

NUMERICAL TREATMENT OF DELAY DIFFERENTIAL EQUATIONS IN BIOSCIENCE

A THESIS SUBMITTED TO THE UNIVERSITY OF MANCHESTER
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
IN THE FACULTY OF SCIENCE

April 2000

By
Fathalla A. Rihan
Department of Mathematics

Contents

Abstract	11
Declaration	13
Copyright	14
Acknowledgements	16
1 Studies of Biological Systems Using Delay Models	17
1.1 Introduction	17
1.1.1 Models with delays in bioscience	19
1.2 Delay Models in Population Dynamics	20
1.2.1 Delayed logistic equation	20
1.2.2 Delayed logistic equation with a distributed delay	22
1.2.3 Delayed Lotka-Volterra system	22
1.3 Delay Models in Dynamic Diseases	23
1.3.1 Immunology	23
1.3.2 Physiology	27
1.3.3 Epidemiology	31
1.4 Delay Models in Cell Divisions	33
1.5 Optimal Control Using Delay Models	35
1.6 Concluding Remark	36
2 Numerical Methods for Solving Delay Differential Equations	37
2.1 Introduction	37

2.2	Propagation and Location of Discontinuities in DDEs	40
2.3	Method of Steps for DDEs	41
2.4	Existence and Uniqueness Solution of DDEs	44
2.5	Numerical Approach for DDEs	44
2.5.1	General approach	45
2.5.2	Θ -methods for DDEs	46
2.5.3	Continuous one-step Runge-Kutta methods for ODE	47
2.5.4	Runge-Kutta method for DDEs	52
2.6	More General Classes of DDEs	55
2.6.1	Neutral delay differential equations (NDDEs)	55
2.6.2	Equations with state-dependent lags	57
2.6.3	Equation with a small or vanishing lag	58
2.7	Software Aspects	60
2.7.1	Discretization error	61
2.7.2	Location of jump discontinuities	62
2.7.3	Stepsize control	63
2.7.4	Interpolation to $\tilde{y}(t)$	64
2.7.5	DDE solvers	65
2.7.6	Stiffness	66
2.8	Concluding Remark	66
3	Stability Concepts for Delay Differential Equations	67
3.1	Introduction	67
3.2	Stability of DDEs	68
3.2.1	Stability of linear constant coefficient DDEs	69
3.2.2	Asymptotical stability region for linear DDEs	71
3.2.3	Stability of linear NDDEs	71
3.2.4	Asymptotic stability region for linear NDDEs	73
3.2.5	Stability of nonlinear DDEs	73
3.3	Stability of Numerical Methods for DDEs	79
3.3.1	Stability regions for DDEs: P-stability and GP-stability	80

3.3.2	Stability regions for linear NDDEs	84
3.3.3	Contractivity Concepts and <i>GPN</i> -Stability	86
3.3.4	Contractivity Concepts and GRN-Stability	90
3.4	Concluding Remark	92
4	Numerical Treatment of Parameter Identification in DDEs	101
4.1	Introduction	101
4.2	Parameter Estimation With DDEs	103
4.2.1	Fitting of model to data	103
4.2.2	Nonlinearity of model predictions	104
4.3	Computation of the Estimates	106
4.3.1	Basic iteration	106
4.3.2	Acceptability	107
4.3.3	Convergence	108
4.4	Discontinuities Associated With Delay	109
4.5	Solving the Minimization Problem	113
4.6	Models and Goodness Fit for Cell Growth	114
4.6.1	The exponential growth model	116
4.6.2	A time-lag growth model	116
4.7	Patterns of Cell Growth	118
4.7.1	Problem 1: Pre-B-cell growth in fetal calf serum	119
4.7.2	Problem 2: Growth of fission yeast	120
4.8	Concluding Remark	122
5	Sensitivity Analysis of Models Described by DDEs	130
5.1	Introduction	130
5.1.1	Sensitivity issues and nonlinearity effect in the model	132
5.1.2	Uniqueness of best fit	133
5.2	A Special Case: <i>Modelling With Linear Neutral-DDE</i>	134
5.2.1	Sensitivity of $y(t, \mathbf{p})$ to the parameter \mathbf{p}	135
5.2.2	Sensitivity of the optimum parameter $\hat{\mathbf{p}}$ to the data	137
5.2.3	Standard Deviation of Parameter Estimates	139

5.3	Nonlinearity and Indications of Bias	139
5.4	Numerical Models: Growth of <i>Escherichia Coli</i> (<i>E.coli</i>) Colonies . . .	140
5.4.1	An interpretation of the numerical results:	142
5.5	Generalizations of the Model	145
5.5.1	Sensitivity of state variables to parameter estimates	145
5.5.2	Sensitivity of parameter estimates to observations	150
5.5.3	The adjoint equations	151
5.6	Concluding Remark	153
6	Summary and Conclusion	154
6.1	Discussion of the Results	155
6.2	Aspects for Further Investigation	157
A	Fifth-Order Dormand & Prince RK Method	158
B	Non-Linear Biases in Models (4.6.2) & (4.6.3)	160
C	Some Notation for $\frac{\partial}{\partial \mathbf{q}}$	161
D	Second Order Sensitivity Coefficients for (5.2.1)	162
	Bibliography	164
	List of Publications	179

List of Tables

2.1	Features of Archi code.	65
3.1	Some stability concepts in literature	91
4.1	One possible biological meaning of the parameters in the NDDE (4.6.1).115	
4.2	Data for pre-B-cell growth at different concentrations of fetal calf serum.119	
4.3	Least-square estimates and standard deviations, $\sigma(\cdot)$, of the parameters for pre-B-cell growth models.	119
4.4	Data for non-exponential fission yeast growth.	121
4.5	Least-squares estimates and standard deviations of the parameters for fission yeast growth models.	121
5.1	Observed data of E.coli colonie growth [117, Fig.4].	143
5.2	Parameter estimates, STD, Errors and their nonlinear biases (NLB) for E.coli growth models.	143
5.3	Absolute values of the sensitivity coefficients for E.coli colonies growth models.	144
B.1	Mean(s) of perturbed Parameter(s) and their non-linear biases; NLB $= \left(\frac{\mathbf{p}^*}{\tilde{\mathbf{p}}} - 1\right) \times 100\%$, where \mathbf{p}^* is the best fit parameter and $\tilde{\mathbf{p}}$ is the mean of perturbed parameter for pre-B-cell growth model.	160
B.2	Mean(s) of perturbed Parameter(s) and their non-linear biases for fis- sion yeast growth model.	160

List of Figures

1.1	shows the plot of model (1.3.1) for $\tau = 0.5$ and $p_1 = 2, p_2 = 0.8, p_3 = 10^4, p_4 = 0.17, p_5 = 0.5, p_6 = 10, p_7 = 0.12$ and $p_8 = 8$	25
1.2	shows the solution of (1.3.1) with the same parameter of 1.1 except for $p_6 = 300$. The graphs illustrate the periodic outbreak of the disease.	26
1.3	(a) shows the numerical solution of model (1.3.2) with parameter values $\alpha = 0.1, \gamma = 0.1 \text{ days}^{-1}, \lambda = 0.2 \text{ days}^{-1}, m = 10$ and $\tau = 6$ days; (b) shows the numerical simulation with the same parameter values as in (a) except an increase in the delay to $\tau = 20$ days.	29
1.4	(a) to (i) show the numerical solutions of bifurcating periodic solutions of model (1.3.2) with $\gamma = 0.1, \lambda = 2, a = 1, \tau = 20$ and $m = 7, 8, 9, 10, 11, 12, 15, 17, 20$. Note the progression from a simple periodic solution to a complex chaotic behaviour and turn again to a simple periodic, as indicated in (a) to (i).	30
1.5	Solution of Kermack-Mckendrick model (1.3.3)	32
1.6	Model (1.3.4) that illustrate the spread of an infection disease in a population.	33
3.1	Solutions of DDE $x'(t) = \alpha^* x(t)[1 - x(t - 1)]$: (a) for differing α^* , (b) for differing initial functions $\psi(t)$ for $t \leq 0$	69
3.2	Asymptotical stability region in (λ, μ) -plane when solving DDE: $y'(t) = \lambda y(t) + \mu y(t - 1), t \geq 0$	72
3.3	Asymptotical stability regions when solving NDDE: $y'(t) = \lambda y(t) + \mu y(t - 1) + \nu y'(t - 1), t \geq 0$	74

3.4	Stability regions in the (λ, μ) -plane for the explicit Euler method, when solving: $y'(t) = \lambda y(t) + \mu y(t - 1)$ with $h = 1/(m + \theta)$	93
3.5	Numerical solutions of DDE $y'(t) = \lambda y(t) + \mu y(t - 1)$, $t \geq 0$; $y(t) = 1$ for $t \leq 0$ and with $\tau = 1 = (m + \theta)h$; $\lambda = -40$, $\mu = -20$	94
3.6	Stability regions in the (λ, μ) -plane for the implicit Euler method, when solving the DDE $y'(t) = \lambda y(t) + \mu y(t - 1)$ with $h = 1/(m + \theta)$	95
3.7	Stability regions in the (λ, μ) -plane for the trapezium method, when solving the DDE $y'(t) = \lambda y(t) + \mu y(t - 1)$ with $h = 1/(m + \theta)$	96
3.8	Stability regions on the (λ, μ) -plane for the improved Euler method, when solving the DDE $y'(t) = \lambda y(t) + \mu y(t - 1)$ with $h = 1/(m + \theta)$	97
3.9	Stability regions in the space of parameters (λ, μ, ν) for the explicit Euler method, when solving the NDDE $y'(t) = \lambda y(t) + \mu y(t - 1) + \nu y'(t - 1)$ with $\tau = 1 = mh$ ($m = 25$), the middle bold one is for $\nu = 0$	98
3.10	Numerical stability areas, using grid-search technique, of the explicit Euler method when solving the NDDE $y'(t) = \lambda y(t) + \mu y(t - 1) + \nu y'(t - 1)$, with $\tau = mh$, $m = 25$. The first graph corresponds to $\nu = 0$, and the second one is to $\nu = 0.5$	99
3.11	Numerical stability areas, using the grid-search technique, of explicit Euler method when solving the NDDE $y'(t) = \lambda y(t) + \mu y(t - 1) + \nu y'(t - 1)$, with $\tau = mh$, $m = 25$. The first graph is to $\nu = 0.9$, and the second one corresponds to $\nu = 1$	100
4.1	Graphs of $\psi(t)$ and the cell proliferation function for the uniform and bell-shaped initial cell distributions.	118
4.2	(a and b) show, respectively, the exponential and time-lag models for Pre-B-cell growth at different fetal calf serum concentrations, where *'s and o's are the observed data given in TABLE 4.2.	123
4.3	(a-e) show the stationary points of Φ and the dependence of Φ values on the parameter τ_{cell} in a one exponential model for Pre-B-cell growth at different fetal calf serum concentrations.	124

4.4	(a-e) show the stationary points of Φ and the dependence of Φ values on the parameter τ_{cell} in a one time-lag model for Pre-B-cell growth at different fetal calf serum concentrations.	125
4.5	a) shows the best fit solution of a one parameter time-lag model to the observed data in TABLE 4.4. b) Shows the local uniqueness of the best fit and the dependence of Φ values on the parameter τ	126
4.6	a) shows the best fit solution of a two parameter time-lag model to the observed data in TABLE 4.4. b) Shows the local uniqueness of the best fit and the dependence of Φ values on the parameters τ/ρ_1	127
4.7	shows the best fit solution of three parameter time-lag model to the observed data in TABLE 4.4.	128
4.8	a)→f) show the local uniqueness of the best fit and the dependence of Φ values on the parameters τ, ρ_1 and β . Each point in the grid was calculated for fixed values of $\beta = 0.5 : 0.1 : 1$	129
5.1	Intersection of solutions to the different DDEs can cause non-unique best fit in certain data.	134
5.2	Data for synchronous <i>E.coli</i> growth and a graph of the solution of the DDE $y'(t) = \lambda y(t) + \mu y(t - \tau)$ (where $\lambda = -1, \mu = 1.5$ and $\tau = 20$).	145
5.3	A synchronous culture of <i>E. coli</i> K12 λF^- cells was prepared by loading 2×10^{10} cells from an exponential culture into a 15ml tube. The cells were then centrifuged at 2500g for 20 minutes and the top 2% of cells suspended in fresh growth medium. The graphs represent: (a) the exponential growth model for one parameter $\tau_{culture} = \frac{\ln(2)}{\rho_0}$, (b) the time-lag model with one parameter $\tau_{cell} = \frac{1}{\rho_1}$, (c) the time-lag model with three parameters, ρ_0, ρ_1 and τ_{cell} , (d) the NDDE model with four parameters, $\rho_0, \rho_1, \tau_{cell}, \rho_2$ and (e) the NDDE model with five parameters, $\rho_0, \rho_1, \tau_{cell}, \rho_2, \rho_3$	146
5.4	Plot of parameter-square error in one parameter time-lag model. The closeness of the curve to a parabola indicates the small degree of non-linearity in one parameter time-lag model	147

5.5	Pairwise plots of parameter estimates and $\Phi(\mathbf{p})$, in five parameters neutral delay model. For each graph, contours indicate the correlation of the parameter with each other and the inference region of least square estimate. Closeness of the contour to an ellipse, indicates the small degree of nonlinearity of the model to the data.	148
-----	---	-----

Abstract

Many real-life phenomena involve a delayed rather than instantaneous reaction, with a dependence on a memory of past events. Examples occur in biology, economics, immunology, materials with memory, physiology, and population dynamics, where there is a time-lag or after-effect. Models of such phenomena frequently involve retarded functional differential equations (RFDEs).

This thesis presents the author's research in the numerical treatment of some delay differential equations (DDEs) and neutral DDEs (NDDEs) that occur in certain areas of bioscience. The main novelty concerns parameter estimation in DDEs, and a sensitivity analysis of the solution with respect to the parameters and of the parameters with respect to the observations. When modelling in bioscience, DDEs and NDDEs are frequently more consistent with real phenomena than differential equations with no time-lag.

The outline of this thesis is as follows:

In chapter *I*, we indicate the scope for applications of delay differential models in biological systems. We show how delay differential models, of real-life phenomena, have potentially more interesting dynamics than equations that lack memory effects.

In chapter *II*, we review some features of DDEs, such as existence and uniqueness of the solution; propagation and location of discontinuities in DDEs. We investigate how ODEs formulae (in particular continuous Runge-Kutta formulae) can be adapted to solve various types of DDEs. We also recall the methods of steps

and θ -methods for DDEs. We describe, in brief, the theory of accuracy and some issues related to numerical solutions of DDEs.

In chapter *III*, we examine the stability of delay models described by linear and nonlinear DDEs and NDDEs, and conditions that ensure stable behaviour. In particular we study, and get some new results in, numerical stability regions of the solutions. Sufficient conditions for contractivity of the solutions are also discussed.

In chapter *IV*, we produce a numerical method (using a least squares approach) for parameter identification in DDEs and NDDEs. We also discuss some related problems in parameter estimation in DDEs and NDDEs, such as discontinuities arising in the objective function via the solutions of DDEs. We describe, in some detail, some numerical models in cell proliferation phenomena and make a comparison between the exponential and time-lag growth models for *pre-B-cell* growth in ‘fetal calf serum’ and growth of ‘fission yeast’. Numerical results illustrate that (compared with ODEs) DDEs provide better consistency with the nature of cell proliferation phenomena.

In chapter *V*, we formulate an approach to sensitivity analysis of delay differential modes, covering (*i*) the sensitivity of the state variables to the parameter estimates (that is, to measure the sensitivity of the solution with respect to changes in the parameter estimates), (*ii*) the sensitivity of the parameter estimates to the observations (to estimate the change in parameter estimates due to a change in the data) and (*iii*) the nonlinearity effect. Sensitivity coefficients are used to determine the covariance matrix of parameter estimates and hence to determine the standard deviations. Numerical results, based on the growth of *E. coli* colonies, illustrate that the sensitivity of the parameter estimate to the observation is *low* if the sensitivity of the state variable to the parameter estimate is *high*.

In the last chapter, we give a general summary and discussion of our results, and provide some suggestions for further investigation that could be used to extend the present work.

Declaration

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institution of learning.

Copyright

Copyright in text of this thesis rests with the Author. Copies (by any process) either in full, or of extracts, may be made **only** in accordance with instructions given by the Author and lodged in the John Rylands University Library of Manchester. Details may be obtained from the Librarian. This page must form part of any such copies made. Further copies (by any process) of copies made in accordance with such instructions may not be made without the permission (in writing) of the Author.

The ownership of any intellectual property rights which may be described in this thesis is vested in the University of Manchester, subject to any prior agreement to the contrary, and may not be made available for use by third parties without the written permission of the University, which will prescribe the terms and conditions of any such agreement.

Further information on the conditions under which disclosures and exploitation may take place is available from the Head of Department of Mathematics.

*To my parents,
to my wife, and
to my children, Bassel & Nouran*

Acknowledgements

I would like to express my sincere gratitude to my supervisor Prof. Christopher T.H. Baker for his suggestion of the field of study. His constant help, encouragement, fruitful discussions, and advice have been of great help.

I would also like to thank Prof. Joan Walsh for her great help. I learned much about my project from my discussion with Prof. Gennadii Bocharov during his visit to Manchester University. I gratefully acknowledge his collaboration. I also express my deep appreciation to Dr Chris Paul for his comments and his assistance. Furthermore, I have to thank all the staff and the fellow students in the department of Mathematics, as I spent a nice time with them.

This work was generously supported by the Egyptian Government.