Contents

Deutsche Kurzfassung i

Nomenclature and Conventions ix

1. Motivation and Background 1
- 1.1. Contribution . . . 2
- 1.2. Probability . . . 4

2. Introduction 7
- 2.1. Available Data in Relation to Modelling Frameworks . . . 7
- 2.2. Modelling Using Ordinary Differential Equations . . . 9
  - 2.2.1. Parameter Estimation . . . 12
  - 2.2.2. Model Structure Specifications in Relation to Data . . . 12
  - 2.2.3. Graph Representation of Ode Models . . . 16
  - 2.2.4. Steady State Data . . . 18
  - 2.2.5. Model Output Sensitivity . . . 19
  - 2.2.6. Logarithmic Space . . . 19
- 2.3. Measurement and Prediction Uncertainty . . . 20
  - 2.3.1. Bayesian Model Analysis . . . 21
  - 2.3.2. Goodness of Fit . . . 23

3. Existing Methods for Parameter Estimation via Markov Chain Monte Carlo 25
- 3.1. Monte Carlo . . . 25
- 3.2. Markov Chains in the Reals . . . 28
- 3.3. Geometry of Parameter Spaces . . . 31
- 3.4. MCMC Algorithm Type Overview . . . 33
- 3.5. Metropolis-Hastings Type Algorithms . . . 33
  - 3.5.1. Metropolis . . . 36
  - 3.5.2. Metropolis-Hastings . . . 37
  - 3.5.3. Adaptive Metropolis . . . 37
  - 3.5.4. Delayed Rejection . . . 38

3.5.5. SMMALA . . . 40
3.6. Hamiltonian Type Algorithms . . . 40
3.6.1. HMC . . . 41
3.7. Riemannian Manifold Hamiltonian Monte Carlo . . . 42
3.8. Sensitivity Analysis for Steady States . . . 43

4. Discussion on Tuning **45**
4.1. Comparing Two Algorithms from Different Families Requires Careful Tuning . . . 45
4.2. Algorithm-Independent Tuning . . . 48

5. Algorithm Development **53**
5.1. Calculation of Steady States . . . 53
5.1.1. Newton-Raphson Method . . . 54
5.1.2. NR+SMMALA for Models with Steady State Observations 55
5.1.3. Circuit Breaking Algorithm . . . 56
5.1.4. CBA in Conjunction with SMMALA . . . 59
5.2. Near Steady State Sensitivity Approximation . . . 63
5.2.1. SSMMALA for Models with Time Series Data . . . 66
5.3. Discussion . . . 67
5.3.1. Comparing Different Data Cases Fairly . . . 67
5.3.2. Hamiltonian Type Algorithms Benefit Greatly from Speedups in the Model's Response . . . 70
5.3.3. Adaptive Metropolis Rationale Is Sometimes Not Appropriate . . . 71
5.3.4. Initial Conditions Naturally Select Stable Branches in Bifurcation Diagrams . . . 81
5.4. Model Assisted Design of Experiments . . . 83
5.4.1. Entropy Based Selection of Experiments . . . 83
5.4.2. Variance Based Design of Experiments . . . 87

6. Software Development **93**
6.1. MCMC Package Written in C . . . 93
6.2. `mcmc_clib` – Usage Structure . . . 94
6.3. `mcmc_clib` Is Capable of Dealing with Large Models . . . 96

7. Conclusions **101**

A. Modelling in Systems Biology **107**
A.1. Scale and Granularity 107
A.2. Stochastic and Dynamic Modelling 108

B. Models **113**
B.1. Test-Model for the `mcmc_clib` Package 113
B.2. Test-Model for the Comparison of SMMALA Type Algorithms . 115
B.3. Models Used in the MATLAB Study of RMHMC and SMMALA . . 119

C. Treatment of Special Cases in Measurement Setups **123**
C.1. Measurement Times Can Be Different between Experiments . 123
C.2. Log-Normal Measurement Errors and Poor Data 123

Bibliography **127**