05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

MATHEMATICAL MODELS FOR VECTOR-BORNE INFECTIOUS DISEASE MAPPING WITH APPLICATION TO DENGUE DISEASE IN MALAYSIA

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun PustakaTBainun ptbupsi

Nor Azah SAMAT

Ph.D. Thesis **2012**

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

MATHEMATICAL MODELS FOR VECTOR-BORNE INFECTIOUS DISEASE MAPPING WITH APPLICATION TO DENGUE DISEASE IN MALAYSIA

Nor Azah SAMAT

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

Centre for Operations Management,
Management Science & Statistics,
University of Salford, Manchester, UK

Submitted in Partial Fulfilment of the Requirements of
the Degree of Doctor of Philosophy, January 2012

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

TABLE OF CONTENTS

TABLE OF CONTENTS i
LIST OF TABLES vi
LIST OF FIGURES vii
LIST OF ABBREVIATIONS xi
ACKNOWLEDGEMENTS xiii
ABSTRACT xiv

CHAPTER 1. INTRODUCTION 1
1.1 Background and Motivation 1
1.2 Objectives of the Research 4
1.3 Organization of the Thesis 5

CHAPTER 2. VECTOR BORNE DISEASES: MODELLING AND ANALYSIS OF TRANSMISSION MECHANISM FOR DISEASE MAPPING 10
2.1 Introduction 10
2.2 Vector Borne Infectious Diseases 10
2.2.1.1. Dengue Disease 12
2.2.1.2. Signs and Symptoms 13
2.2.1.3. Cause of Dengue and Transmission of the Dengue Virus 14
2.2.1.4. Treatment and Vaccine Development 15
2.2.2 Prevention and Control 16
2.2.2.1. Known Facts about Aedes Mosquitoes and the Transmission Process 17
2.3 Modelling and Analysis of Transmission Mechanism for Disease Mapping 18
2.3.1 Modelling Disease Transmission 18
2.3.2 Analysis of Disease Mapping 22
2.3.2.1. Tract-Count Data Analysis 23

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

2.3.2.2. Case-Event Data Analysis 27

CHAPTER 3. 'DISCRETE TIME, DISCRETE SPACE' STOCHASTIC SIR-SI MODEL 30

3.1 INTRODUCTION 30

3.2 SIR MODELS FOR DIRECT DISEASE TRANSMISSION 30

3.2.1 Deterministic SIR Model 30

3.2.2 Stochastic SIR Model 33

3.3 SIR-SI MODELS FOR INDIRECT DISEASE TRANSMISSION 35

3.3.1 Deterministic SIR-SI Model 35

3.3.2 Stochastic SIR-SI Model 39

CHAPTER 4. 'CONTINUOUS TIME, DISCRETE SPACE' STOCHASTIC SIR-SI MODEL 44

4.1 INTRODUCTION 44

4.2 DIFFERENTIAL EQUATIONS FOR SIR-SI MODEL OF DENGUE DISEASE TRANSMISSION 45

4.3 ASYMPTOTIC BEHAVIOUR OF SOLUTIONS OF THE SIR-SI DIFFERENTIAL EQUATIONS 46

4.4 NUMERICAL ANALYSIS OF SOLUTIONS OF THE SIR-SI DIFFERENTIAL EQUATIONS 55

CHAPTER 5. 'DISCRETE TIME, CONTINUOUS SPACE' AND 'CONTINUOUS TIME, CONTINUOUS SPACE' STOCHASTIC SIR-SI MODEL 59

5.1 INTRODUCTION 59

5.2 THE DATA 60

5.3 THE MODEL 61

5.3.1 Homogeneous Poisson Process and Heterogeneous Poisson Process 61

5.3.2 Spatial Poisson Process Model 62

5.3.3 Spatial Bayesian Poisson Process Model for SIR-SI Vector Borne Infectious Disease Transmission over Continuous Space 63

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

5.4 SUMMARY 69

CHAPTER 6. RELATIVE RISK ESTIMATION BASED ON STOCHASTIC DIFFERENCE AND DIFFERENTIAL EQUATIONS FOR DISEASE TRANSMISSION 71

6.1 INTRODUCTION 71

6.2 RELATIVE RISK ESTIMATION BASED ON STOCHASTIC SIR-SI MODEL 73

CHAPTER 7. APPLICATION TO RELATIVE RISK ESTIMATION FOR DENGUE DISEASE MAPPING IN MALAYSIA 76

7.1 INTRODUCTION 76

7.2 APPLICATION TO RELATIVE RISK ESTIMATION FOR DENGUE DISEASE MAPPING BASED ON DISCRETE TIME, DISCRETE SPACE DATA 77

7.2.1 Relative Risk Estimation for Dengue Disease Mapping based on Standardized Morbidity Ratio and Poisson-Gamma Model 78

7.2.1.1. WinBUGS Code for Relative Risk Estimation based on the SMR Model and the Poisson-gamma Model 82

7.2.2 Relative Risk Estimation for Dengue Disease Mapping based on the Discrete Time SIR Model 84

7.2.2.1. WinBUGS Code for Relative Risk Estimation based on the Discrete Time SIR Model 87

7.2.3 Relative Risk Estimation for Dengue Disease Mapping based on the Discrete Time Discrete Space Stochastic SIR-SI Model 88

7.2.3.1. The Data Set 88

7.2.3.2. Converting Daily Rates into Weekly Rates 89

7.2.3.3. Estimation of Vector Mosquito Populations 92

7.2.3.4. Comparison of Posterior Expected Relative Risk for Four Different Estimation Methods of Vector Mosquito Population 102

7.2.3.5. WinBUGS Code for Relative Risk Estimation based on the Discrete Time, Discrete Space Stochastic SIR-SI Model 110

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

7.2.4 Comparison of Posterior Expected Relative Risk for Dengue Disease Mapping based on SMR Model, Poisson-Gamma Model, Discrete Time SIR Model and Discrete Time, Discrete Space Stochastic SIR-SI Model 118

7.2.4.1. Maps for the Relative Risk of Dengue Disease in Malaysia during Epidemiology Week 53 120

7.2.5 Summary 125

7.3 Application of Dengue Disease Transmission Model for Relative Risk Estimation based on Continuous Time, Discrete Space Data 127

7.3.1 The Data Set 128

7.3.2 Application of Asymptotic Analysis of the Stochastic SIR-SI Model for Dengue Disease Transmission to Continuous Time, Discrete Space Data 130

7.3.3 Application of Numerical Analysis of Solutions for the SIR-SI Model of Dengue Disease Transmission to Continuous Time, Discrete Data 133

7.3.3.1. Estimation of Vector Mosquito Populations 134

7.3.3.2. Comparison of Posterior Expected Relative Risks for Four Different Estimation Methods of the Vector Mosquito Population 139

7.3.4 Maps of the Relative Risk Estimates for Dengue Disease Mapping in the Six Zones of Kuala Lumpur 147

7.3.5 WinBUGS Code for Relative Risk Estimation based on the Continuous Time, Discrete Space, Stochastic SIR-SI Model 149

7.3.6 Summary 152

CHAPTER 8. PREDICTING RELATIVE RISK BASED ON DISCRETE TIME AND CONTINUOUS TIME STOCHASTIC SIR-SI MODELS 155

8.1 Introduction 155

8.2 Posterior Predictive Distribution 156

8.3 Predictive Relative Risk Estimation Equations 159

8.4 Predictions of Relative Risks for Dengue Disease in Malaysia 161

8.4.1 Forecasting Relative Risks in Discrete Time and Discrete Space 161

8.4.1.1. WinBUGS Code for Predicting Relative Risks based on the Discrete Time, Discrete Space, Stochastic SIR-SI Model 165

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

8.4.2 Forecasting Relative Risks in Continuous Time and Discrete Space 167

8.4.2.1. WinBUGS Code for Predicting Risks based on the Continuous Time, Discrete Space, Stochastic SIR-SI Model 171

8.5 SUMMARY 173

CHAPTER 9. CONCLUSIONS, CONTRIBUTIONS AND RECOMMENDATIONS 175

9.1 CONCLUSION OF THE RESEARCH 175

9.2 CONTRIBUTION OF THE RESEARCH 180

9.3 RECOMMENDATIONS FOR FUTURE RESEARCH 184

REFERENCES 187

APPENDICES 198

APPENDIX 1: KNOWLEDGE DISSEMINATION 198

APPENDIX 2: WINBUGS OUTPUT OF SUMMARY STATISTICS FOR RELATIVE RISK ESTIMATION BASED ON DISCRETE TIME, DISCRETE SPACE, STOCHASTIC SIR-SI MODEL USING ASSUMPTION 1 200

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

LIST OF TABLES

Table 2-1: Major Vector-borne Diseases, Associated Vectors and Regions of Prevalence (WHO, 2000) 11

Table 7-1: Relative risk based on the SMR model and posterior expected relative risks based on the Poisson-gamma model for epidemiology week 53 81

Table 7-2: Example of WinBUGS output for posterior expected relative risks in the state of Perlis, Malaysia, for epidemiology weeks 1 to 10, obtained using the Poisson-gamma model 84

Table 7-3 Posterior expected relative risks based on the discrete time SIR model for epidemiology week 53 86

Table 7-4: Converting daily rates to weekly rates 90

Table 7-5: Posterior expected relative risk based on four assumptions of imputed vector mosquito data for epidemiology week 53 106

Table 7-6: Deviance information criterion for relative risk estimation based on the discrete time, discrete space stochastic SIR-SI model using four assumptions for estimation of mosquito population 108

Table 7-7: Example of WinBUGS results for the posterior summaries of relative risk estimation based on discrete time, discrete space, stochastic SIR-SI model for the state of Selangor from epidemiology week 10 to epidemiology week 19 for the year 2008/2009 114

Table 7-8: Estimated relative risks in epidemiology week 53 for dengue disease mapping using four different models 119

Table 7-9: Deviance information criterion for relative risk estimation based on the continuous time, discrete space, stochastic SIR-SI model using four assumptions for imputing the mosquito population 146

Table 8-1: Comparison between the posterior expected relative risks and posterior predictive expected relative risks for epidemiology week 53 163

Table 9-1: Contributions of this research to the knowledge of relative risk estimation in disease mapping 180

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

LIST OF FIGURES

Figure 2-1: World distribution of dengue viruses and their mosquito vector *Aedes Aegypti* in 2005 12

Figure 2-2: Transmission of dengue virus by *Aedes* mosquito 14

Figure 2-3: *Aedes* mosquito life cycle (Hopp and Foley, 2001) 18

Figure 3-1: Compartmental SIR model for direct disease transmission 32

Figure 3-2: Compartmental SIR-SI model for dengue disease transmission 36

Figure 5-1: Illustration plots for spatial intensity function where *(a)* surface plot and *(b)* contour plot 66

Figure 5-2: Illustration plots for spatial intensity function where *(a)* 3-D surface plot and *(b)* 2-D contour plot 67

Figure 7-1: Time series plots of the estimated relative risk based on the SMR model for different states in Malaysia 79

Figure 7-2: Time series plots of the estimated relative risk based on the Poisson-gamma model for different states in Malaysia 79

Figure 7-3: Standardized morbidity ratio in WinBUGS 83

Figure 7-4 Poisson-gamma model in WinBUGS 83

Figure 7-5 Time series plots for relative risk estimation based on the discrete time SIR model for all states in Malaysia 85

Figure 7-6: Discrete time SIR model in WinBUGS 88

Figure 7-7: Time series plots for imputed infective mosquitoes without seasonality for all states in Malaysia 96

Figure 7-8: Time series plots for imputed infective mosquitoes with piecewise constant seasonality for all states in Malaysia 97

Figure 7-9: Time series plots for imputed infective mosquitoes with sinusoidal seasonality for all states in Malaysia 98

Figure 7-10: Time series plots for imputed infective mosquitoes based on propagation for all states in Malaysia 101

Figure 7-11: Time series plots for posterior expected relative risk based on discrete time, discrete space stochastic SIR-SI model for dengue disease transmission using Assumption 1 104

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

Figure 7-12: Time series plots for posterior expected relative risk based on discrete time, discrete space stochastic SIR-SI model for dengue disease transmission using Assumption 2 104
Figure 7-13: Time series plots for posterior expected relative risk based on discrete time, discrete space stochastic SIR-SI model for dengue disease transmission using Assumption 3 105
Figure 7-14: Time series plots for posterior expected relative risk based on discrete time, discrete space stochastic SIR-SI model for dengue disease transmission using Assumption 4 105
Figure 7-15: Discrete time, discrete space stochastic SIR-SI model for Assumptions 1, 2 and 3 in WinBUGS 110
Figure 7-16: Discrete time, discrete space stochastic SIR-SI model for Assumption 4 in WinBUGS 111
Figure 7-17: Example of the WinBUGS results of the 'history' plot for convergence of the relative risk estimation based on discrete time, discrete space stochastic SIR-SI model using Assumptions 1 113
Figure 7-18: Example of the WinBUGS results of the posterior densities of the relative risk estimation based on discrete time, discrete space stochastic SIR-SI model using Assumptions 1 116
Figure 7-19 Example of the WinBUGS results of the quantiles graph of the relative risk estimation based on discrete time, discrete space stochastic SIR-SI model using Assumptions 1 117
Figure 7-20: Disease map of estimated relative risks based on the standardized morbidity ratio 121
Figure 7-21: Disease map of posterior expected relative risks based on the Poisson-gamma model 122
Figure 7-22: Disease map of posterior expected relative risks based on the discrete time SIR model 123
Figure 7-23: Disease map of posterior expected relative risks based on the discrete time, discrete space, stochastic SIR-SI model 124
Figure 7-24: Parliamentary constituencies division of Kuala Lumpur 129
Figure 7-25: Time series plot for imputed infective mosquitoes without seasonality for six zones in Kuala Lumpur 135

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

Figure 7-26: Time series plot for imputed infective mosquitoes with piecewise constant seasonality for six zones in Kuala Lumpur 136
Figure 7-27: Time series plot for imputed infective mosquitoes with sinusoidal seasonality for six zones in Kuala Lumpur 136
Figure 7-28: Time series plot for imputed infective mosquitoes based on propagation for six health administrative zones of Kuala Lumpur 137
Figure 7-29: Time series plots of fitted values of susceptible, infective and recovered human populations and susceptible and infective vector mosquito populations in the City Centre zone using Assumption 4 139
Figure 7-30: Time series plots of posterior expected relative risk based on the continuous time, discrete space, stochastic SIR-SI model for dengue disease transmission using Assumption 1 140
Figure 7-31: Time series plots of posterior expected relative risk based on the continuous time, discrete space, stochastic SIR-SI model for dengue disease transmission using Assumption 2 140
Figure 7-32: Time series plots of posterior expected relative risk based on the continuous time, discrete space, stochastic SIR-SI model for dengue disease transmission using Assumption 3 141
Figure 7-33: Time series plot of posterior expected relative risk for City Centre 141
Figure 7-34: Time series plot of posterior expected relative risk for Kepong 142
Figure 7-35: Time series plot of posterior expected relative risk for Setapak 142
Figure 7-36: Time series plot of posterior expected relative risk for Cheras 142
Figure 7-37: Time series plot of posterior expected relative risk for Klang Lama 143
Figure 7-38: Time series plot of posterior expected relative risk for Damansara 143
Figure 7-39: Time series plots of posterior expected relative risk based on the continuous time, discrete space, stochastic SIR-SI model for dengue disease transmission using Assumption 4 144
Figure 7-40: Time series plot of relative risk based on Standardized Morbidity Ratio 148
Figure 7-41: Disease map of posterior expected relative risks based on the continuous time, discrete space stochastic SIR-SI model for one representative day during the year 2009 148
Figure 7-42: Continuous time, discrete space, stochastic SIR-SI model for Assumptions 1, 2 and 3 in WinBUGS 150

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

Figure 7-43: Continuous time, discrete space, stochastic SIR-SI model for Assumption 4 in WinBUGS 151
Figure 8-1: Time series plot for the posterior predictive expected relative risks in epidemiology weeks 1 to 53 spanning 2009-2010 for 16 states in Malaysia 162
Figure 8-2 Disease map of posterior predictive expected relative risks based on the discrete time, discrete space, stochastic SIR-SI model for epidemiology week 53 165
Figure 8-3: Predictions for discrete time, discrete space, stochastic SIR-SI model in WinBUGS 166
Figure 8-4: Time series plot for the posterior predictive expected relative risks during the year 2010 for six zones in Kuala Lumpur, Malaysia 168
Figure 8-5: Details of the time series plots of the posterior predictive expected relative risks during the year 2010 for 6 zones in Kuala Lumpur, Malaysia 169
Figure 8-6: Disease map of posterior predictive relative risks based on the continuous time, discrete space stochastic SIR-SI model during the year 2010 170
Figure 8-7: Predictions for continuous time, discrete space, stochastic SIR-SI model in WinBUGS 172

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

LIST OF ABBREVIATIONS

SIR-SI	*Susceptible-infective-recovered* for human populations; *susceptible-infective* for vector populations
SIR	*Susceptible-infective-recovered* for human populations
GIS	Geographic information system
WHO	World Health Organization
CDC	Centre for Disease Control and Prevention
DF	Dengue fever
DHF	Dengue haemorrhagic fever
SI	*Susceptible-infective* for human populations
SIS	*Susceptible-infective-susceptible* for human populations
SIRS	*Susceptible-infective-removed or recovered-susceptible* for human populations
SEIR	*Susceptible-exposed-infective-removed or recovered* for human populations
SIRS-SI	*Susceptible-infective-removed or recovered-susceptible* for human populations; *susceptible-infective* for vector populations
SEIR-SI	*Susceptible-exposed-infective-removed or recovered* for human populations; *susceptible-infective* for vector populations
SMR	Standardized morbidity or mortality ratio

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

CSR	Complete spatial randomness
HPP	Homogeneous Poisson process
HEPP	Heterogeneous Poisson process
NHPP	Non-homogeneous Poisson process
CAR	Conditional autoregressive
MCMC	Markov chain Monte Carlo
GOF	Goodness-of-fit
AIC	Akaike information criterion
BIC	Bayes information criterion
DIC	Deviance information criterion

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who have made it possible for me to complete this thesis.

My foremost thanks go to my supervisor Professor David F. Percy, who created many of the ideas and directions for the research, suggested methods for the analysis, verified the results, and proofread numerous drafts. I thank him for all advice; for the time he has given to this research; for the assistance that gave me time to work; and most of all, for making me confident with my work. Without him, this thesis would not have been possible.

I thank my final oral defense examiners, Professor Rose D. Baker and Professor Damian Clancy, for carefully reading the dissertation and for their suggestions on improving it. I warmly thank all members from the Centre for Operations Management, Management Science & Statistics, especially to Ms. Susan J. Sharples and Mrs. Julie Brady, for their kind support and guidance, which have been wonderful in helping with this study.

I thank all my friends, not only for help and support but more so for making my four years in Salford fun and meaningful. I also thank the Ministry of Health, Malaysia, for its cooperation in providing data for this research that enabled me to do the analysis and subsequently write this thesis.

I owe my loving thanks to my husband Affandi Kastor, my son Muhammad Afiq Aiman and my daughters Marsya Ayuni and Mirsya Ardini. Without their encouragement and understanding it would have been impossible for me to finish this work. My special gratitude is due to my father Samat Samuri, my late mother Marpuah Sumadi and my siblings for their devoted and loving support.

Finally, financial support from the Ministry of Higher Education, Malaysia, and Universiti Pendidikan Sultan Idris is gratefully acknowledged.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

ABSTRACT

Few publications consider the estimation of relative risk for vector borne infectious diseases. Most of these articles involve exploratory analysis that includes the study of covariates and their effects on disease distribution and the study of geographic information systems to integrate patient-related information. The aim of this research is to introduce an alternative method of relative risk estimation based on stochastic SIR-SI models (susceptible-infective-recovered for human populations; susceptible-infective for vector populations) for the transmission of vector borne infectious diseases, particularly dengue disease.

Firstly, we describe deterministic compartmental SIR-SI models that are suitable for dengue disease transmission. We then adapt these to develop corresponding stochastic SIR-SI models using 'discrete time, discrete space' and 'continuous time, discrete space' data. Our first type of stochastic models comprises extensions of the discrete time stochastic SIR model proposed by Lawson (2006) and involves the theoretical construction and iterative evaluation of SIR-SI difference equations. Our second type of stochastic models involves continuous extensions of the first type of models and involves the theoretical construction and numerical analysis of SIR-SI differential equations. Determining solutions for the latter models involves investigating their asymptotic properties and applying simple computational algorithms for solving the SIR-SI system of ordinary differential equations. Further discussion on modelling continuous space data regardless of the measurement scale of times is also presented in this thesis.

Finally, an alternative method of estimating the relative risk for dengue disease mapping based on these stochastic SIR-SI models is developed and applied to analyse dengue data from Malaysia. This new approach offers better models for estimating relative risks for dengue disease mapping compared to the other common approaches, because it takes into account the transmission process of the disease while allowing for covariates and spatial correlation between risks in adjacent regions. Although the SIR-SI model for dengue disease is the focus of this research, the methods extend readily to apply more generally to other vector borne infectious diseases.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

CHAPTER 1. INTRODUCTION

1.1 BACKGROUND AND MOTIVATION

This research is concerned with the study of geographical distributions of infectious diseases. Lawson (2001) classified this study into three main areas of application, which are disease mapping, disease clustering and ecological analysis. In disease mapping, the purpose of the analysis is to estimate the true relative risk of a disease of interest across a geographical study area, where the main aim is to reduce the noise in a disease map. In contrast, the purpose of the analysis in disease clustering is to examine potential environmental hazards based on whether a disease map reveals localised clusters of cases and to determine the locations of any such clusters, which are important in public health surveillance. Finally, ecological analysis focuses on the analysis of geographical distributions of disease in relation to explanatory variables, where various supplementary issues relating to disease mapping can be identified.

In this research, disease mapping is the focus of our attention. Disease mapping is a method to display the geographical distribution of disease occurrence, given observed data on disease rates, which are generally subject to random variability. Generally, it involves the usage and interpretation of coloured or shaded maps that show the incidence of specified diseases in regions of interest. Good maps of disease risk have been recognized as an important tool for disease control. Maps that show relative risks of a disease in a geographical region are important for identifying areas that deserve closer scrutiny or more attention and for identifying etiological factors. Disease maps may be especially useful for government agencies to allocate resources or identify

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

hazards related to disease (Meza, 2003). The production of such maps relies on modelling to estimate and predict the risks, so better estimates and predictions of risk would subsequently produce more accurate maps of disease risk.

Numerous studies of disease mapping use a regression-type model where observable (fixed effects) and unobservable (random effects) variables are included to give a clean map and hence depict the true excess risk surface (see, for example, Besag *et al.*, 1991; Bernardinelli *et al.*, 1995; Waller *et al.*, 1997; Knorr-Held and Besag, 1998; Boehning *et al.*, 2000; Lawson and Clark, 2002; MacNab and Dean, 2002). In spite of this, there are only a few studies that use disease transmission models for disease mapping (see, for example, Gemperli *et al.*, 2006).

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

For the case of dengue, there are only a few studies that use statistical methods to estimate the relative risk for disease mapping (see, for example, Ferreira and Schmidt, 2006, and Kismiantini *et al.*, 2006). However most dengue studies are based on exploratory analysis which includes the study of covariates and their effects on dengue disease distribution in a map (see, for example, Gubler, 1998; Rosa-Freitas *et al.*, 2003). Furthermore, there are also studies that use a geographic information system (GIS) to integrate the patient-related information (see, for example, Tran *et al.*, 2004; Seng *et al.*, 2005; Mohd Din *et al.*, 2007).

In Malaysia, current approaches for identifying hot spots or high-low risk areas are still based on the total numbers of dengue occurrences across the regions. For instance, large numbers of dengue cases in certain areas represent high risks of

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

dengue occurrences without considering other factors like the population size or the land size of individual areas. Current prevention and control strategies for dengue disease in Malaysia, which comprise six aspects including disease surveillance and control, vector surveillance and control, public education, inter-agency collaboration and community participation, quality assurance, and research and training, are only implemented after the dengue cases have occurred.

Therefore, we are interested in introducing an alternative method to estimate and predict the high-low risk areas, based on transmission models for dengue disease, which takes into account significant covariates in order to help prevent dengue disease before it occurs.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

Most of the mathematical modelling and statistical analysis used for dengue disease transmission models until now has been deterministic, ignoring the possible importance of random effects. Deterministic models are preferred because of the availability of the data and because they are relatively easy to define and implement, in comparison to the stochastic models. However, some studies have highlighted the effects that stochasticity can have on transmission of a disease (see, for example, Bartlett, 1964 and 1978; Daley and Gani, 1999; Keeling and Rohani, 2007; Keeling and Ross, 2008). Moreover, many published studies of general infectious diseases used stochastic models in the analysis (see, for example, Addy *et al.*, 1991; O'Neill, 2002; Clancy, 2005; Clancy and O'Neill, 2008). Most studies indicate that the use of stochastic terms in the analysis of infectious diseases allows for a probabilistic statement about the progression of the disease to be made, and it is generally agreed

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

that this renders the modelling as more realistic. Therefore, this research will introduce stochastic models for dengue disease transmission, which consider covariates that are significant for dengue disease including space-time factors and interactions between vector and human host. These models are extensions of the stochastic SIR models suggested by Lawson (2006).

1.2 OBJECTIVES OF THE RESEARCH

The objectives of this research are as follows:

1. To develop and propose a discrete time, discrete space, stochastic model based on difference equations in the form of a SIR-SI model for vector-borne infectious disease transmission.

2. To develop and propose a continuous time, discrete space, stochastic model based on differential equations in the form of a SIR-SI model for vector-borne infectious disease transmission.

3. To introduce and discuss discrete time, continuous space, stochastic SIR-SI models and continuous time, continuous space, stochastic SIR-SI models for vector-borne infectious disease transmission.

4. To propose an alternative method of relative risk estimation for vector-borne infectious disease mapping based on disease transmission models.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

5. To estimate the relative risk for dengue disease mapping based on discrete time, discrete space, and continuous time, discrete space, stochastic SIR-SI models for dengue disease transmission in Malaysia.

6. To compare the results of relative risk estimation based on the discrete time, discrete space, and continuous time, discrete space, stochastic SIR-SI models of dengue disease transmission with other existing statistical methods for disease mapping using dengue data from Malaysia.

7. To propose a procedure for generating infectious disease maps based on the posterior distribution for relative risk, as determined using Markov chain Monte Carlo methods for implementing Bayesian analysis.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

8. To develop procedures for predicting regional infectious disease for future time periods conditional upon the observed history, in order to permit cross-sectional and longitudinal comparisons of disease status and progression.

The following section contains an outline of the thesis, and gives an overview of the work that it contains.

1.3 ORGANIZATION OF THE THESIS

This thesis is organized into nine chapters. Chapter 1 introduces the background of, and the motivation for, this research. Then, the objectives underpinning this research are explained.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

In Chapter 2, a brief explanation about vector borne infectious disease modelling is included, specifically referring to some basic facts about dengue disease. These include the signs and symptoms, cause and transmission of the dengue virus, prevention and control, and treatment and vaccine development for dengue disease. This chapter also discusses previous work that has been published on developing disease transmission models, especially for dengue disease, and the analysis of disease maps. The former includes an explanation about deterministic and stochastic disease transmission models, while the latter includes a discussion about previous and current analytical methods for disease mapping.

Chapter 3 presents and explains a development of discrete time, discrete space, stochastic SIR-SI models of indirect disease transmission, which are an extension of the SIR model of direct disease transmission proposed by Lawson (2006). We describe the deterministic difference equations of the SIR-SI model and subsequently adapt this system of difference equations to develop a stochastic SIR-SI model. In this research, the SIR-SI model used relates specifically to dengue disease transmission. However, it can easily be adapted for use with any other indirect disease transmission, especially for diseases where the virus is transmitted by a vector.

Then, the development of a continuous time, discrete space, stochastic SIR-SI model for dengue disease transmission will be disclosed in Chapter 4. This model is obtained by extending the model proposed in Chapter 3, but with a different approach related to continuous time data. This includes the description of deterministic nonlinear differential equations for the SIR-SI model for dengue disease transmission. We

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

follow this development by considering two methods of solution, which involve investigating their asymptotic properties and applying simple computational algorithms for solving the SIR-SI system of ordinary differential equations.

Chapter 5 investigates and describes possible models for continuous space data regardless of the measurement scale of times for the SIR-SI model of dengue disease transmission. Our preliminary investigations suggest that these models are potentially superior in their ability to encapsulate more information than corresponding discrete space models, but without considerable extra effort in modelling each specific disease under consideration and in collecting more detailed data, they are unlikely to offer any practical advantages and are also less amenable to computational evaluation.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

Furthermore, an alternative method for estimating the relative risk in order to improve disease mapping based on the standard disease transmission models is developed and this will be elaborated upon in Chapter 6. This includes the estimation of relative risk based on stochastic difference and stochastic differential equations for the SIR-SI model of vector-borne infectious disease transmission.

Chapter 7 presents and demonstrates the results of our application to relative risk estimation for disease mapping to observed dengue data from Malaysia. These involve calculating and comparing the results of analysis for both discrete time, discrete space data and continuous time, discrete space data. Firstly, the findings of relative risk estimation based on discrete time, discrete space data are presented. This includes the results of relative risk estimation using the classical model based on

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

standardized morbidity ratios, the earliest example of Bayesian mapping methods using the Poisson-gamma model and the discrete time SIR model proposed by Lawson (2006). Next, the estimation of relative risk based on discrete time, discrete space, stochastic SIR-SI model of dengue disease transmission that we proposed is discussed. All related findings are then compared and presented in tables and maps.

Also in Chapter 7, the results of our application to continuous time, discrete space, data are presented. These involve the theoretical construction and numerical analysis of SIR-SI differential equations, which include the investigation of their asymptotic properties and applying simple computational algorithms for solving the nonlinear SIR-SI system of ordinary differential equations. Results of the asymptotic analysis give some information about the steady state counts of susceptible, infective and recovered human populations, and susceptible and infective vector mosquito populations. The numerical analysis involves the use of a discrete algorithm within WinBUGS software for generating approximate solutions based on the continuous time model. It generates information about susceptible, infective and recovered human populations, and susceptible and infective vector mosquito populations in finite time, which are subsequently used in the analysis of relative risk estimation for dengue disease mapping.

In Chapter 8, a procedure for predicting relative risk is included to suggest approximate future dengue disease progression patterns for Malaysia. Predictions of relative risk could help in controlling and preventing dengue disease before it occurs. Predictive dengue risk maps produced from these predictions will show the high-low

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

risk areas of dengue risk for the future. Several management strategies, including publicity campaigns and environmental interventions, could be planned in targeted areas based on predictive risk maps such as these, in order to prevent dengue disease from advancing.

Finally, Chapter 9 summarises the thesis and discusses the findings of this research. It describes and highlights the original contributions that we offer and proposes some recommendations for future work.

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi

05-4506832 pustaka.upsi.edu.my Perpustakaan Tuanku Bainun Kampus Sultan Abdul Jalil Shah PustakaTBainun ptbupsi