

**MATHEMATICAL ANALYSIS OF PARASITE
DYNAMICS OF LYMPHATIC FILARIASIS USING
RANGE MODELLING AND OTHER APPROACHES IN
RELATION TO OBSERVATIONAL DATA FROM
SRI LANKA**




by

NALEEN CHAMINDA GANEGODA

Thesis submitted to the University of Sri Jayewardenepura for the
award of the Degree of Doctor of Philosophy in Mathematics in

2011

The work described in this thesis was carried out by me under the supervision of Prof. D. A. Tantrigoda, Dr. S.K. Boralugoda and Dr. S.S.N. Perera and a report on this has not been submitted in whole or in part to any University or any other institution for another Degree/Diploma.



.....

N.C. Ganegoda

We certify that the above statement made by the candidate is true and that this thesis is suitable for submission to the University for the purpose of evaluation.


.....

Prof. D. A. Tantrigoda

24. 01. 2013
.....


Date


.....

Dr. S.K. Boralugoda

29/01/2013
.....

Date


.....

Dr. S.S.N. Perera

29-01-2013
.....

Date

N.C. Ganegoda
Department of Mathematics
University of Sri Jayewardenepura
23.01.2013

Faculty of Graduate Studies
University of Sri Jayewardenepura


Resubmission of the Ph.D. thesis after minor corrections

Hereby I resubmit my Ph.D. thesis incorporating minor corrections recommended by the examiners at the viva-voce examination held on 9th January 2013. Required certification by the supervisors and the Head of the Department is also included here.



N.C. Ganegoda

We certify that the Ph.D. thesis of N.C. Ganegoda is resubmitted^{ing} herewith incorporating the minor corrections suggested by the examiners.



Prof. D.A. Tantirigoda
(Supervisor)



Dr. S.K. Boralugoda
(Supervisor)



Dr. S.S.N. Perera
(Supervisor)



Dr. R. Sanjeewa
(Head/ Dept. of Mathematics)

CONTENTS

LIST OF TABLES	vi
LIST OF FIGURES	vii
ACKNOWLEDGEMENT	x
ABSTRACT	xii
CHAPTER 1 INTRODUCTION	01
1.1 Basic information of Lymphatic Filariasis	02
1.1.1 Lymphatic Filariasis in Sri Lanka	03
1.2 Mathematical modelling aspect	05
1.2.1 Causality of modelling Lymphatic Filariasis in Sri Lanka	06
1.3 Research objectives and modelling framework	07
1.4 Structure of the thesis	09
CHAPTER 2 LITERATURE REVIEW	11
2.1 Catalytic models	11
2.2 Deterministic modelling with differential equations	13
2.3 Stochastic modelling	16
2.4 Modelling approaches in Sri Lankan context	18
2.5 Computer simulation models and trials	23
2.6 Directions for rationale of the study	23
CHAPTER 3 METHODOLOGY	25
3.1 Research material	25
3.1.1 Study area	25
3.1.2 Data retrieving	26

3.2 Approaches of modelling, validation and analysis	28
3.2.1 Range modelling approach	28
3.2.2 Approach of model validation	29
3.2.3 Approach of mathematical analysis	31
3.3 Mathematical tools and techniques	31
3.3.1 Differential equations	32
3.3.2 Uniform distribution	33
3.3.3 Lebesgue measure and ‘almost everywhere’ condition	34
3.3.4 Discrete Fourier transform and periodicities	35
3.3.5 Wavelets and decomposition	36
3.3.6 Eigenvectors	37
3.3.7 Computational approach	38
CHAPTER 4 MATHEMATICAL MODEL FOR PARASITE DYNAMICS IN THE VECTOR MOSQUITO	40
4.1 Background of vector-parasite interaction	40
4.2 Model-based initiator for L1 larvae yield (L1-initiator)	42
4.2.1 Model equations and parameterization	42
4.2.2 Phase plane analysis	46
4.3 Model-based initiator for L3 larvae yield (L3-initiator)	51
4.3.1 Model equations and parameterization	52
4.3.2 Model solution	53
4.4 Simulation results	54
4.4.1 Phase plane simulations	55
4.4.2 Sensitivity analysis of L1-initiator	57
4.4.3 Sensitivity analysis of L3-initiator	60
4.5 Discussion of mathematical incorporations	61
4.5.1 Remarks on model variables	61
4.5.2 Phase plane tactics	63
4.5.3 Range modelling tactics	64
4.5.4 More generalised initiator	67

4.6 Summary	69
CHAPTER 5 MATHEMATICAL MODEL FOR PARASITE DYNAMICS IN THE HUMAN HOST	70
5.1 Background of parasite dynamics in the human host	70
5.2 Model equations and parameterization	71
5.2.1 Modelling filarial worm load and anti-L3 immunity	72
5.2.2 Modelling microfilariae (Mf) production and anti-fecundity immunity	85
5.3 Simulation results	88
5.3.1 Sensitivity analysis of anti-L3 immune response	88
5.3.2 Sensitivity analysis of adult worm load and Mf production	91
5.4 Validating structure for the accumulated history of infection	98
5.4.1 Introductory remarks	98
5.4.2 Mathematical preliminaries	99
5.4.3 Segment-into-point (SIP) reduction	101
5.4.4 Zero and non-zero accumulations	105
5.4.5 Smoothness of non-zero accumulations	107
5.4.6 Unit integral behaviour of non-zero accumulations	108
5.4.7 Discussion	109
5.5 Discussion of mathematical incorporations	113
5.5.1 Range modelling tactics	113
5.5.2 Hyperbolic saturating function for immune response	115
5.5.3 Variations of Mf count	117
5.6 Summary	119
CHAPTER 6 OVERALL MODEL, VALIDITY AND MODEL-BASED EXPERIMENTS	121
6.1 Coordinating overall model	121
6.1.1 Involvement of vector abundance	122

6.1.2	Involvement of treatment	123
6.1.3	Recursive criteria for Mf-positive prevalence	126
6.1.4	Computational flow	129
6.2	Material and methods for model validity	133
6.2.1	Decomposed error spectrum	134
6.2.2	Wavelet-based error taming: a central measure	141
6.3	Validation of overall model	151
6.3.1	Validating for vector mosquito abundance	153
6.3.2	Validating for Mass Drug Administration (MDA) programme	158
6.3.3	Validating for immunity	164
6.3.4	Validating for age distribution	165
6.4	Model-based experiments	166
6.4.1	Mf-positive prevalence in the first half of study period	166
6.4.2	Mf-positive prevalence without MDA programme	168
6.4.3	Continuous MDA	169
6.4.4	Vector control instead of anti-filarial drugs	170
6.4.5	Effect of losing immunity	171
6.5	New index for the effectiveness of MDA	172
6.5.1	Mathematical formulation	173
6.5.2	Key illustrations regarding indices Q and Q_p	176
6.5.3	Discussion	181
6.6	Discussion of mathematical incorporations	181
6.6.1	Range modelling tactics	182
6.6.2	Dealing with variation in Mf-positive prevalence	184
6.7	Summary	185
CHAPTER 7	GENERAL DISCUSSION AND CONCLUSIONS	186
7.1	Parsimony and model adequacy	186
7.2	Evaluation of information and modelling tactics	188
7.3	Development of mathematical tools and techniques	190

7.4 Decision making based on mathematical results	192
7.5 Concluding remarks	194
7.6 Future directions	195
REFERENCES	198
APPENDIX I: Computer simulation programme	208
APPENDIX II: Additional results on Mf-positive prevalence	219
APPENDIX III: List of publications/ scientific communications	223

LIST OF TABLES

Table Code	Description	Page Number
4.1	Values of parameter a in L1-initiator corresponding to the L1 parasite loss.	66
5.1	Range modelling tactic on host's age.	74
6.1	Categories of Mf-carriers and number of days carrying Mf.	131
6.2	Annual prevalence (%) of premises consisting vector mosquitoes (V).	153
6.3	Upper and lower baselines for annual prevalence (%) of premises consisting vector mosquitoes (V) and corresponding ranges	154
6.4	Combinations of initial P , initial M and maximum M for the L1-initiator	154
6.5	DES-C for Mf-positive prevalence subjected to lower baseline, upper baseline and data of annual prevalence (%) of premises consisting vector mosquitoes (V) for Panadura MOH area.	156
6.6	DES-W for Mf-positive prevalence subjected to lower baseline, upper baseline and data of annual prevalence (%) of premises consisting vector mosquitoes (V) for Panadura MOH area.	156
6.7	Percentages of population covered under MDA drug distribution.	159
6.8	Compliance for drug consumption under MDA.	159
6.9	DES-C for Mf-positive prevalence subjected to lower baseline, upper baseline and data of MDA drug consumption for Panadura MOH area.	161
6.10	DES-W for Mf-positive prevalence subjected to lower baseline, upper baseline and data of MDA drug consumption for Panadura MOH area.	162
6.11	Increasing (\uparrow) and decreasing (\downarrow) behaviour of exposed population fractions v_1 and v_2 subject to increasing a , b and w .	180

LIST OF FIGURES

Figure Code	Description	Page Number
1.1	Cycle of parasite dynamics of Lymphatic Filariasis.	2
1.2	Endemic area of Lymphatic Filariasis in Sri Lanka.	4
1.3	Modelling framework for parasite dynamics of Lymphatic Filariasis.	9
3.1	Map of the study area (MOH areas: Panadura, Kalutara and Beruwala)	26
4.1	Trajectories close to the equilibrium level (0,0) of L1-initiator model with increasing rate of infected mosquitoes ($r > 0$).	47
4.2	Increasing (\uparrow) and decreasing (\downarrow) behaviour of populations of L1 parasites (P) and infected mosquitoes (M) in different phase plane quadrants.	48
4.3	Periodic fluctuations of populations of L1 parasites (P) and infected mosquitoes (M).	49
4.4	Trajectories close to equilibrium level (0,0) of L1-initiator with decreasing rate of infected mosquitoes ($r < 0$).	51
4.5	Simulation process combining L1-initiator and L3-initiator	55
4.6	Complete solution trajectories and resultant segments for 12-hours period of L1-initiator (with $r > 0$) for different initial values.	56
4.7	Complete solution trajectories and resultant segments for 12-hours period of L1-initiator (with $r < 0$) for different initial values.	56
4.8	Dynamics of L1 parasites (P) and infected mosquitoes (M) for different sets of parameter values with a fixed initial combination $P = 4, M = 3$.	57
4.9	Number of L1 parasites per infected mosquito (α) for different values of parameters a and b in L1-initiator.	58
4.10	Number of L1 parasites per infected mosquito (α) for different values of parameters r and s in L1-initiator.	59
4.11	Mean number of L3 parasites resultant by L3-initiator for different values of L1 parasites per infected mosquito (α) and parasite loss (h).	61
5.1	Behaviour of exposure index (ei) for a given cut-off age (c).	73
5.2	Behaviour of immature worm population (N) for different infection rates (λ).	75
5.3	Behaviour of accumulation for history of infection (A) for different infection rates (λ).	78

5.4	Banding of immunological memory period (T) by band-off length (T_b).	79
5.5	Behaviour of accumulation for history of infection (A) for different immunological memory periods (T).	80
5.6	Mf count distribution of Mf-positive individuals.	86
5.7	Modified version of Mf count distribution of Mf-positive individuals.	87
5.8	Immune response (I) for different infection rates (λ).	89
5.9	Immune response (I) for different immunological memory period (T) and number of worms for immunity boosting (W^*) values.	90
5.10	Worm load (W) for different infection rates (λ).	92
5.11	Worm load (W) without immune response (I) for different infection rates (λ).	93
5.12	Mf count (B) for different infection rates (λ).	94
5.13	Worm load (W) for different number of worms for immunity boosting (W^*) values.	95
5.14	Mf count (B) for different number of worms for immunity boosting (W^*) values.	96
5.15	Mf count (B) for different production rates (η_a).	97
5.16	Framework of model formulation and validation for number of immature worms (N) and accumulation for history of infection (A).	99
5.17	An illustration of number of immature worms (N)	100
5.18	An illustration of a function for immature worms (N) with three segments.	102
5.19	Illustration of segment-into-point reduction.	103
5.20	Accumulation (A) for the SIP-reduced function.	104
5.21	Illustrations of SIP-reduced N : (A) – a.e.-zero and (B) – a.e. non-zero.	106
5.22	Structural illustration to validate accumulation for history of infection (A) via SIP reduction.	111
5.23	Behaviour of hyperbolic saturating functions: (A) $I = \frac{\gamma A}{\delta + A}$ and (B) $I = \frac{\gamma A^2}{\delta + A^2}$.	116
5.24	An illustration of Mf count (B) and corresponding Fourier transform amplitudes.	118
5.25	Mf count (B) and Fourier transform amplitudes after infusing short-term periodic variations.	119
6.1	Modelling stages and influencing factors of the overall model for parasite dynamics of Lymphatic Filariasis.	122

6.2	Logical condition to execute L1-initiator with regard to annual prevalence of premises consisting vector mosquitoes (V).	123
6.3	Detection for Mf-positive prevalence and Mf-carrier prevalence.	128
6.4	Computational flow associated with the overall model.	129
6.5	Illustration of a data series and its simulated series.	138
6.6	Taming process of n number of simulated series $S_1, S_2, S_3, \dots, S_n$.	144
6.7	Mf-positive prevalence subjected to annual prevalence (%) of premises consisting vector mosquitoes (V) for Panadura MOH area.	155
6.8	Mf-positive prevalence subjected to annual prevalence (%) of premises consisting vector mosquitoes (V) for Kalutara MOH area.	157
6.9	Mf-positive prevalence subjected to annual prevalence (%) of premises consisting vector mosquitoes (V) for Beruwala MOH area.	158
6.10	Mf-positive prevalence subjected to MDA drug consumption for Panadura MOH area.	161
6.11	Mf-positive prevalence subjected to MDA drug consumption for Kalutara MOH area.	163
6.12	Mf-positive prevalence subjected to MDA drug consumption for Beruwala MOH area.	163
6.13	Mf-positive prevalence subjected to immune response (I) for Panadura MOH area.	164
6.14	Age distribution among Mf-positive cases of Panadura MOH area.	165
6.15	Mf-positive prevalence of Panadura MOH area from 1978 to 1993 by a model-based experiment.	167
6.16	Mf-positive prevalence without MDA for Panadura MOH area by a model-based experiment.	169
6.17	Mf-positive prevalence subjected to continuous MDA for Panadura MOH area by a model-based experiment.	170
6.18	Mf-positive prevalence subjected to vector control for Panadura MOH area by a model-based experiment.	171
6.19	Predictions of Mf-positive prevalence with the effect of loosing immunity.	172
6.20	Tree-diagram for probabilities of treating in a year with MDA.	173
6.21	Behaviour of index values Q and Q_p for the different probabilities of treating selectively (a).	178
6.22	Behaviour of index values Q and Q_p for the different probabilities of treating under MDA (b).	179
6.23	Behaviour of index values Q and Q_p for the different probabilities of timely aware (w).	180

ACKNOWLEDGEMENT

First, I wish to express my sincere gratitude to supervisors of this study Prof. D.A. Tantrigoda, Dr. S.K. Boralugoda and Dr. S.S.N. Perera for their valuable guidance and encouragement. Gratitude must go to Prof. A. P. de Zoysa as well who proposed and initially supervised this research work.

Anti Filariasis Campaign (AFC) of Sri Lanka has helped me a lot by providing data and necessary information to carry out the research. I must be thankful to former Directress of AFC Dr. T. Liyanage and Regional Medical Officer attached to Kalutara Unit of AFC Dr. S.Y.C. Perera for their immense dedication. Assistance made by present Director of AFC Dr. W.A.S. Settinayake, Medical Officer at the Head office Dr. W.D.Y. Premakumara and all the other staff members of AFC should also be acknowledged.

Next, I would like to thank Dr. W.A. Stolk from Netherlands who first directed me to have training on mathematical modelling of Lymphatic Filariasis at Vector Control Research Centre (VCRC), Pondicherry, India. It is a pleasure to mention that Dr. S. Subramanian, Dr. P. Vanamail and Dr. A. Srividya who are the scientists at VCRC provided a good training and laid the foundation for collaborative research activities. At the same time, I wish to thank former Dean of the Faculty of Applied Sciences, University of Sri Jayewardenepura (USJP) Prof. A.M. Abesekara and former Dean of the Faculty of Graduate Studies, USJP Prof. K. Wijewardene for assisting me to obtain the grant for the above training via SIDA-SAREC Programme – Health and

Social Care for the Socially Marginalized People. I must also be thankful to that granting agency for their worthwhile investment.

Finally, I would like to thank Dean of the Faculty of Graduate Studies Prof. S. Piyasiri, Dean of the Faculty of Applied Science Prof. S. Liyanage, former and present Heads of the Department of Mathematics, USJP and all the other staff members for their administrative, professional and academic directives to fulfil my research goals. Conceptual directives set by some of them will drive me towards successes forever. Family members and friends who rendered their valuable time and thoughts must also be appreciated.

MATHEMATICAL ANALYSIS OF PARASITE DYNAMICS OF LYMPHATIC
FILARIASIS USING RANGE MODELLING AND OTHER APPROACHES IN
RELATION TO OBSERVATIONAL DATA FROM SRI LANKA

by

NALEEN CHAMINDA GANEGODA

ABSTRACT

Some observational data regarding Lymphatic Filariasis transmission are available over a long period of time in Sri Lanka although the data collection is not in a systematic way. However, these data had not been properly utilised to analyse parasite dynamics regarding Lymphatic Filariasis. Aim of this study is to develop and validate a comprehensive mathematical model to facilitate model-based analysis of parasite dynamics. Range modelling approach has been used here, where we can incorporate whatever reliable bounds available instead of seeking exact distributions of data. Furthermore, several mathematical tools and techniques have been designed to facilitate validation and model-based analysis. These tools are applicable outside the epidemiology of Lymphatic Filariasis too.

Dynamics of filarial parasites consists of two phases as dynamics in vector mosquito and dynamics in human host. Ultimately, overall population level dynamics of vector mosquitoes and humans are needed to establish a complete framework for the model. In the vector mosquito phase of the model, mosquito-parasite interactions and parasite

development within mosquito body are mathematically formulated via a system of differential equations. Here, corresponding phase plane trajectories illustrate possible dynamics subject to the range modelling tactics used for variables and parameters. For the phase of human host, incorporation of hyperbolic saturating function to cope with saturation as well as boosting associated with immune response is the key feature. Furthermore, this boosting has been equipped with a numerical scheme that maintains realistic values for adult parasite population.

The model is validated using three approaches as behavioural validity, numerical validity and simulation validity. Structure for validating the effect of history of infection is one of the main developments in behavioural validity. It is based on 'almost everywhere' principle in measure theory. Technique of decomposed error and wavelet-based central measure are the highlights of both numerical and simulation validity. In addition, an index to compare the effectiveness of main anti-filarial treatment programmes has been formulated here. It is structured as an application of eigenvectors. Next, model-based simulation experiments pave the way for assessing model applicability along with the possibility of using it as a decision support system. To achieve such needs, a computational flow has been adopted to design a computer simulation package for the overall model.

Three major aspects of a typical applied mathematical research namely modelling, analysis and computation have been covered by the present study showing how far mathematics can benefit real world problem solving. On the other hand, mathematical tools and techniques developed in this study show how an interdisciplinary research allows mathematics to have its own developments.