

Contents

Abstract	iii
Zusammenfassung	v
Acknowledgments	vii
Curriculum Vitae	ix
List of Figures	xvii
Abbreviations	xix
1 Introduction to the Thesis	1
1.1 Brief introduction to cortical organization	2
1.2 Motivation – The logic behind cortical development	3
1.3 Problem statement – Looking for cortical growth rules	4
1.4 Approach to understand cortical development	6
1.4.1 Information representation for developmental data	7
1.4.2 A model of cortical development based on local rules	8
1.4.3 Developmental programs are specified by the genetic code	10
1.5 Contribution	11
1.6 Outline of the Thesis	12
2 Introduction to cortical development: experiments and models	15
2.1 Introduction to cortical architectures and cortical development	16
2.1.1 Principles of cortical organization	16
2.1.2 Canonical microcircuits	18
2.1.3 The cerebral cortex originates from different transient embryonic regions	19
2.1.3.1 <i>Preplate neurons</i>	19
2.1.3.2 <i>Subplate neurons</i>	20
2.1.3.3 <i>Excitatory neurons</i>	20
2.1.3.4 <i>Glial cells</i>	22
2.1.3.5 <i>Interneurons</i>	22
2.1.4 Genetic characterization of neural progenitors	23
2.2 Models of development: from neurons to cortical architectures	24
2.2.1 The protomap versus protocortex hypothesis	24
2.2.2 Ontogenetic columns and the radial unit hypothesis	24

2.2.3	Evolution of cortical architectures	26
2.3	Experimental approaches for the study of cortical histogenesis	28
2.3.1	Dissociated cultures of neural precursors	28
2.3.2	Transplantation	30
2.3.3	Mitotic history of neuronal populations	31
2.3.4	Retroviral clonal analysis	31
2.3.5	Lineage analysis	32
3	Inferring cell lineages underlying cortical development	35
3.1	Introduction to models of cortical development	36
3.1.1	Two different approaches to model cortical development	36
3.1.1.1	<i>Population models</i>	36
3.1.1.2	<i>Single-cell models</i>	40
3.2	Objectives of this Chapter	41
3.3	Methods: Models of corticogenesis	42
3.3.1	Mitotic history of neuronal populations	42
3.3.2	Global fitting of cell cycle parameters	43
3.3.3	Ordinary differential equations model of cell cycle progression	44
3.3.4	Distribution of cell division modes	45
3.3.5	Lineage trees reconstruction by generative functions	46
3.4	Results: Reconstruction of cortical cell lineages	47
3.4.1	ODE model of cell cycle progression and cell differentiation	47
3.4.2	Distribution of cell division modes	53
3.4.3	Lineage trees reconstruction with probability generative functions	55
3.5	Discussion	59
3.5.1	The final cortical cytoarchitecture is defined by mode of cell divisions	59
3.5.2	Why are lineage trees important?	60
4	Analysis of developmental pathways in murine cortical development	63
4.1	Introduction	64
4.1.1	Development as a self-construction process	64
4.1.2	Lineage trees are composed of cell division patterns	65
4.1.3	Models of lineage evolution	65
4.1.4	Inference of transcriptional networks	66
4.2	Objectives of this Chapter	69
4.3	Methods: Inference of Markov Branching Processes	70
4.3.1	Graphical representation of cell lineages	70
4.3.2	Spectral decomposition	70
4.3.3	Multi-type Markov Branching Process	72
4.3.4	Dimensionality reduction	73
4.3.4.1	<i>Homogeneous Markov Model (HM model)</i>	74
4.3.4.2	<i>Time-dependent Markov Model (TM model)</i>	74
4.3.4.3	<i>Non-homogeneous Markov Model (NM model)</i>	74
4.4	Results: A state machine model of cortical development	75
4.4.1	The Cell Lineage Tree	75
4.4.2	The State Diagram	75
4.4.3	Spectral Decomposition	77

4.4.3.1	<i>Label propagation</i>	77
4.4.3.2	<i>Discrete-time Markov branching process</i>	79
4.4.3.3	<i>Dimensionality reduction</i>	80
4.4.4	Spectral Decomposition of cortical lineages	81
4.4.4.1	<i>Cortical cell lineages reconstruction</i>	81
4.4.4.2	<i>State diagrams of murine cortical neurogenesis</i>	82
4.4.5	Transcriptional networks	85
4.4.5.1	<i>Transcriptomic Atlas of mouse neocortical layers</i>	85
4.4.5.2	<i>A transcriptional model of cortical development</i>	85
4.5	Discussion	88
4.5.1	A novel approach for cell lineage data analysis	88
4.5.2	Hidden generative models	89
4.5.3	Computational models of cortical neurogenesis	90
5	A genetic language for developmental programs	93
5.1	Introduction to gene regulatory networks	94
5.1.1	The biological principles of the genomic regulatory code	94
5.1.2	Computational aspects of gene regulatory networks	96
5.1.2.1	<i>Cis-regulatory modules constitute the computational units</i>	96
5.1.2.2	<i>Coding properties of transcriptional networks</i>	97
5.1.3	Structural properties of transcriptional networks	99
5.1.3.1	<i>Modularity</i>	99
5.1.3.2	<i>Motifs</i>	100
5.1.3.3	<i>Path length and redundancy</i>	101
5.1.3.4	<i>Composability</i>	101
5.1.4	Gene regulation and development	102
5.1.4.1	<i>What is the link between genes and development?</i>	102
5.1.4.2	<i>Asymmetric distribution of cell fate determinants</i>	103
5.1.4.3	<i>Epigenetic control of cell fate specification</i>	103
5.1.5	The choice of the modeling formalism	104
5.2	Objectives of this Chapter	105
5.3	Methods: Mathematical models for transcriptional networks	106
5.3.1	Reaction kinetics of the binding of a single transcription factor	106
5.3.2	The rate equation	110
5.3.3	Gene Reaction Network model	112
5.3.3.1	<i>An algebraic representation of combinatorial transcription factor binding</i>	112
5.3.3.2	<i>Gene regulation without order</i>	114
5.3.3.3	<i>Gene regulation with order</i>	114
5.3.3.4	<i>Relationship with conventional logic theory</i>	115
5.3.3.5	<i>Example of combinatorial transcriptional regulation</i>	119
5.3.3.6	<i>Asymmetric cell division</i>	120
5.4	Results: Genetic control of developmental processes	122
5.4.1	Formal genetic language definition	122
5.4.2	Toward a genetic model of development: Gene Regulatory Motifs	124
5.4.2.1	<i>A Gene Regulatory Motif: the Bistable Switch System</i>	124
5.4.2.2	<i>A Gene Regulatory Motif: the Multistable Switch System</i>	127

5.4.3	State-dependent computation with Gene Regulatory Motifs	128
5.4.3.1	<i>Encoding state transitions with bistable switches</i>	128
5.4.3.2	<i>Epigenetic control over cell state transitions</i>	132
5.4.3.3	<i>Probabilistic cell divisions encode probabilistic state transitions</i>	132
5.4.4	Reverse engineering of gene regulatory networks	134
5.4.4.1	<i>The inverse problem</i>	134
5.4.4.2	<i>Sequences of multistable switches</i>	134
5.5	Discussion	137
5.5.1	A formal model of development	137
5.5.2	Genetic modules based on gene cooperation and competition	137
5.5.3	Counting divisions without a counter	138
5.5.4	Reverse engineering of gene regulatory networks	139
6	Simulation of cortical self-construction	141
6.1	Introduction to self-organization in developmental processes	142
6.1.1	The origin of order	142
6.1.2	Self-organization has many definitions	143
6.1.2.1	<i>Self-organization according to Erwin Schrödinger</i>	143
6.1.2.2	<i>Self-organization according to Watson, Crick, Monod, and Fisher</i>	143
6.1.2.3	<i>Self-organization according to Waddington</i>	144
6.1.2.4	<i>Self-organization according to Stuart Kaufmann</i>	145
6.1.2.5	<i>Self-organization according to Von Neumann</i>	146
6.1.3	Cortical development as a self-constructing process	146
6.2	Objectives of this Chapter	148
6.3	Methods: A gene regulatory network for cortical areas 3 and 6	149
6.4	Results: Simulation of cortical lamination	151
6.4.1	The attractor landscape	151
6.4.2	The attractor landscape of bistable switches	152
6.4.3	Building of a laminated volume of cortex in CX3D	155
6.4.3.1	<i>Preplate formation</i>	157
6.4.3.2	<i>Cortical plate formation</i>	157
6.5	Discussion	159
6.5.1	Reverse engineering of cortical gene regulatory networks	159
6.5.2	Simulation of the mouse cortical lamination	160
7	Conclusions	161
7.1	Summary	162
7.1.1	Symmetric and asymmetric divisions define the final cortical cytoarchitecture	162
7.1.2	Reconstruction of the Cell Lineage Tree	163
7.1.3	State models of corticogenesis	164
7.1.4	Transcriptional network models of corticogenesis	166
7.2	Outlook	168

A Experimental data	169
A.1 Cell cycle parameters of murine cortex in area 3 and 6	169
A.2 Number of neurons in the adult rodent cerebral cortex	170
Bibliography	171