) provided new models which took into account genetic data and were designed for use on outbreaks between human hosts. Around the same time Morelli et al. (2012) used a Markov Chain Monte Carlo approach to attempt outbreak reconstruction, this method is heavily computational and for larger outbreaks with many parameters this method has only become feasible as computing power has increased. Crucially these approaches seek to estimate transmission rates between groups in isolation from other epidemiological properties; this approach relegates the study of the group structure of an outbreak to an afterthought, to be performed after more pragmatic epidemiological analyses have been undertaken.

In this paper I will develop a group framework for an existing method for outbreak reconstruction by [Jombart]. In this approach, epidemiological and genetic data collected from outbreaks are used to infer who infected

who using a computationally intensive Bayesian model. I will show how this method can be extended to include further data about the group structure of the population and see how well I can estimate parameters representing transmission probabilities between different groups. Additionally, this group 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, which speeds up the search for likely transmission trees [Jombart]. By introducing this group framework to an effective existing model it is hoped that this will allow the study of the group structure of the population during an outbreak to begin sooner, as well as improving the model's ability to infer who infected whom in certain situations.

I will measure my success by studying analysing the results of two different simulations. In the first simulation I will test how well my extended model infers the group transmission probability parameters. In the second simulation I will consider whether adding the group framework to the model has helped with the model's original task of outbreak reconstruction. In the Methods section I will discuss in more detail the methods used in previous outbreak construction models. I will then explain the techniques used in the Outbreaker method and show how I have added to them.

Chapter 2

Methods

2.1 Past Models

The Outbreaker package by Jombart et al. (2014) 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 dates of disease onset or dates of DNA sequence collection obtained 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, the average number of secondary cases caused by each case, of individuals through time (which has important properties concerning the potential of an outbreak to become an epidemic, see Grassly and Fraser (2008)).

The Outbreaker model builds upon previous methods by Haydon et al.

(2003), Cottam et al. (2008),Morelli et al. (2012) and Ypma et al. (2013) that use a similar process of assigning a likelihood value to transmission trees (out of potentially millions 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 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 more affordable, Cottam et al. (2008) 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 infer the immediate ancestor of each case. Many 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. This likelihood depends on how similar the two sampled DNA sequences are, the genetic likelihood of one case being the ancestor of another is higher when their DNA sequences are more similar. Cottam et al. (2008) 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. A new model was formulated 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.

Simultaneously, 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 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 has also been written as a package for the programming language R (R Core Team (2014)) 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.

2.2 Bayesian Statistics

Before covering MCMC methods it is necessary to cover some basic concepts of Bayesian statistics.

2.3 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 use a large amount of samples from specific probability distributions, these samples may then be used for other purposes such as aproximating parameters of a probability 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:

$$E(X) = \int_{-\infty}^{\infty} x \cdot p(x) dx \tag{2.1}$$

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:

$$E(X) \approx \frac{1}{N} \sum_{i=1}^{N} X_i \tag{2.2}$$

Put simply, Monte Carlo methods are a way of approximating values of interest given a large amount of samples from a specific probability distribution.

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 find Markov Chains that have a specified stationary distribution, as described in [source mcmc in practice]. 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.

2.4 The Metropolis-Hastings Algorithm

Voss (2014) describes how we can use the Metropolis-Hastings algorithm to sample from our target density τ as follows:

- Start with a value X_0 that is from the target density, thus $\tau(X) > 0$.
- 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

$$\alpha(X_0, X_1) = min\left(\frac{\tau(X_1)p(X_1|X_0)}{\tau(X_0)p(X_0|X_1)}, 1\right) \tag{2.3}$$

- 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 τ. 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 τ.

The need to find the values $\tau(X)$ 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 $\tau(\theta|D)$ with parameter θ and observed data D then we can write this as

$$\tau(\theta|D) = \frac{\tau(D|\theta) \times \tau(\theta)}{\tau(D)} \propto \tau(D|\theta) \times \tau(\theta) \tag{2.4}$$

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

$$\alpha(X_0, X_1) = min\left(\frac{\tau(D|X_0)\tau(X_0)p(X_1|X_0)}{\tau(D|X_1)\tau(X_1)p(X_0|X_1)}\right) \tag{2.5}$$

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.

2.5 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, group, and DNA sequence data fit together between the cases. We can now go on to to discuss the new group structure data and group likelihood.

2.6 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, there is some evidence from Glass et al. (2011) that the reproduction numbers for adults and children differ for pandemic influenza outbreaks, suggesting that transmission rates within and between adults and children may differ.

We represent these differing rates of transmission between l groups as parameters in an $l \times l$ transmission probability matrix where the element m_{ij} is the probability that a case's infector is in group j given that the case is in group i.

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

To introduce these parameters into the MCMC process we need to define a likelihood function that will be used to accept or reject candidate probabilities depending on how well they fit the data and a transition density (also known as a "move") that will produce candidate transmission probabilities.

2.7 Group Likelihood

The existing likelihood function of the outbreaker model by Jombart et al. (2014) is composed of the product of the genetic and epidemiological likelihoods. The genetic likelihood between a case i and a proposed ancestor α_i is given by:

$$\Omega_i^1 = p(s_i|\alpha_i, s_{\alpha_i}, \kappa_i, \mu) \tag{2.6}$$

Where s_i is the DNA sequence of case i, s_{α_i} is the DNA sequence of case α_i, κ_i is the number of unsampled cases between i and α_i, and μ is the rate

of mutation of the DNA sequences of the pathogen.

The epidemiological likelihood between a case i and a proposed ancestor α_i is given by:

$$\Omega_i^2 = p(t_i|T_i^{inf})p(T_i^{inf}|\alpha_i, T_{\alpha_i}^{inf}, \kappa_i)p(\kappa_i|\pi) \tag{2.7}$$

Where t_i is the collection date of s_i, T_i^{inf} is the collection date of s_i, $T_{\alpha_i}^{inf}$ is the collection date of s_{α_i}, and π is the proportion of sampled cases from the outbreak.

Jombart et al. (2014) then define their full likelihood as:

$$\Omega_i^1 \times \Omega_i^2 \times p(\alpha_i) \tag{2.8}$$

To write the group likelihood, Ω_i^3, 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, M, is given by:

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

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 indepen-

dent 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.

2.8 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. Because the Dirichlet distribution is not symmetrical we need to introduce a correction factor. The probability distribution function for the Dirichlet distribution for K probabilities with concentration parameters $(\alpha_1, \cdots, \alpha_K)$ is given by:

$$Dir(\alpha, x) = \frac{1}{B(\alpha)} \prod_{i=1}^{K} x_i^{\alpha_i - 1} \tag{2.9}$$

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 prior 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, $\mathbf{p}_n = \{p_{i1}, p_{i2}, \cdots, p_{il}\}$ and sample candidate probabilities: $\mathbf{p}_{n+1} \sim Dir(x; m\mathbf{p})$ where m is the multiplying constant.

- Calculate the log ratio:

$$\begin{aligned} &\log(\Omega_3(\mathbf{p}_{n+1})) - \log(\Omega_3(\mathbf{p}_n)) \\ &+ \log(Dir(\mathbf{p}_{n+1}; \mathbf{p}_n)) - \log(Dir(\mathbf{p}_n; \mathbf{p}_{n+1})) \\ &+ \log(Dir(\alpha; \mathbf{p}_{n+1})) - \log(Dir(\alpha; \mathbf{p}_n)) \end{aligned} \tag{2.10}$$

Where $\log(\Omega_3(\mathbf{p}_{n+1})) - \log(\Omega_3(\mathbf{p}_n))$ is the ratio of the group likelihoods

of the old and new parameters and

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

is the correction factor for the proposal distribution, and

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

are the values of the prior distributions with the user-specified multiplication constant c and concentration parameter α with α_i all equal.

- If the log ratio is greater than 0, we accept $\mathbf{p}_{n+1}$ as a sample from the posterior distribution
- If the log ratio is less than 0 then we generate a random uniform number, U, and if $\log(U)$ is less than or equal to the log ratio then we accept $\mathbf{p}_{n+1}$ as a sample from the posterior distribution. If the log ratio is less than 0 and $\log(U)$ then we reject $\mathbf{p}_{n+1}$ and draw a new candidate $\mathbf{p}_{n+1}$.

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.

2.9 Simulating Outbreaks With Group Structure

To test the new group 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 tranmission 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 group 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. Imported cases are assigned to the existing groups with a probability proportional to the relative sizes of the groups, here we are assuming a scenario where imported cases inherit the group transmission probabilities of a group once they join it.

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 group structure.

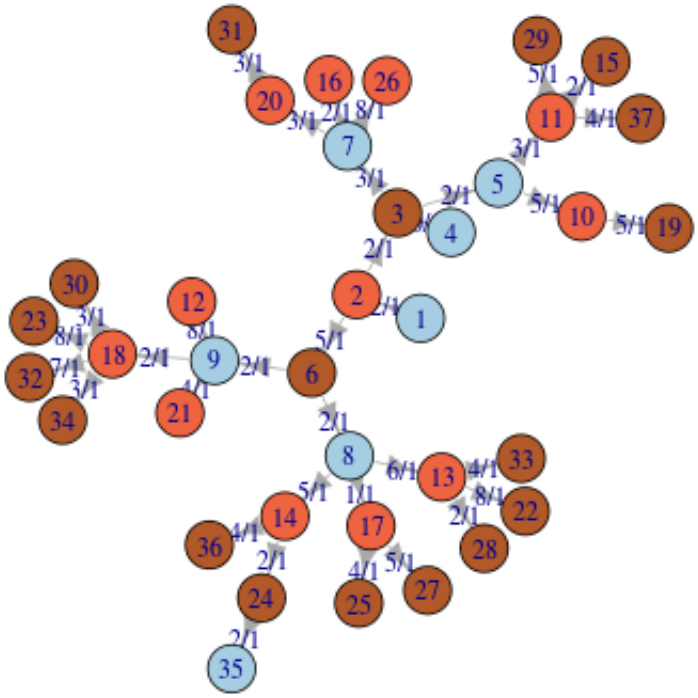


Figure 2.1: A transmission tree constructed from a randomly generated outbreak using the group transmission probability matrix defined above. The direction of arrows between nodes determines the direction of infection. The nodes are coloured by the group of the individual

Chapter 3

Results

3.1 Testing Procedures

We tested the extended method on simulated data with a group structure generated by the new `simOutbreak` function. As explained in the Introduction, I ran two different simulations which tested different aspects of the new group framework. The first simulation aimed to see how well outbreaker estimated the transmission probabilities parameters. To do this ran the extended outbreaker model on datasets where the original outbreaker model already does a good job of inferring correct ancestries. From this I can see if outbreaker does a good job at inferring transmission probability parameters when it infers correct ancestries. The second simulation aimed to see whether the group framework can improve the inference of correct ancestries on datasets where the original outbreaker model does not perform very well. If we give outbreaker strong prior parameters with regards to the group structure of the data, does this help outbreaker infer correct ancestries?

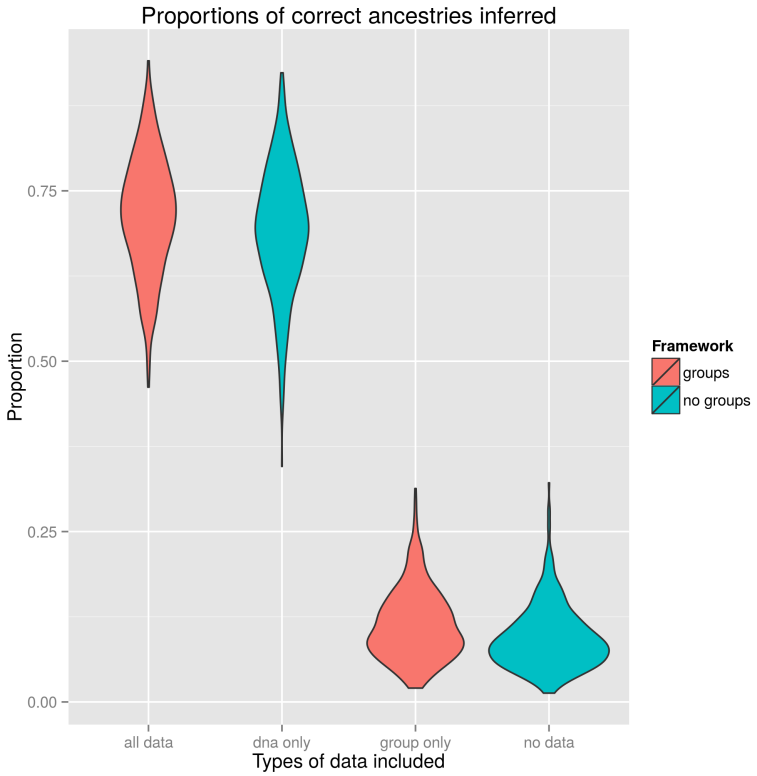
3.2 Simulation 1: Estimating Transmission Probabilities

For the first set of simulations we required datasets where outbreaker could already infer the majority of correct ancestries, we could then give outbreaker the group data and an uninformative prior and see how well the posterior distributions of the transmission probability parameters capture the group dynamics of the data.

We used an imagined scenario of collecting outbreak data from districts within a city in West Africa during the 2014 Ebola Virus Disease (EVD) outbreak. The study of the outbreak led the WHO Ebola Response Team (2014) to hypothesise that the geographical spread of EVD was in part due to a large amount of population movement between cities in bordering countries. We aimed to recreate this migration led transmission on a smaller scale between districts in a city. We simulated datasets where infected individuals are divided into groups based upon their district of residence and the probabilities of transmission between groups is dependent on the amount people travelling between the two districts. If many people commute between districts A and B regularly then it is more likely that an individual unknowingly infected with EVD will travel from district A to district B (or vice versa) and transmit EVD to the people who live there during their trip. To make the scenario as realistic as possible we used the estimated epidemiological properties of EVD estimated during the recent analysis by WHO Ebola Response Team (2014).

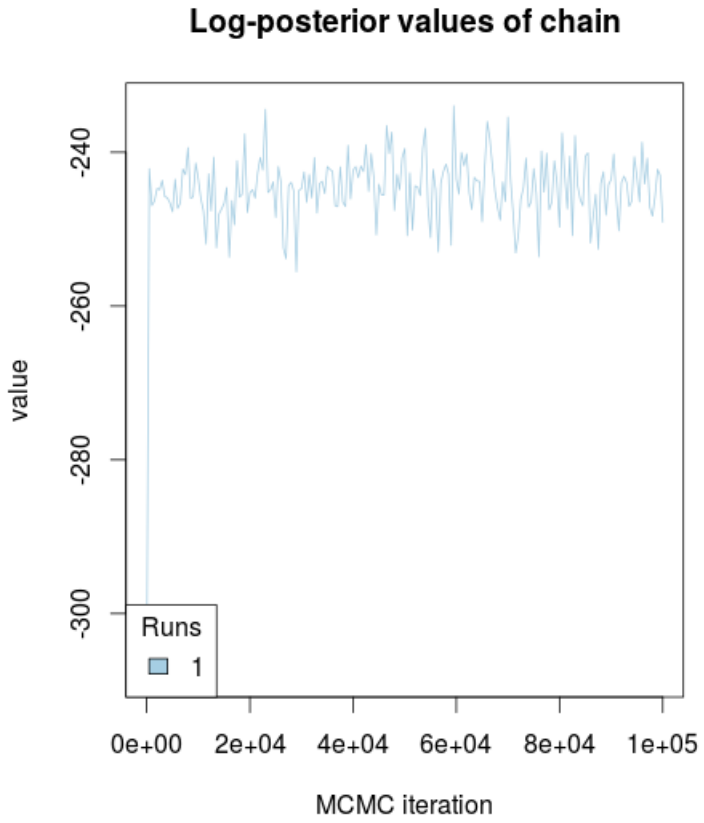
Parameter	Value	Source
Serial Interval	Gamma distribution with mean = 13.5, s.d. = 9.2	WHO Ebola Response Team (2014)
$R0$	2.1	WHO Ebola Response Team (2014)
Mutation Rates	Substitution rate per site per day = 5.479452e-06	Gire et al. (2014)
Sequence Length	19000 bases	Volchkov et al. (1999)

We simulated 440 datasets using these parameters and ran several instances of outbreaker on each dataset. I discarded 14 datasets where there was not at least one case from each group in the outbreak leaving 426 datasets and corresponding results. For each dataset outbreaker was run using DNA and group data, DNA data only, group data only and neither of the two types of data (leaving only dates of symptom onset and the epidemiological likelihood of the model). We then analysed the proportion of correct ancestries inferred on each run for each dataset to check that the transmission tree was adequately inferred using DNA sequence data alone and that the outbreaker model including the group framework was behaving correctly. The violin plot below shows the proportions of correct ancestries by each run over all of the simulated datasets. In line with previous results from Jombart et al. (2014), outbreaker infers a much higher proportion of correct ancestries when DNA sequence data is included. Comparing runs with and without group data also shows that the outbreaker model including the group framework performs as well as, if not very slightly better, than the original outbreaker model. We also checked the convergence of the model



Impact of group framework on proportion of correct ancestries inferred

Figure 3.1: This violin plot shows the distribution of the proportion of correctly inferred ancestries in the consensus ancestries of outbreaker runs with difference parameters.



Mixing quality of an extended outbreaker run

Figure 3.2: This plot shows the values of the log-posterior density at every 500 steps of the chain for an example run of the extended outbreaker model on a simulated dataset

likelihood including the group likelihood for several datasets to ascertain that the model with the group data was mixing well and converged upon a posterior distribution suitably, an example of one of these MCMC traces is shown below. The outbreaker runs including group data had uninformative priors that suggested that all group transmission probabilities are equal. Once we were satisfied that the extended outbreaker model was running properly we could then begin to scrutinise the posterior density samples for the transmission probability parameters. Each simulation was generated us-

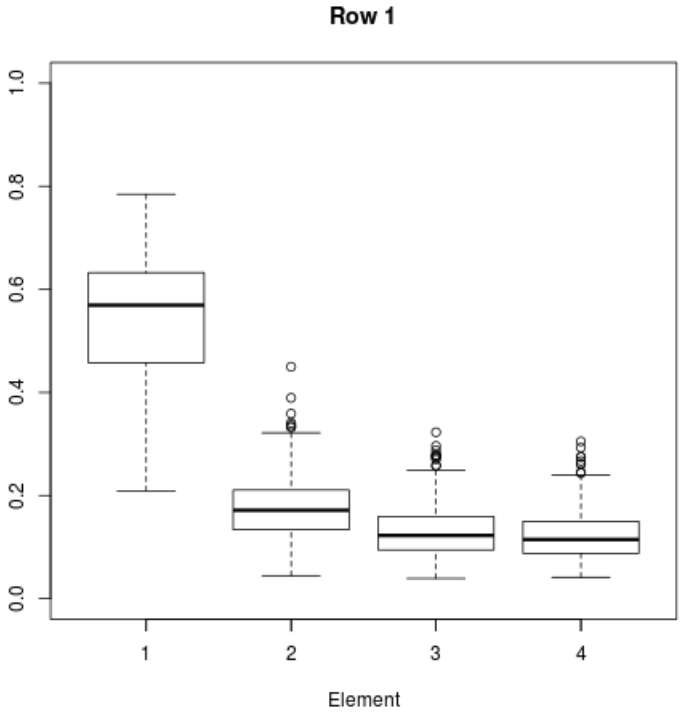
ing the same transmission probability matrix but the number of cases varied so the simulations as a whole should give a good idea of how well the parameters are inferred in a variety of situations. Our first step in evaluating the posterior samples for each run was to see in the true parameter value (used to generate the dataset) fell inside the 95% equal-tails interval, we then counted how many times this occurred for each parameter over all of the simulations to give us a rough idea of how often outbreaker infers a posterior distribution with a reasonable probability of giving the true parameter value. The matrix of true transmission parameters is as follows:

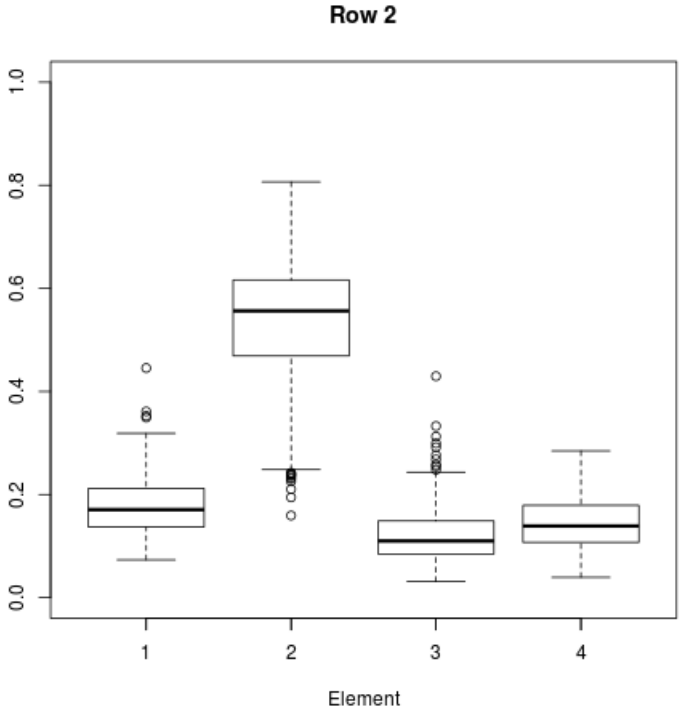
$$\begin{pmatrix} 0.65 & 0.1 & 0.15 & 0.1 \\ 0.1 & 0.6 & 0.1 & 0.2 \\ 0.05 & 0.15 & 0.4 & 0.4 \\ 0.15 & 0.05 & 0.4 & 0.4 \end{pmatrix}$$

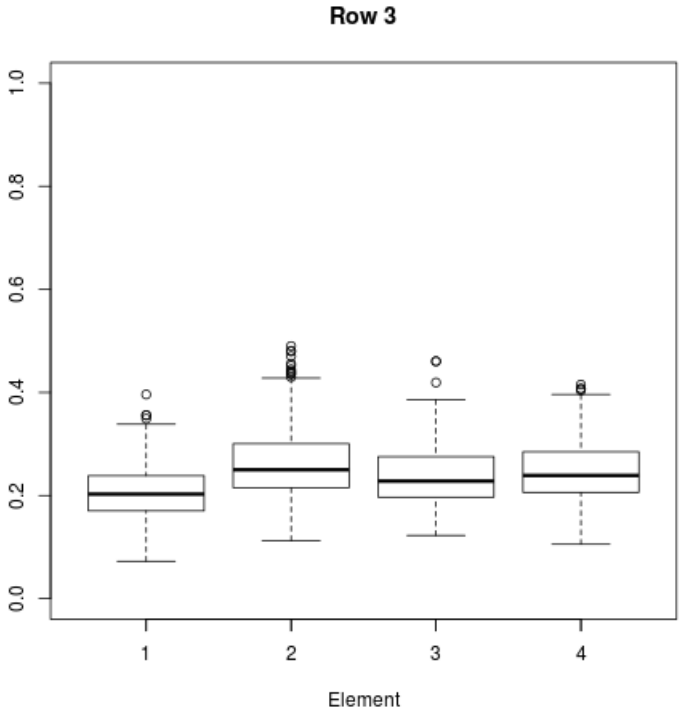
The matrix below shows the corresponding proportion of times that the true parameter was within the 95% equal-tails interval of each run.

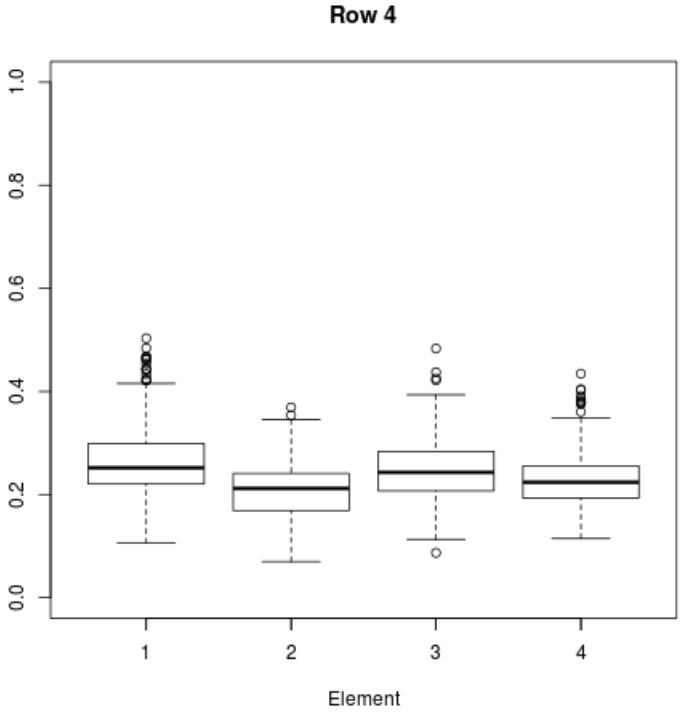
$$\begin{pmatrix} 0.8 & 0.87 & 0.97 & 0.99 \\ 0.86 & 0.89 & 0.99 & 0.89 \\ 0.54 & 0.88 & 0.88 & 0.91 \\ 0.89 & 0.48 & 0.91 & 0.87 \end{pmatrix}$$

We also calculated the posterior sample median for each transmission probability parameter and produced a boxplot to describe where the sample medians fell over all of the simulations:


Row 1
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Element

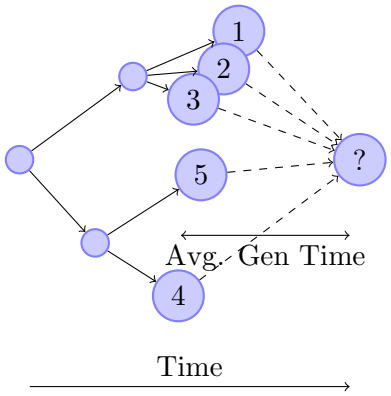

Row 2
1.0
0.8
0.6
0.4
0.2
0.0
1
2
3
4
Element


Row 3
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
Element


Row 4
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
Element

3.3 Inferring Correct Ancestries

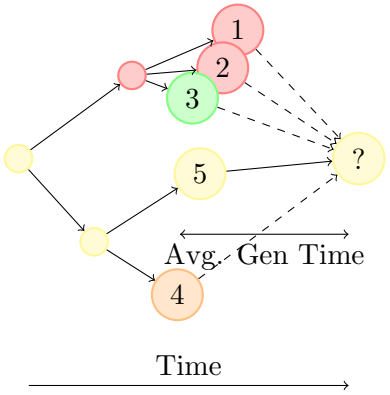
We also hoped to show that the group likelihood could help to infer correct ancestries in situations where the genetic and epidemiological likelihoods were not so effective. These situations are characterised by an outbreak where there not much mutation occurring in the DNA sequences between cases and a fairly long generation time. In these situations the original outbreaker model without group data struggles to infer the correct ancestor for two reasons. The genetic likelihood cannot narrow down the ancestor because there are few mutations between cases so most previous cases will have very similar genetic likelihoods. Secondly, the epidemiological likelihood struggles because the fairly long generation time means that for a newly infected case we have to look quite far back into the past for potential ancestors, this will bring up many candidate ancestors and we have no other way to determine who the correct ancestor is likely to be. In the transmission tree below, if there are not many mutations between cases, we would have trouble inferring an ancestor out of cases 1 to 5.



The group likelihood can help in this situation if the cases are divided into groups and we have are confident of what the group transmission probabil-

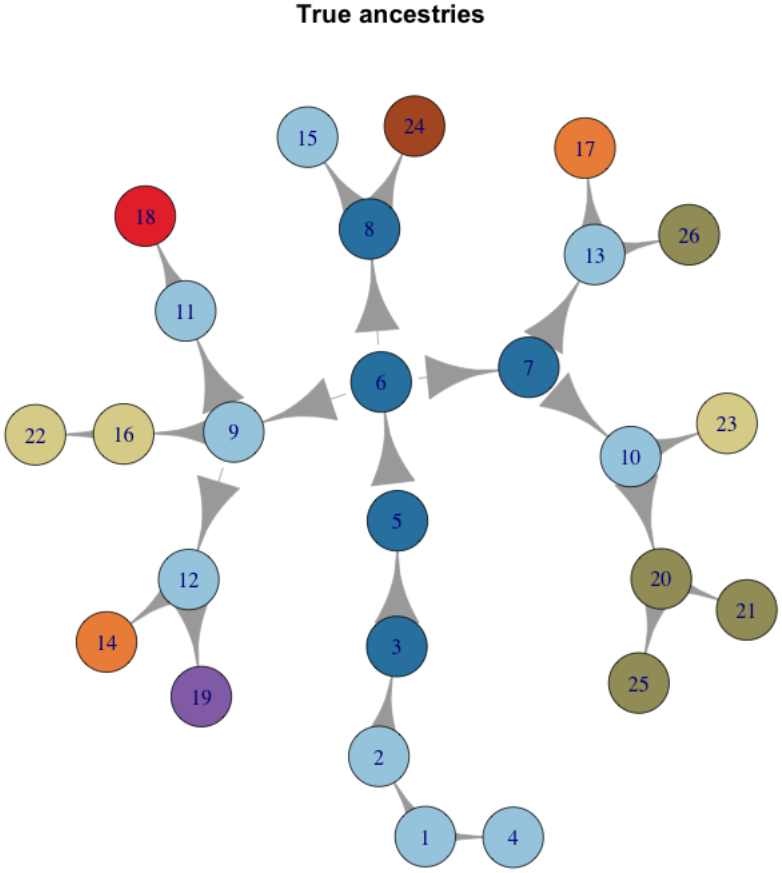
ities in the situation are. If we are sure that most transmission takes place within groups we could provide a prior that heavily promotes unequal transmission probabilities, this can give us another way of determining the most likely ancestor of a case when the genetic and epidemiological likelihoods are not useful. An unequal transmission probability prior will reward candidate transmission probabilities that are unequal, this gives a transmission probability matrix with values that are more unequal (because there is a higher probability of accepting candidate probability values that are more unequal due to our specified prior). If the data has a true group structure where transmission happens overwhelmingly within groups this will be inferred quickly by the model because it is encouraged by the prior. Therefore when we go to assess the group likelihood of a particular ancestry, it will give a much higher likelihood value to two cases within the same group. Returning to the scenario from the previous paragraph, if the newly infected case belongs to group A and there are 5 candidate ancestors, one of whom belongs to group A, then the likelihood of the connection between the two cases from group A will be much higher and therefore outbreaker will infer this ancestry. Therefore if our prior knowledge that the transmission rates are very unequal is true then we will have biased outbreaker towards the correct ancestries based on their group membership. This is how the group structure of the data and a strong prior can help outbreaker infer correct ancestries in certain situations where the other data is not as useful. In the transmission tree below the nodes are coloured by group membership. If we are trying to guess an ancestor for the new case and we suspect that most transmission occurs within groups then we would guess node 5. If our prior knowledge is accurate then we are making a sensible guess because it would be most likely to have been node 5 that infected our new case. Adding

in a group structure and prior knowledge has helped us infer the correct ancestor.



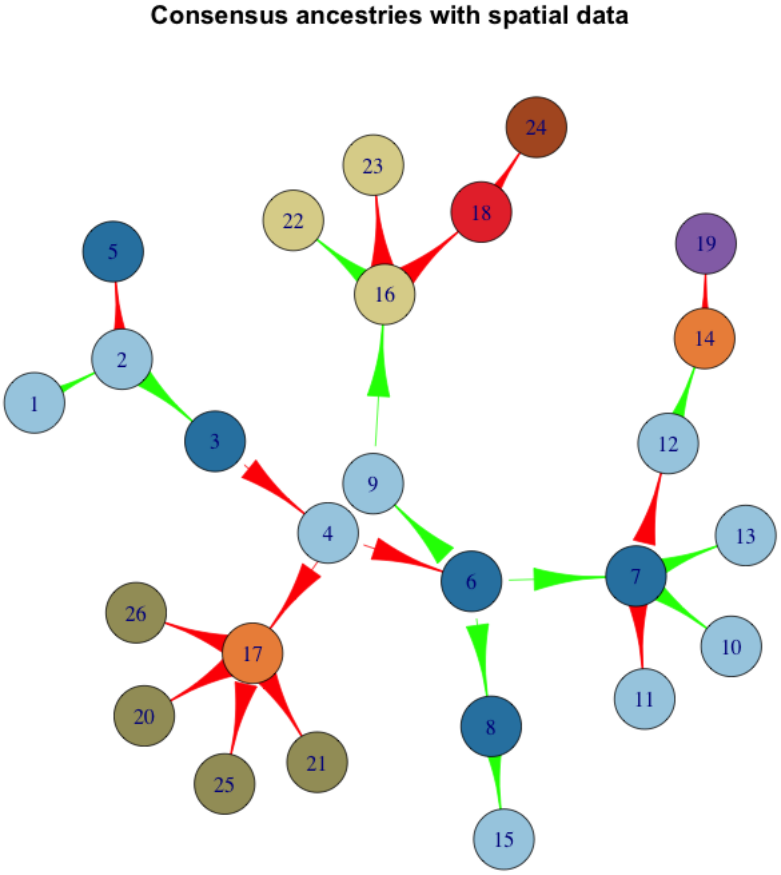
To test this we created datasets that had small groups with 3-4 people in (households) and one larger group (the community), the true transmission probabilities were such that cases with a household had very high probabilities of infecting individuals in the same household, a much lower probability of infecting individuals in the community and an extremely low probability of infecting individuals in other households. Cases in the community had a reasonable probability of infecting others in the community and the rest of the probability was assigned equally to infected a member from each household. The aim of this was to try and create datasets where most transmission happened within households and infection spread from household to household via the community where the equal probability of moving to a new household modelled random mixing in a community setting. In these datasets there would be several new cases occurring in different households at the same time, if we take into account the household structure then we would assume that a new case in household A was infected by a previous case in household A. If we do not have any group framework in outbreaker then we have a collection of cases that happened around the same time with barely any differences in the DNA sequences between them. The transmission tree

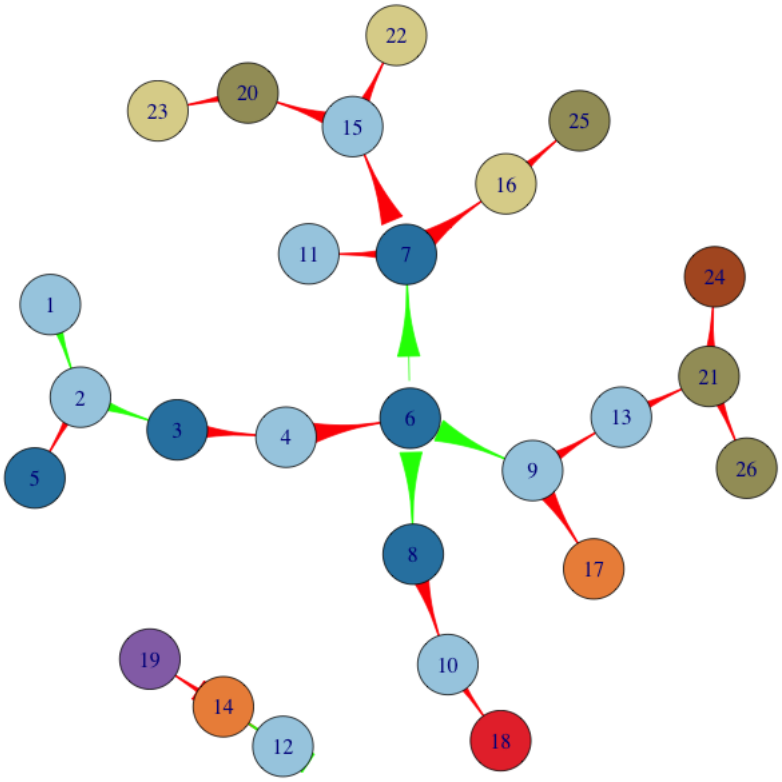
below is from such a dataset, the node colours represent the group that the case belongs to. The light blue nodes are members of the community, other colours are members of different households.



As described, most transmission takes place between members of the same household and the infection mostly moves from household to household via the community. We ran two different instances of outbreaker on this dataset to see which one could infer the correct ancestries better, one run had no group data and the other had group data and priors that strongly favoured unequal transmission probabilities. For this ancestry the outbreaker run with group data inferred 42% of correct ancestries (11 out of 25) whereas the run without group data inferred 23% of correct ancestries (6 out of 25). The plots below show the consensus transmission trees obtained from

outbreaker's `get.tTree()` function. The nodes are again coloured based on group membership and the edges are coloured green if they are correct inferences of the true ancestry above.




Consensus ancestries with no spatial data
22
20
23
15
25
16
11
7
24
1
21
2
13
3
4
6
26
5
9
8
17
19
10
14
18
12

Chapter 4

Discussion

4.1 Results Analysis

4.1.1 Estimating Transmission Parameters

The results of the EVD group simulations show that with uninformative priors the model is able to infer transmission probability parameters well where the true parameter values are greater than 0.05. For the case where the true parameter value was 0.05 the true parameter value only fell inside the 95% equal-tails interval of the posterior samples around half of the time. One explanation for this could be that the priors used in the test were uninformative which means that there was a bias in the model towards equal transmission probabilities within a row. We can see from the boxplots of the posterior medians for each simulation that the posterior samples for elements (3,2) and (4,1) are slightly lower than the other elements in their respective rows, perhaps a prior which favoured more unequal probabilities across rows would allow for more accurate inference of very small transmission probabilities.

One area the model did well in was inferring the larger transmission

probabilities of elements (1,1) and (2,2). The true parameter was within the equal-tails interval for each run in the majority of cases, although if we study the boxplots of the posterior medians we can see that the posterior medians vary a lot between runs. This suggests that the equal-tails intervals for these elements were quite wide for many runs because there must be cases where the posterior median was not close to the true parameter value but the true parameter value was still in the equal-tails interval of the posterior. The posterior median boxplots for rows 1 and 2 do not show the same features for other parameters, this means that the output of the model is still suggesting that the elements (1,1) and (2,2) could be larger than the others even if the posterior median is not as large as it should be. This could suggest to people using the model that transmission probabilities are not equal even if it does not deliver an accurate inference of the true parameter values.

4.1.2 Inferring Correct Ancestries

For the particular outbreak shown in the results section, adding the group framework to outbreaker greatly improved the proportion of correct ancestries inferred by outbreaker. Other datasets with a similar group signal and outbreak properties are also much better reconstructed by the extended outbreaker model. The benefits of including group data can be seen from the consensus ancestries in the results section, given what we know about the rates of transmission between groups the outbreaker model with the group likelihood produces more sensible results in several cases. The group data has caused outbreaker to infer the correct ancestry between cases 16 and 22, it has also caused outbreaker to guess an ancestry from 16 to 23 which is a sensible inference since it was unlikely that the true ancestry would look as it does with two separate infections of the same household (this is

unlikely because households are small relative to the overall population so if two members of a household are infected it is very unlikely that the individual who infected the third member would no be one of the other two members). However, the majority of the ancestries correctly inferred by outbreaker with group data which were not also inferred by outbreaker without group data are transmission events between members of the community and members of households. One explanation for this could be that correct (or more sensible) inferences involving household members elsewhere in the tree made the the correct inferences between individuals 7 and 10 or 7 and 13 more probable. One feature that appeared during creating and testing the datasets was that there is no good general value for the group prior, some datasets were well reconstructed with a group prior of ~ 1 and the proportion of correct ancestries inferred got lower as the group prior got smaller. For other datasets the outbreaker model with group data performed similarly to the original outbreaker model when the group prior was equal to 1 and much better than the original model when the group prior was very small. Further study could perhaps enlighted us as to what features of the dataset can help us choose a good prior value.

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 group 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

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 types of scenario where we have imagined that this method will be useful match 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.

Chapter 5

Not finished yet

5.1 Equine Flu Data

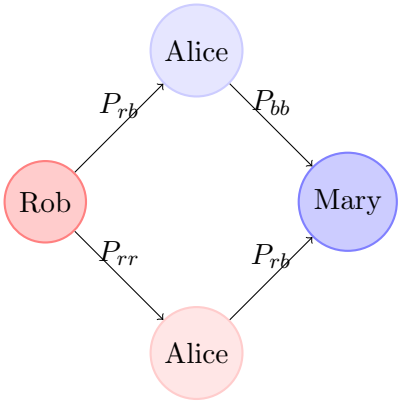
To test the method on real outbreak data we used some of the dataset of the 2003 equine influenza outbreak in Newmarket provided with the R package OutbreakTools, the dataset contains pathogen DNA sequence data and sequence collection dates for 121 individuals in 25 different paddocks. We chose to define 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].

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.

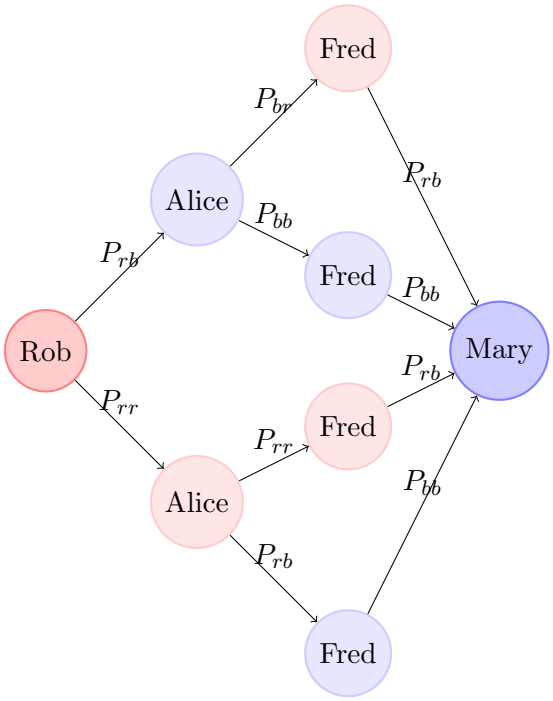
For small values of κ we can easily calculate the sum of these likelihoods, in

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.

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