Contents

Zusammenfassung i

Summary v

Symbols and abbreviations ix

Contents xi

1. Introduction 1

1.1. Biological oscillations 1
1.2. Robustness and sensitivity 2
1.3. The objectives and the approach 3
1.3.1. Robustness of the steady state 3
1.3.2. Robustness of oscillations 4
1.3.3. The approach used in this work 5
1.3.4. The approach in the context of published results 7

2. Robustness measure and methods 9

2.1. Mathematical models of biological oscillations 9
2.1.1. ODE systems 9
2.1.2. Rate coefficients, nl-parameters, cooperativity parameters . . . 10
2.1.3. Visualization of ODE models as networks 11
2.1.4. Determining feedback loops by the Jacobian matrix 14
2.1.5. Steady states and stability 17
2.1.6. Limit cycle oscillations 18
2.1.7. Bifurcation diagrams and Hopf bifurcations 20
2.2. Quantifying sensitivity: The chosen measures 22

2.3. Sensitivity estimation 26
2.3.1. Parameter sampling 28
2.3.2. Determining the stability of the steady state and performing model simulations 30
2.3.3. Checking for regular oscillations and determining period and amplitude 31
2.3.4. Calculation of the sensitivity 32
2.3.5. Oscillation probability 32
2.4. Methods of statistical analysis 33
2.4.1. Median, quartiles, 90% data range 33
2.4.2. Confidence interval of the median 35
2.4.3. Box-plot visualization 36
2.4.4. Spearman's rank correlation coefficient R_S 37
2.4.5. Testing the significance of differences 38
2.5. Summary and discussion: Robustness measure and methods 42
2.5.1. ODE models and oscillation detection 42
2.5.2. Mean amplitude as amplitude characteristic 43
2.5.3. Sensitivity measure 44
2.5.4. Sampling approach and sensitivity estimation 45
2.5.5. Statistical evaluation and data interpretation 47

3. The influence of the structure on robustness 49
3.1. Circadian and calcium oscillations 49
3.1.1. Circadian oscillations 49
3.1.2. Calcium oscillations 51
3.1.3. Differences between circadian and calcium oscillations 53
3.2. Model structure or choice of the parameter set 54
3.2.1. The chosen models 56
3.2.2. Results of the sensitivity analysis 56
3.3. Summary and discussion: The influence of the structure on robustness 60
3.3.1. Structural properties to be examined in this work 62

4. The effect of feedbacks on sensitivity **63**
4.1. Feedbacks and feedback loops in general 63
4.1.1. Feedbacks and feedback loops in biology 63
4.1.2. Known effects of feedbacks on oscillatory properties 64
4.1.3. Feedback vs. feedback loop in ODE systems 67
4.2. The chain models 68
4.2.1. Implementation of the feedback 70
4.2.2. Stability analysis and fixation of the Hill coefficients 72
4.3. Sensitivity analysis for different feedback types 74
4.4. Further investigation of the sensitivities of the chain models 77
4.4.1. Branching in the period sensitivity of the negative feedback chain model 77
4.4.2. Bifurcation analyses of the negative feedback chain model . . 79
4.4.3. Bifurcation analyses and birhythmicity in the positive feedback chain model 82
4.5. Summary and discussion: The effect of feedbacks on sensitivity 85
4.5.1. Relation to other findings 86
4.5.2. Influence of the model assumptions on sensitivity 89
4.5.3. Oscillation probability 91
4.5.4. More possibilities of feedback implementation 92

5. The effect of matter flow on sensitivity **95**
5.1. Matter flow: conversion vs. regulated production 95
5.1.1. Matter flow vs. flow of information in biology 98
5.2. Matter flow in the chain models 100
5.2.1. Matter flow properties influence the regulatory structure . . . 101
5.2.2. Is a further simplification of the analysis possible? 102
5.3. Sensitivity analysis for different matter flow properties 103
5.4. Origins of particular effects of matter flow on sensitivity 105
5.4.1. Increase of sensitivities in the negative feedback chain models 105
5.4.2. Decrease in dispersion of the period sensitivity in the negative feedback chain models 108
5.4.3. Increase of sensitivities in the positive feedback chain models . 110

5.5. Summary and discussion: The effect of matter flow on sensitivity . . 113
5.5.1. Matter flow from more than one source species 115
5.5.2. Lacking matter flow in signaling processes 116
5.5.3. Applicability of the results 116

6. The effect of saturating kinetics on sensitivity 117
6.1. Mass action kinetics vs. Michaelis-Menten kinetics and saturation . . 118
6.1.1. Mass action kinetics 118
6.1.2. Michaelis-Menten kinetics 118
6.1.3. Saturation 119
6.1.4. The meaning of Michaelis-Menten kinetics in this work 122
6.1.5. Known effects of saturating kinetics on oscillations 123
6.2. The effect of saturating kinetics on steady state sensitivity 124
6.2.1. Zero-order ultrasensitivity in the Goldbeter-Koshland switch . 125
6.2.2. Sensitivity of the steady state and ultrasensitivity: The response coefficient R_ν 127
6.2.3. Re-examination of the Goldbeter-Koshland switch 129
6.2.4. Open switch: The Goldbeter-Koshland switch with production and degradation 131
6.2.5. Short chain: The open switch without backward reaction . . . 135
6.2.6. Enhanced sensitivity of the steady state 138
6.3. The effect of saturating kinetics on period and amplitude sensitivity . 138
6.3.1. Michaelis-Menten kinetics in the chain model 139
6.3.2. Sensitivity analysis for different kinetics 140
6.3.3. Influence of the K_M-values 143
6.3.4. The influence of the number of saturated reactions 145
6.3.5. Influence of particular reactions being saturated 148
6.4. Saturation and oscillation probability 151
6.5. Summary and discussion: The effect of saturating kinetics on sensitivity 154
6.5.1. Saturating kinetics in conversions vs. saturating kinetics in regulated productions 155
6.5.2. Possible extensions of the examination of kinetics 156

7. Further applications **159**
7.1. It is not only feedback that matters . . . 159
7.2. Inferring structural properties from sensitivities . . . 163
7.2.1. Results of the sensitivity analyses . . . 164
7.2.2. Circadian rhythm models . . . 166
7.2.3. Calcium oscillations models . . . 171
7.3. Summary, discussion and outlook: Further applications . . . 177
7.3.1. Applicability of structure prediction . . . 179
7.3.2. Suggesting structure to tune sensitivity . . . 180
7.3.3. Determining sensitivity to obtain indications on the biological potential of oscillations . . . 181

8. Discussion: Mechanisms underlying the robustness of oscillatory properties **183**

A. Appendix **189**
A.1. Robustness measure and methods . . . 189
A.1.1. Influence of the parameter perturbation on the sensitivity . . . 189
A.1.2. Influence of the definition of the sensitivity measure on the sensitivity results . . . 192
A.1.3. Influence of the sampling interval on the sensitivity results . . . 193
A.1.4. Values obtained for special rate equations by the sampling method . . . 195
A.1.5. Median vs. arithmetic mean . . . 196
A.2. The effect of feedbacks on sensitivity . . . 198
A.2.1. Definition of the feedback strength and stability of the steady state . . . 198
A.2.2. Positive feedback term and Hill coefficient . . . 199
A.2.3. Length of the feedback loop . . . 201
A.3. The effect of matter flow on sensitivity . . . 203
A.3.1. Transformation of models with different matter flow properties 203
A.3.2. Equivalent models may have different sensitivities . . . 208

A.3.3. Sensitivity analysis of the negative feedback chain models with different matter flow properties . . . 211
A.3.4. Sensitivity analysis of the positive feedback chain models with different matter flow properties . . . 217
A.4. The effect of saturating kinetics on sensitivity . . . 220
A.4.1. Derivation of Michaelis-Menten kinetics . . . 220
A.4.2. Steady state response coefficients as in the main text . . . 221
A.4.3. Steady state response coefficients according to MCA . . . 228
A.4.4. Stability of the chain models with saturating kinetics . . . 234
A.4.5. Hill coefficients in the chain models with saturating kinetics . 235
A.4.6. Influence of the definition of a saturated reaction . . . 236
A.4.7. Particular reactions being saturated . . . 237
A.4.8. Chain models only partly employing saturating kinetics . . . 240
A.4.9. Matter flow and saturating kinetics . . . 241
A.5. Further applications . . . 243
A.5.1. Sensitivity of synthetic oscillators . . . 243
A.5.2. Sensitivity of an NF-κB model . . . 244
A.6. Tables for sensitivity values . . . 245
A.6.1. Chain models with positive or negative feedback . . . 245
A.6.2. Chain models with different matter flow properties . . . 246
A.6.3. Chain models with saturating kinetics . . . 248
A.6.4. Models of Tsai et al. and alterations . . . 248
A.6.5. Circadian and calcium oscillations models . . . 249
A.6.6. Synthetic oscillators . . . 251
A.6.7. NF-κB oscillations model . . . 251
A.7. Model equations . . . 252
A.7.1. Circadian and calcium oscillations models . . . 252
A.7.2. Chain models of length four with mass action kinetics . . . 261
A.7.3. Chain models with different matter flow properties . . . 262
A.7.4. Chain models with saturating kinetics . . . 262
A.7.5. Chain models of length five . . . 263
A.7.6. Models according to Tsai et al. [2008] and alterations . . . 263
A.7.7. Synthetic oscillators . . . 265