Individual Level Models of Infectious Disease Transmission for Animal Experiments

by

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Abstract

INDIVIDUAL LEVEL MODELS OF INFECTIOUS DISEASE TRANSMISSION FOR ANIMAL EXPERIMENTS

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The control of infectious disease transmission among animals is crucial in minimizing risk to public health. Typically, such diseases are controlled with the help of treatments, or vaccines. Through mathematical and statistical modelling, we can develop models that simulate the effects of treatment designs, and other variables, on disease spread, to gain perspective on their underlying characteristics. We present a series of four individual-level models (ILMs) to explore disease spread in animal experiments that are arranged in multiple sub-populations, such as pens or cages. Model parameters are then estimated within a Bayesian framework, using Markov chain Monte Carlo (MCMC) techniques. Average posterior means and MSEs are used to compare and analyze the accuracy of parameter estimates and the trend in bias among varying sizes of the sub-populations.
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Chapter 1

Introduction

Infectious diseases are caused by pathogens that are passed between individuals, whether they be humans, plants, or animals (Grassly & Fraser, 2008). The transmission of infectious diseases can pose harmful health-related, economical and environmental consequences. Understanding the transmission dynamics is a crucial factor in the control and prevention of such diseases. Mathematical and statistical modelling is essential when it comes to understanding the underlying characteristics of these systems.

Deardon et al. (2010) describes a common statistical method which involves modelling the disease movement using an individual-level model (ILM). In such models, the individuals transition, in discrete time, through a number of possible states. In the commonly used SEIR framework, these states are susceptible (S), exposed (E), infectious (I) and removed (R). Other frameworks, such as SIR, SI, SIS and SIRS, are also frequently used.

The Markov chain Monte Carlo (MCMC) techniques within a Bayesian framework are often used in model fitting. An overview is given in Deardon, Fang, and Kwong (2014). Here, the unknown parameter, $\theta$, is assumed to be a random variable that has a prior distribution,
\( p(\theta) \). The \( p(\theta) \) can be decided based on expert knowledge, subjective assessment or results from previous studies. The incorporation of these parameter uncertainties is an advantageous quality of the Bayesian model. The main objective is to find the posterior distribution, \( p(\theta|y) \), where \( y \) is the observed data. This is essentially an update of the prior distribution and is a product of the prior distribution and likelihood function, \( p(y|\theta) \), over a normalization constant:

\[
p(\theta|y) = \frac{p(y|\theta)p(\theta)}{\int p(y|\theta)p(\theta)d\theta}
\]

(1.1)

Deardon et al. (2014) further explain how the MCMC can be used to obtain the posterior distribution by means of constructing a Markov chain whose stationary distribution is the target posterior distribution. The Markov chain is simulated until convergence is reached. In order to implement this procedure, the random-walk Metropolis Hastings algorithm is often used and proceeded in the following steps:

1. Initialize the MCMC iteration, \( m = 0 \), and assign arbitrary values for the set of parameters, \( \alpha = \alpha^{(0)} \) and \( \beta = \beta^{(0)} \)

2. Generate proposal densities \( z_\alpha \sim U[-A,A] \) and \( z_\beta \sim U[-B,B] \) at iteration \( m \)

3. Propose candidate values for \( \alpha \) and \( \beta \) as \( \alpha' = \alpha^{(m)} + z_\alpha \) and \( \beta' = \beta^{(m)} + z_\beta \)

4. Calculate the acceptance probability, \( \psi \):

\[
\psi = \min \left( 1, \frac{f(y|\alpha',\beta') f(\alpha') f(\beta')}{f(y|\alpha^{(m)},\beta^{(m)}) f(\alpha^{(m)}) f(\beta^{(m)})} \right)
\]

(1.2)
5. Accept $\alpha^{(m+1)} = \alpha'$ and $\beta^{(m+1)} = \beta'$ with probability $\psi$. Otherwise, $\alpha^{(m+1)} = \alpha^{(m)}$ and $\beta^{(m+1)} = \beta^{(m)}$

6. Repeat steps 2-5 until convergence and stationarity is reached

We can use the ILMs as described in Deardon et al. (2010), along with Bayesian MCMC model-fitting techniques, to run simulation-based experiments in controlled settings. In simulation studies, disease spread is simulated according to a pre-specified transmission pattern, such as rate of transmission, and factors, such as treatment designs and spatial layouts, to explore their effects on the control of disease spread. Such experiments can be implemented on animals arranged in some layout of herds or pens, where different treatments are applied to animals in each herd or pen. Studies that involve designing and optimizing such experimental models are valuable when it comes to the control and management of public health.

This thesis, presented in a manuscript format, contains a paper for submission in Chapter 2. This paper looks at four SI individual-level models that are used to understand disease spread in certain animal experiments. Specifically, we look at poultry arranged in experimental layouts of one and multiple poultry cages, while treatment and spatial effects are also considered in certain scenarios of the study. The models are then fitted to simulated epidemic data within a Bayesian MCMC framework. Various cage sizes are compared in each model to ascertain their resulting bias and accuracy of parameter estimates.
Chapter 2

Individual level models of infectious disease transmission for animal experiments

2.1 Introduction

Infectious diseases can have a large impact on the environment, agriculture, economy, and the human population. These diseases, such as influenza, avian influenza and west nile virus are passed among individuals, whether it is through direct or indirect contact, caused by the transmission of a pathogen \cite{Grassly2008}. It is of utmost importance to understand how these diseases spread and to identify their associated risks in order to control them. For example, with advancements in public health, many diseases have become manageable through the intervention of vaccines and antibiotics. Disease models can help us decide how to best deploy such resources.
As infectious disease transmission continues to pose harmful risks to society, research in the spread of disease through mathematical or statistical modelling remains an important priority in the area. Due to experimental costs, the difficulty in collecting relevant data from observational studies, and limited resources, simulation studies can play an important role. Under a controlled pre-specified setting of a simulation model, we are able to better understand the underlying characteristics of disease spread among humans, plants and animals.

Keeling and Rohani (2008) explain three substantial elements that can be used to evaluate the performance of a mathematical model. The first element is accuracy, which describes how well a model can be used to predict the future disease trend. An accurate predicted model is useful in making controlling policies or gaining insight on disease complexities. Second, a model’s transparency determines its ability to understand the impacts of model components and quantify their affects on the disease dynamics. Lastly, the flexibility of a model describes how easy a model can adapt to modifications that reflect environmental changes influential to disease spread. However, there is sometimes a trade-off to balance these three elements. Additionally, they note that by building simple models to more complex ones, we gain insight on infection patterns which helps to better our understanding of real-world complexities.

Although there are obvious ethical issues in running experiments on humans which involve infectious disease transmission under controlled conditions, it is sometimes possible to run such experiments on populations of animals and plants. In such controlled situations, disease might be introduced in order to ascertain transmission rates, infectious periods, change in viral shedding over time, or the effect of some treatment (e.g. vaccination) or treatments designed to help control the spread of disease. This could be done in isolated herds or pens.
of animals, for example, with different treatments applied to animals in each herd or pen.

However, since infectious disease models are inherently nonlinear in nature, many standard design of experiments results do not automatically hold. This is primarily because the optimal design in a nonlinear situation depends upon the parameters of the model (which is not the case in a linear model). This often means that a Bayesian and/or sequential approach is taken to designing the experiment. In the Bayesian framework, uncertainty about the parameters before the experiment is run is characterized by a prior distribution. Results from an experiment optimally designed accounting for a priori parameter uncertainty, can either be used as an end in themselves, or can be used to inform the prior used to design the next stage of a sequential experiment.

Since the posterior distribution for such analyses is generally intractable, we often use a simulation-based experimental design approach, which requires multiple simulations of the experiment in question with parameters drawn from the aforementioned prior. This can be done for multiple designs, and an optimality criterion maximized over the design space (or subset of the design space). A description of such approaches is given in Muller (1999). An infectious disease application can be found in Cook, Gibson, and Gilligan (2008).

Clyde (2001) addresses the importance of developing an optimal experimental design, the inclusion of influential factors, such as the choice of treatments, aspects of the randomization of an experiment, and the required sample size. Simulation-based experiments enable us to determine factors that are influential to a particular design, and adjust them so that the design is optimized. Höhle, Jørgensen, and O’Neill (2005) provide an example about studying the influential factors relating to control measures on the within-farm spread of diseases. Such studies provide important information for decision making in health management. Factors
and control measures that should be considered include the spatial layout of confinement units, e.g. animal pens, and vaccination strategies.

Deardon et al. (2010) describes a model which allows us to explore the spatial-temporal effects on the spread of infectious disease at the individual level. These models can be extremely useful in evaluating the dynamic of disease spread. In a disease transmission model, individuals (an individual is the unit of interest, such as people, animals, or plants) sit within a “compartmental framework”, meaning they may find themselves in one of a number of possible states or compartments. Typically, four such states are considered: susceptible ($S$), exposed ($E$), infectious ($I$) or removed ($R$). Usually, the model is fitted to the data and parameter estimates are produced using Markov Chain Monte Carlo (MCMC) methods under the Bayesian framework.

The original aim of this paper was to explore the use of such models for designing infectious disease transmission experiments for poultry in which the aim is to ascertain some treatment effect on the rate of transmission. In such experiments, cages of poultry are placed in an experimental area, but as well as transmission occurring within the cage, transmission can occur between animals in different cages. This means transmission rates observed depend not only upon the treatment applied to a given cage, but also of these surroundings (i.e. we have inter-cage “interference”).

In experiments like these run at the Arkell Research Station, two major sources of such between-cage transmission exist. First, there is a source resulting from the fact that cages are typically stacked vertically, so material can fall down from one cage to those below. Another source of transmission is that cages within a horizontal row share a tray on which poultry feces fall, and in order to clean multiple cages these trays are pulled out. This potentially
transmits infectious material from cage to cage in the direction in which the tray is pulled, and these trays are typically always pulled in the same direction. As a result, the inter-cage transmission does not likely occur in a spatially homogeneous way.

To deal with such situations, we propose a spatially explicit model for use in such experiments that allows for directionally-dependent spatial spread. However, in order to use such models, either for inference from data obtained from an experiment, or in order to design the experiment itself, we need to be confident that sound inferences are made. In the course of carrying out our research plan, we discovered that this is not necessarily the case when data is collected from small populations, as would obviously be the case in an experimental setup.

Hence, the purpose of this paper is twofold. First, we introduce a series of models based on the framework of Deardon et al. (2010), that can be used to describe infectious disease transmission in experiments for animals in which there is inter-cage interference. Second, we quantify the bias that is observed when analyzing data from such experimental situations for different cage/population sizes.

The remainder of this paper is laid out as follows. In Section 2.2, the series of four models introduced are described in further detail, followed by an explanation of the simulation study in Section 2.3. Results of our simulation study are presented in Section 2.4, and finally Section 2.5 provides a discussion of the paper and future work.
2.2 Individual-level models

The models being considered here are known as individual-level models (ILMs), as described in Deardon et al. (2010), and are placed within a “susceptible-infectious” (SI) framework. This means that each individual can be in one of two states: $S$, if individuals are susceptible to a disease; or $I$, if individuals are infectious, at any given discrete time point. $S(t)$ and $I(t)$ represent the sets of susceptible and infected individuals at time $t$, respectively. Any individuals in a susceptible state, $S$, will have probability of transitioning to an infected state, $I$, at each discrete time point, $t$. If an individual has been infected, they will remain in that state.

Four different models are considered, modelling disease transmission among individuals in populations of varying structure.

Model 1

The first model is applicable to one population and assures a homogeneously mixing population. Each susceptible individual, $i$, has probability, $P_i(t)$, of being infected at discrete time point, $t$:

$$P_i(t) = 1 - \exp(-\beta_0 N(t)),$$

where $\beta_0$ is an infectivity parameter and $N(t)$ is the number of individuals infected in the population at time $t$.

The likelihood function is given by
\[ f(y|\beta_0) = \prod_{t=0}^{t_{\text{max}}} \left[ \prod_{i \in I(t+1) \setminus I(t)} P_i(t) \right] \left[ \prod_{i \in S(t+1)} (1 - P_i(t)) \right], \quad (2.2) \]

where \( y \) is the observed data, \( I(t+1) \setminus I(t) \) is the set of newly infected individuals within the time interval \((t, t+1]\), and \( S(t+1) \) is the set of individuals not infected in this time interval.

**Model 2**

Model 2 is applicable to situations where we have a number of similar sub-populations arranged on a lattice. For example, this could represent cages of animals in an experimental layout. Here, each sub-population is assumed to contain the same number of individuals.

The model is given by

\[ P_{i,j,k}(t) = 1 - \exp(-\beta_0 N_{i,j}(t)). \quad (2.3) \]

where, \( P_{i,j,k}(t) \) is the probability that individual \( k \) in sub-population \((i, j)\) is infected at time \( t \), for \( i = 1, \ldots, m \) and \( j = 1, \ldots, n \); \( m \) and \( n \) represent the total number of rows and columns on the lattice, respectively; \( \beta_0 \) is the infectivity parameter; and \( N_{i,j}(t) \) is the number of individuals infected in sub-population \((i, j)\) at time \( t \).

Similar to equation (2.2), its likelihood is given by

\[ f(y|\beta_0) = \prod_{t=0}^{t_{\text{max}}} \left[ \prod_{i,j,k \in I(t+1) \setminus I(t)} P_{i,j,k}(t) \right] \left[ \prod_{i,j,k \in S(t+1)} (1 - P_{i,j,k}(t)) \right]. \quad (2.4) \]
Model 3

Here, we allow for treatment effects; for example, individuals in the sub-populations are randomly assigned one of $L + 1$ treatments. All individuals in a particular sub-population are assured to share the same treatment status. The probability for susceptible individual $k$ in sub-population $(i, j)$ to become infected at time $t$ is now given by:

$$P_{i,j,k}(t) = 1 - \exp\left(-\left(\beta_0 + \sum_{l=1}^{L} \beta_l V_{i,j}^{(l)} N_{i,j}(t)\right)\right), \quad (2.5)$$

where

$$V_{i,j}^{(l)} = \begin{cases} 1, & \text{if sub-population (i,j) has treatment type } l \\ 0, & \text{otherwise} \end{cases}$$

Each $V_{i,j}^{(l)}$ is associated with a treatment parameter, $\beta_l$. An assumption is made that treatment types $l = 1, \ldots, L$ retard disease spread compared with the baseline, represented by $V_{i,j}^{(1)} = \cdots = V_{i,j}^{(L)} = 0$. The likelihood is computed such that

$$f(y|\beta_0, \beta_1, \beta_2) = \prod_{t=0}^{t_{\text{max}}} \left[ \prod_{i,j,k \in I(t+1) \setminus I(t)} P_{i,j,k}(t) \right] \left[ \prod_{i,j,k \in S(t+1)} (1 - P_{i,j,k}(t)) \right]. \quad (2.6)$$

Model 4

Finally, we devise a model to account for the addition of spatial effects, where susceptible individual $k$ in sub-population $(i, j)$ has probability of becoming infected at time $t$ given by
\[ P_{i,j,k}(t) = 1 - \exp\left(-\left(\beta_0 + \sum_{l=1}^{L} \beta_l V^{(l)}_{i,j}\right) \times \left[N_{i,j}(t) + \alpha_a N_{i+1,j}(t) + \alpha_b N_{i-1,j}(t) + \alpha_l N_{i,j-1}(t) + \alpha_r N_{i,j+1}(t)\right]\right) \]  

(2.7)

where \( N_{i+1,j}(t) \) is the number of infectious individuals in the sub-population above \((i, j)\); \( N_{i-1,j}(t) \) is the number of infectious individuals in the sub-population below \((i, j)\); \( N_{i,j-1}(t) \) is the number of infectious individuals in the sub-population to the left of \((i, j)\); and \( N_{i,j+1}(t) \) is the number of infectious individuals in the sub-population to the right of \((i, j)\).

The likelihood is similar to that of equation (2.6), such that

\[ f(y | \beta_0, \ldots, \beta_L, \alpha_a, \alpha_b, \alpha_l, \alpha_r) = \prod_{t=0}^{t_{\text{max}}} P_{i,j,k}(t) \left[ \prod_{i,j,k \in I(t+1) \setminus I(t)} P_{i,j,k}(t) \prod_{i,j,k \in S(t+1)} (1 - P_{i,j,k}(t)) \right]. \]  

(2.8)

The spatial effects in this model allow for infection from up to four of the possible adjacent cages. Each neighbour effect is associated with a spatial parameter \( \alpha_a \), \( \alpha_b \), \( \alpha_l \), and \( \alpha_r \), respectively.

### 2.3 Simulation Study

In the simulation study, the sub-populations represent multiple identical cages in an experimental situation. Here, the individuals occupying each cage are assumed to be chickens. Model 1 explores disease transmission among chickens in a single cage while the remaining
models explore multiple cages arranged on a lattice of three rows and six columns. We experiment with varying cage sizes (number of chickens per cage) as well as different parameter values in each of the four models. All epidemics are run for a fixed amount of time, \( t = 1, \ldots, t_{\text{max}} \), where we have defined \( t_{\text{max}} \) to be 5.

Under scenario 1, epidemics are simulated within one population, or cage, of either 5, 10, 15, 30, 50, 70, 100 or 150 individuals. Each cage size is tested with three different parameter values: \( \beta_0 = 0.1, \beta_0 = 0.3 \) and \( \beta_0 = 0.5 \).

Similarly, in scenario 2, we simulate epidemics with eighteen cages of 5, 10, 15, 30, 50, 70, 100 or 150 chickens per cage. Again, parameter values of \( \beta_0 = 0.1, \beta_0 = 0.3 \) and \( \beta_0 = 0.5 \) are used.

The third scenario includes three possible treatments (i.e. \( L = 2 \)) with cage sizes of 10, 50 or 100 chickens per cage. These three treatments can be thought of as being two types of vaccine with the baseline \( V^1_{i,j} = V^2_{i,j} = 0 \) representing no vaccine. The cage sizes are chosen based on results from the first two scenarios. Two different sets of parameter values are tested: \( \beta_0 = 0.03, \beta_1 = 0.05, \beta_2 = 0.1 \) and \( \beta_0 = 0.1, \beta_1 = 0.2, \beta_2 = 0.4 \). The treatment parameter values are chosen so that the two vaccines have differing effectiveness, with both vaccines offering some protection (i.e. they have a lower rate of infection than having no vaccine at all).

Finally, spatial effects are added to the fourth scenario. Again, we use cage sizes of 10, 50 and 100, but only one set of parameter values: \( \beta_0 = 0.1, \beta_1 = 0.2, \beta_2 = 0.4, \alpha_a = 0.4, \alpha_b = 0.1, \alpha_t = 0.5 \) and \( \alpha_r = 0.1 \). Values of the spatial parameters are chosen so that certain neighbouring cages have differing effects. We assume that a cage with individuals above it would have a higher risk of infection than from individuals in the cage below. It is also
assumed that in the process of cleaning the cages, the lining on the bottom of the cages is pulled and replaced from left to right, thus a cage with individuals to its left should have a higher risk of infection than from individuals in the cage to the right.

All epidemics begin with one individual in each cage being randomly infected at time \( t = 1 \). Susceptible individuals may become infected at each following time point with probability given by equations 2.1, 2.3, 2.5, or 2.7 depending on the model. Epidemics are run over 5 time points, whether or not all individuals in each cage have been infected by time \( t = 5 \). Each simulation is repeated 20 times for the first three scenarios and 10 times for the fourth scenario.

The \( \alpha \) and \( \beta \) parameters are estimated using Metropolis-Hastings Markov Chain Monte Carlo (MCMC) methods within a Bayesian framework. Flat uniform priors on the positive real line are placed on the \( \alpha \) and \( \beta \) parameters. The uniform distribution, symmetric about the origin, is used for the random walk proposal density, where specific proposals for each parameter are tuned to reach stationarity efficiently for each epidemic realization. For the first three scenarios, the MCMC was run for 10,000 iterations. It was found that when spatial effects are added, in the fourth case, at least 100,000 iterations are required to achieve convergence. In all cases, convergence is confirmed visually and MCMC results are used to estimate posterior distributions and means for each \( \alpha \) and \( \beta \) parameter. These results are analyzed to determine under which cage sizes and parameter values the models work best.
2.4 Results

2.4.1 Scenario 1

A plot of the posterior means and MSEs for each cage size when $\beta_0 = 0.1$ is provided in Figure 2.1a and Figure 2.2a, respectively; the line in the plot joins the average posterior means. Overall, $\beta_0$ is over estimated and there appears to be strong bias in small cage sizes. The smallest cage size produced extremely large posterior means. Figures 2.1b and 2.2b provide the same plots but on the log scale to get a better idea of what the posterior means look like for higher cage sizes. Estimates are significantly better by cage size 30. From here, the average posterior means fluctuate slightly as cage size increases. Posterior means are closest to the true value of $\beta_0$ when the cage size is 100 and 150; the average posterior means are 0.104 and 0.100, respectively, while average posterior MSEs are 0.0003 and 0.0002, respectively.
Figures 2.3a and 2.3b show plots of the posterior means of 20 simulations for each cage size when $\beta_0 = 0.3$ and $\beta_0 = 0.5$, respectively (Figures 2.4a and 2.4b provide similar plots
for posterior MSE). Again, there is a tendency for over estimation of posterior means. The highest average posterior means and MSEs are produced with smaller cage sizes, namely 5 and 10. These values, however, are not as extreme compared to when $\beta_0 = 0.1$. The posterior mean tends to decrease as the cage size increases. As before, the best estimates occur when the cage size is 100 and 150.

(a) Plot of posterior means over 20 simulations by cage size for $\beta_0 = 0.3$.

(b) Plot of posterior means over 20 simulations by cage size for $\beta_0 = 0.5$.

Figure 2.3: Posterior means for scenario 1; $\beta_0 = 0.3$ & $\beta_0 = 0.5$
2.4.2 Scenario 2: Experiment of 18 isolated cages and no treatment effects

Similar trends are observed in posterior mean and MSE for $\beta_0 = 0.1$ and $\beta_0 = 0.3$ in that estimates tend to be bias for smaller cage sizes. Figures 2.5a and 2.5b provide plots of the posterior mean of 20 simulations for each cage size when $\beta_0 = 0.1$ and $\beta_0 = 0.3$, respectively, while Figures 2.6a and 2.6b plot the posterior MSE.

When $\beta_0 = 0.1$, the average posterior mean is highest for cage sizes 5, 10, and 15. It begins to level off around cage size 30. By cage size 150, the average posterior mean is 0.100 with an average posterior MSE of 1.057E-05.

Again, the average posterior mean is highest for cage size 5 when $\beta_0 = 0.3$. It dips to 0.302 at cage size 10, slightly fluctuates and then steadily decreases from cage size 50. However, there is a continual decrease in average posterior MSE with an increase in population size.
The average posterior mean for 150 chickens per cage is 0.299 and the average posterior MSE is 0.0002.

Figures 2.5c and 2.6c show plots of posterior mean and MSE, respectively, of 20 simulations for each cage size when $\beta_0 = 0.5$. The average posterior mean is 0.528 when the cage size is smallest. Similar to $\beta_0 = 0.3$, there is some fluctuation in average posterior mean, until cage size 50 is reached. At 150 chickens per cage, the average posterior mean and MSE has decreased to 0.502 and 0.0003, respectively.

(a) Plot of posterior means over 20 simulations by cage size for $\beta_0 = 0.1$.
(b) Plot of posterior means over 20 simulations by cage size for $\beta_0 = 0.3$.
(c) Plot of posterior means over 20 simulations by cage size for $\beta_0 = 0.5$.

Figure 2.5: Posterior means for 18 cages without treatment effects
(a) Plot of posterior MSE over 20 simulations by cage size for $\beta_0 = 0.1$.
(b) Plot of posterior MSE over 20 simulations by cage size for $\beta_0 = 0.3$.
(c) Plot of posterior MSE over 20 simulations by cage size for $\beta_0 = 0.5$.

Figure 2.6: Posterior MSE for 18 cages without treatment effects

2.4.3 Scenario 3: Experiment of 18 isolated cages with treatment effects

From the results of the simulation studies in scenarios 1 and 2, it is observed when $\beta_0$ is small (0.1), a large cage size is required to obtain a less biased estimate. So, to accommodate a small treatment effect, we only consider cage sizes of 10, 50 and 100. Figures 2.7 and 2.8
provide plots of posterior means and MSE, respectively, for 20 simulations over each cage size when \( \beta_0 = 0.03, \beta_1 = 0.05 \) and \( \beta_2 = 0.1 \). For treatment parameters \( \beta_0 \) and \( \beta_2 \), the bias and average posterior MSE decreases as cage size increases. For \( \beta_1 \), the smallest cage size appears to have an average posterior mean estimate close to its true value of 0.05. However we can see there is a larger variability in posterior means and the MSE remains higher compared to cage sizes 50 and 100. \( \beta_0 \) is over estimated while \( \beta_1 \) and \( \beta_2 \) are typically under estimated.

Plots for \( \beta_0 = 0.1, \beta_1 = 0.2 \) and \( \beta_2 = 0.4 \) are shown in Figures 2.9 (posterior mean) and 2.10 (posterior MSE). As before, the smallest cage size results in bias estimates. In addition, we can see the decrease in MSE in Figure 2.10 as cage size increases. \( \beta_0 \) is over estimated while \( \beta_1 \) and \( \beta_2 \) tend to change, depending on cage size.
(a) Plot of posterior means over 20 simulations by cage size for $\beta_0 = 0.03$.

(b) Plot of posterior means over 20 simulations by cage size for $\beta_1 = 0.05$.

(c) Plot of posterior means over 20 simulations by cage size for $\beta_2 = 0.1$.

Figure 2.7: Posterior mean for 18 cages with treatment effects; $\beta_0 = 0.03$, $\beta_1 = 0.05$ and $\beta_2 = 0.1$
(a) Plot of posterior MSE over 20 simulations by cage size for $\beta_0 = 0.03$.

(b) Plot of posterior MSE over 20 simulations by cage size for $\beta_1 = 0.05$.

(c) Plot of posterior MSE over 20 simulations by cage size for $\beta_2 = 0.1$.

Figure 2.8: Posterior MSE for 18 cages with treatment effects; $\beta_0 = 0.03$, $\beta_1 = 0.05$ and $\beta_2 = 0.1$
(a) Plot of posterior means over 20 simulations by cage size for $\beta_0 = 0.1$.

(b) Plot of posterior means over 20 simulations by cage size for $\beta_1 = 0.2$.

(c) Plot of posterior means over 20 simulations by cage size for $\beta_2 = 0.4$.

Figure 2.9: Posterior means for 18 cages with treatment effects; $\beta_0 = 0.1$, $\beta_1 = 0.2$ and $\beta_2 = 0.4$
Figure 2.10: Posterior MSE for 18 cages with treatment effects; $\beta_0 = 0.1$, $\beta_1 = 0.2$ and $\beta_2 = 0.4$.

### 2.4.4 Scenario 4: Experiment of 18 cages with treatment & spatial effects

The prominent trend in bias estimates with varying cage size observed throughout the first three scenarios is not as clear when the addition of spatial effects are considered. Figures 2.11 and 2.12 provide plots of posterior means over 10 simulations for each cage size for the
\(\beta\) and \(\alpha\) parameters, respectively. Table 2.1 provides average posterior means and MSEs for all parameters under cage sizes 10, 50 and 100. In this case, results are more sporadic; out of the seven parameters in this model, only two, \(\alpha_B\) and \(\alpha_R\), show evidence of bias estimates for smaller cage sizes. Meanwhile, the smallest cage size produces the most accurate estimates for two treatment parameters, \(\beta_0\) and \(\beta_1\). These inconsistent results make it difficult to ascertain a true trend in bias.

Table 2.1: Table comparing posterior means and MSEs of parameters for 18 cages with treatment & spatial effects.

<table>
<thead>
<tr>
<th></th>
<th>Average Posterior Mean</th>
<th>Average Posterior MSE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10  50  100</td>
<td>10  50  100</td>
</tr>
<tr>
<td>(\beta_0) = 0.1</td>
<td>0.100 0.125 0.134</td>
<td>0.000992 0.00188 0.00186</td>
</tr>
<tr>
<td>(\beta_1) = 0.2</td>
<td>0.224 0.254 0.279</td>
<td>0.00789 0.00734 0.0106</td>
</tr>
<tr>
<td>(\beta_2) = 0.4</td>
<td>0.463 0.457 0.519</td>
<td>0.0296 0.0168 0.020</td>
</tr>
<tr>
<td>(\alpha_A) = 0.4</td>
<td>0.451 0.424 0.322</td>
<td>0.0780 0.0552 0.0332</td>
</tr>
<tr>
<td>(\alpha_B) = 0.1</td>
<td>0.268 0.193 0.114</td>
<td>0.0818 0.0409 0.0137</td>
</tr>
<tr>
<td>(\alpha_L) = 0.5</td>
<td>0.457 0.336 0.374</td>
<td>0.0749 0.104 0.0690</td>
</tr>
<tr>
<td>(\alpha_R) = 0.1</td>
<td>0.343 0.153 0.0535</td>
<td>0.127 0.0271 0.00488</td>
</tr>
</tbody>
</table>
Figure 2.11: 18 cages with treatment & spatial effects; treatment ($\beta$) parameters.
2.5 Discussion

This simulation study investigates the analysis of data from infectious disease transmission in poultry experiments under four scenarios, using $SI$ individual-level models. These models are fitted to simulated epidemic data within a Bayesian MCMC framework. Various cage
sizes are tested in each model and are shown to have an impact on overall model performance. Our main concern is the bias of our parameter estimates that result from the four scenarios.

In the first scenario, where only a single cage is considered, there is a tendency for over-estimation and bias estimates among small cage sizes. This is highly apparent when the parameter is smallest, i.e. $\beta_0 = 0.1$. In general, if the true parameter value is small, relatively large cage sizes are required to produce estimates that are less biased. The posterior mean and MSE for smaller cage sizes (5 and 10, specifically) when $\beta_0 = 0.1$ are much higher compared to $\beta_0 = 0.3$ and 0.5. The smallest posterior MSEs and most accurate posterior means are produced from the largest cage sizes, 100 and 150, for all values of $\beta_0$.

Modifying our experimental design to include a total of 18 cages but no inter-cage transmission, we see that the variation in cage size produces similar trends in estimates to scenario 1. Biased parameter estimates occur when cage sizes are small, and the bias is reduced as cage size becomes larger. As before, when $\beta_0 = 0.1$, the posterior means and MSEs are noticeably higher compared to $\beta_0$ values of 0.3 and 0.5 for smaller cage sizes (5, 10 and 15, specifically). Typically, by cage size 50, bias is significantly reduced for all $\beta$ values; the two largest cages sizes result in the best parameter estimates and smallest posterior MSE.

It might be worth noting that there is a noticeable improvement in posterior means and MSEs in the model with 18 cages compared to the model with only one cage. This is observed among each $\beta_0$ value in all cage sizes.

The addition of treatment effects produces similar results overall, in that a larger cage size results in smaller posterior MSE and less bias. This is seen in both sets of $\beta_0$, $\beta_1$ and $\beta_2$ values.

Lastly, the presence of spatial effects in the fourth scenario does not necessarily result
in bias estimates when cage sizes are small. This trend is only noticeable in parameters $\alpha_B$ and $\alpha_R$. In fact, in some instances, e.g. $\beta_0$ and $\beta_1$, the smallest cage size produces the most accurate estimates, which is ideal since smaller cage sizes are more realistic in practice. However, these results are not consistent among all parameter estimates in this particular model, making it difficult to quantify an overall trend in bias for varying cage sizes.

Throughout each scenario, the choice of cage size is a common experimental factor that influences bias and precision of parameter estimates. Overall, experiments with smaller cage sizes appear to result in more bias parameter estimates, which is especially evident in the simplest model. As cage size increases, bias appears to reduce and there tends to be a threshold at which point models begin to generate fairly consistently accurate results. However, there is no question that the largest cage sizes achieve the most precise parameter estimates.

Additionally, the actual value of our parameter that is being estimated is another factor that impacts results, although only to a certain extent. There tends to be more bias, high posterior MSEs, and large posterior means with the coupling of lower cage sizes and a lower $\beta$ value.

There are some limitations to this simulation study and areas for future work. Firstly, we could further explore the fourth model, with spatial effects, as it considers important experimental factors that the other models do not. As only one set of parameter values was tested, it might be useful to experiment with additional sets of $\beta$ and $\alpha$ values to perhaps provide a better understanding of the underlying characteristics and trends of this type of disease spread.

Additionally, it might be interesting to test models with varying numbers of cages, as
only the results of one cage and 18 cage experiments have been addressed in this study. Experimenting with more and/or less than 18 cages and possibly arranged in different cage structures could be informative when searching for an optimal design. Results from this study imply that large cage sizes are necessary in order to reduce bias and achieve superior parameter estimates. However, such collections of large cage sizes might not be realistic in real-world experiments. Thus, it could be valuable to set up an experimental design where there are large cage sizes coupled with a small number of cages compared to small cage sizes coupled with a large number of cages. This could give us insight on how cage size, along with the number of cages present, affects the bias in parameter estimates, as well as finding an optimal experimental design.

Finally, we could move forward in understanding experimental layout of treatments on estimates of disease transmission by experimenting with different designs, as was part of the original goal of this project. The third scenario presented in this paper is limited to only one type of treatment design, where the treatments are assigned to cages at random. However, it may be that particular spatial layouts (e.g. spatially balanced) help reduce the biasing effect of inter-cage interference in experiments where it exists.

Furthermore, this study only addresses models under an $SI$ ILM framework for short experiments (e.g. 5 time points). It would be possible to increase the duration of the epidemics and extend the models to an $SIR$ framework, making room for a set of individuals to be removed from the population, possibly by death or recovery. This would help us to gain insight into further dynamics of infectious disease transmission.
References


Appendix A

Fortran code

This appendix contains the Fortran code for two programs: epidemic simulation and MCMC model-fitting.

A.1 Epidemic simulation Fortran code

program epidemic

integer :: i, j, k, t, row1, col1, row2, col2, seed, indCount
integer, dimension(1:180) :: inf
real :: rn, above, below, left, right
real :: alpha_a, alpha_b, alpha_l, alpha_r, beta_0, beta_1, beta_2
real, dimension (3,6) :: cageCount, count1, count2, prob
real, dimension(3,6) :: VaccStatus1, VaccStatus2

indCount=10.0

!Treatment and spatial parameter values
beta_0=0.03
beta_1=0.05
beta_2=0.1

alpha_a=0.4
alpha_b=0.1
alpha_l=0.5
alpha_r=0.1

prob=0.0
cageCount=0.0
count1=0.0
inf=0.0
countTime=0.0
!Random treatment design
VaccStatus1=0.0
VaccStatus1(1:2, 3:3:1)=1.0
VaccStatus1(2:3, 5:5:1)=1.0
VaccStatus1(2:2, 6:6:1)=1.0

VaccStatus2=0.0
VaccStatus2(1:2, 1:1:1)=1.0
VaccStatus2(2:2, 2:2:1)=1.0
VaccStatus2(3:3, 4:4:1)=1.0
VaccStatus2(1:1, 6:6:1)=1.0
VaccStatus2(3:3, 6:6:1)=1.0

seed=time()
print*, seed
call srand(seed)

!generate random number to infect one individual in each cage
do i= 0, 18*indCount-indCount, indCount
   rn=rand()
k=int(rn*indCount)+1
   inf(k+i)=1
end do

!simulate epidemic
do t=1,5
do row1=1,3
do col1=1,6
do i=1,indCount
   if(inf(6*indCount*(row1-1)+indCount*(col1-1)+i) .eq. 0) then
      do row2=1,3
do col2=1,6
      cageCount(row2,col2)=0.0
      do j=1,indCount
         if((inf(6*indCount*(row2-1)+indCount*(col2-1)+j) .le. t) .and. &
            (inf(6*indCount*(row2-1)+indCount*(col2-1)+j) .ne. 0)) then
            cageCount(row2,col2)=cageCount(row2,col2)+1
         end if
      end do
      if(row1+1 .lt. 4) then
         above = alpha_a*cageCount(row1+1,col1)
      else
         above=0.0
      end if
      if(row1-1 .gt. 0) then
         below = alpha_b*cageCount(row1-1, col1)
      else
         below=0.0
      end if
      if(col1-1 .gt. 0) then
         left = alpha_l*cageCount(row1,col1-1)
      else
         left=0.0
   end if
end do
end do
end if
end do
end do
end if

if(col1+1 .lt. 7) then
  right = alpha_r*cageCount(row1,col1+1)
else
  right=0.0
end if

count1(row1,col1)=cageCount(row1,col1) + above + below + left +right

prob(row1,col1)=1-exp(-beta_0*count1(row1,col1)-beta_1*VaccStatus1(row1,col1)*count1(row1,col1) &
  -beta_2*VaccStatus2(row1,col1)*count1(row1,col1))

rn=rand()

if(rn .lt. prob(row1,col1)) then
  inf(6*indCount*(row1-1)+indCount*(col1-1)+i)=t+1
end if

end if

end do

end do

end do

end do

!write output to file
open(UNIT=15, FILE="epi_data.txt", ACTION="write", STATUS="replace")
do i=1,3
do j=1,6
do k=1,indCount
  write(15,*) inf(6*indCount*(i-1)+indCount*(j-1)+k)
end do
end do

end do

end program

A.2 MCMC Fortran code

module var
  integer, dimension(1:180) :: inf
  integer :: indCount=10.0
end module var

program mcmc
  use var
  implicit none

  real, dimension(10001) :: beta_0, beta_1, beta_2, llike
  real, dimension(10001) :: alpha_a, alpha_b, alpha_l, alpha_r
  real, dimension(10001) :: ll, b0, b1, b2, aA, aB, aL, aR
  real :: zbeta_0, zbeta_1, zbeta_2, psi, rn
  real :: zalpha_a, zalpha_b, zalpha_l, zalpha_r
  integer :: i,j,k,seed

  !!initialize alpha and beta parameters for first iteration
  beta_0(1)=0.03


```plaintext

beta_1(1)=0.05
beta_2(1)=0.1
alpha_a(1)=0.4
alpha_b(1)=0.1
alpha_1(1)=0.5
alpha_r(1)=0.1

seed=time()
call srand(seed)

!read in epidemic data
open(27, FILE="epi_data.txt")
doi=1,3
do j=1,6
do k=1,indCount
read(27,*) inf(6*indCount*(i-1)+indCount*(j-1)+k)
end do
end do
end do
close(27)

!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
!!!!!!!!!!!!!!!!!!!!!! MCMC CODE !!!!!!!!!!!!!!!!!!!!!!!
!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

!get log-likelihood for alpha(1) and beta(1) parameters
call loglike(beta_0(1), beta_1(1), beta_2(1), alpha_a(1), alpha_b(1), alpha_l(1), alpha_r(1), llike(1))
do i=1,10000 !number of iterations

!generate proposal distributions
rn=rand()
zbeta_0=(rn*0.06)-0.03
rn=rand()
zbeta_1=(rn*0.06)-0.03
rn=rand()
zbeta_2=(rn*0.06)-0.03
rn=rand()
zalpha_a=(rn*0.6)-0.3
rn=rand()
zalpha_b=(rn*0.6)-0.3
rn=rand()
zalpha_l=(rn*0.6)-0.3
rn=rand()
zalpha_r=(rn*0.6)-0.3

!propose candidate values for alpha and beta parameters
beta_0(i+1)=betas_0(i)+zbeta_0
beta_1(i+1)=beta_1(i)+zbeta_1
beta_2(i+1)=beta_2(i)+zbeta_2
alpha_a(i+1)=alpha_a(i)+zalpha_a
alpha_b(i+1)=alpha_b(i)+zalpha_b
alpha_1(i+1)=alpha_1(i)+zalpha_l
alpha_r(i+1)=alpha_r(i)+zalpha_r

!calculate acceptance probability, psi, to reject or accept proposed values
if((beta_0(i+1) .gt. 0) .and. (beta_1(i+1) .gt. 0) .and. (beta_2(i+1) .gt. 0) .and. (alpha_a(i+1) .gt. 0) .and.
(alpha_b(i+1) .gt. 0) .and. (alpha_1(i+1) .gt. 0) .and. (alpha_r(i+1) .gt. 0) &
...)
```

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(beta_0(i+1) .lt. 1) .and. (beta_1(i+1) .lt. 1) .and. (beta_2(i+1) .lt. 1) .and. &
(alpha_a(i+1) .lt. 1) .and. (alpha_b(i+1) .lt. 1) .and. (alpha_l(i+1) .lt. 1) .and. (alpha_r(i+1) .lt. 1)) then

call loglike(beta_0(i+1), beta_1(i+1), beta_2(i+1), alpha_a(i+1), alpha_b(i+1), alpha_l(i+1), alpha_r(i+1), llike(i+1))

psi=min(0.0, llike(i+1)-llike(i)) !acceptance probability

rn=rand()

if(log(rn) .lt. psi) then !accept
    beta_0(i+1)=beta_0(i+1)
    beta_1(i+1)=beta_1(i+1)
    beta_2(i+1)=beta_2(i+1)

    alpha_a(i+1)=alpha_a(i+1)
    alpha_b(i+1)=alpha_b(i+1)
    alpha_l(i+1)=alpha_l(i+1)
    alpha_r(i+1)=alpha_r(i+1)
    llike(i+1)=llike(i+1)
else !reject
    beta_0(i+1)=beta_0(i)
    beta_1(i+1)=beta_1(i)
    beta_2(i+1)=beta_2(i)

    alpha_a(i+1)=alpha_a(i)
    alpha_b(i+1)=alpha_b(i)
    alpha_l(i+1)=alpha_l(i)
    alpha_r(i+1)=alpha_r(i)
    llike(i+1)=llike(i)
end if

else !reject
    beta_0(i+1)=beta_0(i)
    beta_1(i+1)=beta_1(i)
    beta_2(i+1)=beta_2(i)

    alpha_a(i+1)=alpha_a(i)
    alpha_b(i+1)=alpha_b(i)
    alpha_l(i+1)=alpha_l(i)
    alpha_r(i+1)=alpha_r(i)
    llike(i+1)=llike(i)
end if

end do

!write parameter estimates and log-likelihood to file
open(UNIT=18, FILE="results.txt", ACTION="write", STATUS="replace")
do i=1,10000
    write(18,*) beta_0(i), beta_1(i), beta_2(i), alpha_a(i), alpha_b(i), alpha_l(i), alpha_r(i), llike(i)
end do
close(18)
end program

!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!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real, intent(in) :: beta_0, beta_1, beta_2, alpha_a, alpha_b, alpha_l, alpha_r
real, intent(out) :: likeout
real, dimension(3,6) :: cageCount, prob, count1, count2, suscCount, infectCount
real, dimension(3,6) :: VaccStatus1, VaccStatus2

likeout=0.0

cageCount=0.0

count1=0.0

count2=0.0

suscCount=0.0

infectCount=0.0

prob=0.0

!!!! Treatment design

VaccStatus1=0.0

VaccStatus1(3:3, 1:1:1)=1.0

VaccStatus1(1:2, 3:3:1)=1.0

VaccStatus1(2:3, 5:5:1)=1.0

VaccStatus1(2:2, 6:6:1)=1.0

VaccStatus2=0.0

VaccStatus2(1:2, 1:1:1)=1.0

VaccStatus2(2:2, 2:2:1)=1.0

VaccStatus2(3:3, 4:4:1)=1.0

VaccStatus2(1:1, 6:6:1)=1.0

VaccStatus2(3:3, 6:6:1)=1.0

!calculate log-likelihood

do t=1,5

do row1=1,3

do col1=1,6

do i=1,indCount

if(t .lt. (inf(6*indCount*(row1-1)+indCount*(col1-1)+i)-1)) then !susceptible at time t+1

do row2=1,3

do col2=1,6

cageCount(row2,col2)=0.0

do j=1,indCount

if((inf(6*indCount*(row2-1)+indCount*(col2-1)+j) .le. t) .and. 

(inf(6*indCount*(row2-1)+indCount*(col2-1)+j) .ne. 0)) then

cageCount(row2,col2)=cageCount(row2,col2)+1

end if
end do
end do
end do
if(row1+1 .lt. 4) then

above = alpha_a*cageCount(row1+1,col1)
else

above=0.0
end if
if(row1-1 .gt. 0) then

below = alpha_b*cageCount(row1-1, col1)
else

below=0.0
end if
if(col1-1 .gt. 0) then

left = alpha_l*cageCount(row1, col1-1)
else

left=0.0
end if

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left=0.0
end if

if(col1+1 .lt. 7) then
  right = alpha_r*cageCount(row1,col1+1)
else
  right=0.0
end if

count1(row1,col1)=cageCount(row1,col1) + above + below + left + right

prob(row1,col1)=1-exp(-beta_0*count1(row1,col1) - beta_1*VaccStatus1(row1,col1)*count1(row1,col1) &
  - beta_2*VaccStatus2(row1,col1)*count1(row1,col1))
suscCount(row1,col1)=suscCount(row1,col1)+log(1-prob(row1,col1))
end if

if(t .eq. (inf(6*indCount*(row1-1)+indCount*(col1-1)+i)-1)) then !infectious at time t+1
  do row2=1,3
    do col2=1,6
      cageCount(row2,col2)=0.0
    do j=1,indCount
      if((inf(6*indCount*(row2-1)+indCount*(col2-1)+j) .le. t) .and. &
        (inf(6*indCount*(row2-1)+indCount*(col2-1)+j) .ne. 0)) then
        cageCount(row2,col2)=cageCount(row2,col2)+1
      end if
    end do
  end do
end do

if(row1+1 .lt. 4) then
  above = alpha_a*cageCount(row1+1,col1)
else
  above=0.0
end if

if(row1-1 .gt. 0) then
  below = alpha_b*cageCount(row1-1, col1)
else
  below=0.0
end if

if(col1-1 .gt. 0) then
  left = alpha_l*cageCount(row1,col1-1)
else
  left=0.0
end if

if(col1+1 .lt. 7) then
  right = alpha_r*cageCount(row1,col1+1)
else
  right=0.0
end if

count2(row1,col1)=cageCount(row1,col1) + above + below + left + right

prob(row1,col1)=1-exp(-beta_0*count2(row1,col1) - beta_1*VaccStatus1(row1,col1)*count2(row1,col1) &
  - beta_2*VaccStatus2(row1,col1)*count2(row1,col1))
infectCount(row1, col1) = infectCount(row1, col1) + log(prob(row1, col1))

end if
end do
end do
end do
end do

! calculate final log-likelihood, likeout
do row1 = 1, 3
  do col1 = 1, 6
    likeout = likeout + suscCount(row1, col1) + infectCount(row1, col1)
  end do
end do

return

end subroutine loglike