

Contents

1	Introduction	1
1.1	Challenges in targeted cancer therapy	3
1.2	Modelling in systems biology	5
1.3	Perturbation data-based models	7
1.3.1	Dynamic network modelling	8
1.3.2	Modular Response Analysis (MRA)	9
1.4	Obstacles for field application of MRA	12
1.5	Objectives	13
2	Reverse engineering of genetic networks	15
2.1	Introduction	15
2.2	Statistical extension of MRA	18
2.2.1	Maximum likelihood extension	18
2.2.2	Greedy hill-climbing model selection	19
2.3	Parameter benchmark on <i>in silico</i> networks	21
2.3.1	Artificial gene regulatory network generation	21
2.3.2	Parameter benchmark of refined MRA approach	23
2.4	Comparison to alternative methodologies	30
2.4.1	Established steady state prediction methods	31
2.4.2	Performance on default settings with different interaction types	31
2.4.3	Detailed method assessment on transcription factor networks	33
2.4.4	External benchmark: DREAM 4 network challenge	35
2.5	Discussion	37
2.5.1	Top-down analysis of an oncogenic KRAS-controlled tran- scriptional network	39
2.5.2	Future directives to advance in genetic network research . .	41
2.5.3	Improvements for further use of extended MRA	43

3	Modelling EGFR signalling in a colon cancer panel	47
3.1	Introduction	47
3.1.1	Study design	49
3.2	Adjusting MRA to model signalling data	52
3.2.1	Modelling incomplete data	52
3.2.2	Integration of different perturbation types	54
3.2.3	Removing non-identifiable parameters	56
3.2.4	Parameter estimation strategy	60
3.3	Modelling results	61
3.3.1	Model fit suggests extension of the original network model	62
3.3.2	Robustness assertion of model parameters	66
3.3.3	Model fit uncovers differences in network structure	70
3.3.4	Quantitative differences between signalling networks	71
3.4	Model assisted study of the ERK-AKT crosstalk	73
3.4.1	Verification and characterisation of the crosstalk between ERK and AKT	73
3.4.2	Prediction of potentially effective double inhibitions	75
3.4.3	Combined inhibition of EGFR and ERK prevents growth in various tumour cells	77
3.5	Discussion	79
3.6	Concluding Remarks	82
4	Conceptual modelling resolves role of TTP in HIF-1 regulation	85
4.1	Introduction	85
4.1.1	Molecular function of HIF-1	86
4.1.2	Study of normoxic HIF-1 regulation reveals controversial observation	87
4.2	Model-supported hypothesis testing	89
4.2.1	MRA application scheme for hypothesis testing	90
4.2.2	Model scenarios	91
4.2.3	Experimental testing of model hypotheses	95
4.3	Discussion	97
4.3.1	Uses and limitations of MRA for theoretical modelling	98
5	Conclusion	101
5.1	MRA extensions enabled modelling of biological networks	101
5.2	Outlook I: Technical improvement plans	103

5.3	Outlook II: Future applications of MRA in systems biology	105
5.3.1	Analysing signalling in cancer research	106
5.4	Closing remark	109
Appendix		111
A Appendix for chapter: Reverse engineering of genetic networks		113
A 1	Parametrisation of simulated genetic networks	113
A 2	Evaluation statistics	116
A 3	Complete parameter benchmark results of ML MS MRA	117
A 4	Alternative steady state prediction methods	120
A 5	Extended modelling results for DREAM 4 challenge 2	123
A 6	Assessment of two estimates of the global response matrix	125
A 6.1	Error propagation	126
A 6.2	Performance comparison on <i>in silico</i> networks	128
B Appendix for chapter: Modelling EGFR signalling in a colon cancer panel		129
B 1	Phosphorylation kinetics after stimulation	129
B 2	Error model for signalling data	130
B 3	Model reduction example	131
C Appendix for chapter: Conceptual modelling resolves role of TTP in HIF-1 regulation		133
C 1	MRA models to elucidate TTP-HIF-1 α relationship	133
D Appendix for chapter: Conclusion		139
D 1	FDA approved targeted therapy drugs	139
E Abbreviations		142
Bibliography		145
Danksagungen		171