*Modeling and Simulation in Science, Engineering and Technology*

Andreas Deutsch
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# Cellular Automaton Modeling of Biological Pattern Formation

*Characterization, Applications, and Analysis*

Foreword by Philip K. Maini

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*To our parents*

# Foreword

The recent dramatic advances in biotechnology have led to an explosion of data in the life sciences at the molecular level as well as more detailed observation and characterization at the cellular and tissue levels. It is now absolutely clear that one needs a theoretical framework in which to place this data to gain from it as much information as possible. Mathematical and computational modelling approaches are the obvious way to do this. Heeding lessons from the physical sciences, one might expect that all areas in the life sciences would be actively pursuing quantitative methods to consolidate the vast bodies of data that exist and to integrate rapidly accumulating new information. Remarkably, with a few notable exceptions, quite the contrary situation exists. However, things are now beginning to change and there is the sense that we are at the beginning of an exciting new era of research in which the novel problems posed by biologists will challenge the mathematicians and computer scientists, who, in turn, will use their tools to inform the experimentalists, who will verify model predictions. Only through such a tight interaction among disciplines will we have the opportunity to solve many of the major problems in the life sciences.

One such problem, central to developmental biology, is the understanding of how various processes interact to produce spatio-temporal patterns in the embryo. From an apparently almost homogeneous mass of dividing cells in the very early stages of development emerges the vast and sometimes spectacular array of patterns and structures observed in animals. The mechanisms underlying the coordination required for cells to produce patterns on a spatial scale much larger than a single cell are still largely a mystery, despite a huge amount of experimental and theoretical research. There is positional information inherent in oocytes, which must guide patterns, but cells that are completely dissociated and randomly mixed can recombine to form periodic spatial structures. This leads to the intriguing possibility that at least some aspects of spatio-temporal patterning in the embryo arise from the process of self-organization. Spatial patterns also arise via self-organization in other populations of individuals, such as the swarming behaviour of bacteria, and in chemical systems, so that it is a widespread phenomenon.

Modelling in this area takes many forms, depending on the spatio-temporal scale and detail one wishes (or is able) to capture. At one extreme are coupled systems of

ordinary differential equations, in which one assumes that the system is well stirred so that all spatial information is lost and all individuals (for example, molecules) are assumed to have identical states. At the other extreme are cellular automata models, in which each element may represent an individual (or a collection of individuals) with assigned characteristics (for example, age) that can vary from one individual to the next. This approach allows for population behaviour to evolve in response to individual-level interactions. In hybrid cellular automata, one can model intracellular phenomena by ordinary differential equations, while global signalling may be modelled by partial differential equations. In this way, one can begin to address the crucial issue of modelling at different scales. There are many modelling levels between these extremes and each one has its own strengths and weaknesses.

Andreas Deutsch and Sabine Dormann bring to bear on this subject a depth and breadth of experience that few can match. In this book they present many different modelling approaches and show the appropriate conditions under which each can be used. After an introduction to pattern formation in general, this book develops the cellular automaton approach and shows how, under certain conditions, one can take the continuum limit, leading to the classical partial differential equation models. Along the way, many interesting pattern formation applications are presented. Simple rules are suggested for various elementary cellular interactions and it is demonstrated how spatio-temporal pattern formation in corresponding automaton models can be analyzed. In addition, suggestions for future research projects are included. It is also shown that the model framework developed can be used more generally to tackle problems in other areas, such as tumour growth, one of the most rapidly growing areas in mathematical biology at the present time. The accompanying website (www.biomodeling.info) allows the reader to perform online simulations of some of the models presented.

This book, aimed at undergraduates and graduate students as well as experienced researchers in mathematical biology, is very timely and ranges from the classical approaches right up to present-day research applications. For the experimentalist, the book may serve as an introduction to mathematical modelling topics, while the theoretician will particularly profit from the description of key problems in the context of biological pattern formation. The book provides the perfect background for researchers wishing to pursue the goal of multiscale modelling in the life sciences, perhaps one of the most challenging and important tasks facing researchers this century.

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January 2004

# Contents

# List of Figures

# List of Notation

| | |
|---|---|
| CA | cellular automaton |
| LGCA | lattice-gas cellular automaton/automata . . . . . 67 |

**Greek symbols**

| | |
|---|---|
| $\beta \in \mathbb{N}_0$ | number of rest (zero-velocity) channels . . . . . 72 |
| $\Gamma(q)$ | Boltzmann propagator . . . . . 95 |
| $\delta$ | length of temporal unit . . . . . 107 |
| $\epsilon$ | length of spatial unit . . . . . 107 |
| $\boldsymbol{\eta}(r) = (\eta_i(r))_{i=1}^{\tilde{b}} \in \{0,1\}^{\tilde{b}}$ | node configuration in a LGCA . . . . . 72 |
| $\boldsymbol{\eta}_{\mathcal{N}(r)}$ | local configuration in a LGCA . . . . . 72 |
| $\Lambda_M$ | spectrum of the matrix M . . . . . 91 |
| $\mu$ | spectral radius . . . . . 91 |
| $\mu(q)$ | spectral radius according to wave number $q$ . . . . . 96 |
| $\nu = \lvert\mathcal{N}_b^I\rvert$, $\nu_o = \lvert\mathcal{N}_{bo}^I\rvert$ | number of neighbors in the interaction neighborhood . . . . . 70 |
| $\rho(r,k) \in [0,1]$ | local particle density of node $r$ at time $k$ . . . . . 86 |
| $\rho(k) \in [0,1]$ | total particle density in the lattice at time $k$ . . . . . 86 |
| $\varrho(r,k) \in [0,\tilde{b}]$ | local mass of node $r$ at time $k$ . . . . . 86 |
| $\varrho(k) \in [0,\tilde{b}]$ | total mass in the lattice at time $k$ . . . . . 86 |

| | |
|---|---|
| $\sigma \in \{1, \ldots, \varsigma\}$ | single component in a model with $\varsigma$ components . . . . . 69 |
| $\Psi_a(\boldsymbol{\eta}(r,k)) \in \{0,1\}$ | indicator function . . . . . 139 |

**Further symbols**

| | |
|---|---|
| $\lvert \cdot \rvert$ | cardinality of a set |
| $[y]$ | integer closest to $y \in \mathbb{R}^+$ |
| $\lceil y \rceil$ | smallest integer greater than or equal to $y \in \mathbb{R}^+$ . . . . . 222 |
| $\boldsymbol{y}^T$ | transpose of the vector $\boldsymbol{y}$ |
| $A_j \in \mathcal{A}_{\tilde{b}}$ | permutation matrix . . . . . 116 |
| $b$ | coordination number; number of nearest neighbors on the lattice $\mathcal{L}$ . . . . . 68 |
| $\tilde{b} = b + \beta$ | total number of channels at each node . . . . . 72 |
| $c_i \in \mathcal{N}_b, i = 1, \ldots, b$ | nearest neighborhood connections of the lattice $\mathcal{L}$ . . . . . 68 |
| $\mathcal{C}_i\left(\boldsymbol{\eta}_{\mathcal{N}(r)}(k)\right) \in \{-1, 0, 1\}$ | change in occupation numbers . . . . . 78 |
| $\tilde{\mathcal{C}}_i\left(\boldsymbol{f}_{\mathcal{N}(r)}(k)\right) \in [0,1]$ | change of the average number of particles . . . . . 88 |
| $\boldsymbol{D}\left(\boldsymbol{\eta}_{\mathcal{N}(r)}\right)$ | director field . . . . . 164 |
| $\mathcal{E} = \{z^1, \ldots, z^{\lvert\mathcal{E}\rvert}\}$ | (finite) set of elementary states . . . . . 71 |
| $\boldsymbol{f}(r) = (f_i(r))_{i=1}^{\tilde{b}} \in [0,1]^{\tilde{b}}$ | vector of single particle distribution functions; average occupation numbers . . . . . 86 |
| $\boldsymbol{f}^s(k)$ | vector of spatially averaged occupation numbers . . . . . 220 |
| $\boldsymbol{F}(q) = (F_i(q))_{i=1}^{\tilde{b}}$ | Fourier-transformed value . . . . . 94 |
| $\mathtt{I}$ | (general) interaction operator . . . . . 77 |
| $\boldsymbol{J}(\boldsymbol{\eta}(r))$ | flux of particles at node $r$ . . . . . 164 |
| $k = 0, 1, 2, \ldots$ | time step . . . . . 75 |
| $\mathcal{L} \subset \mathbb{R}^d$ | $d$-dimensional regular lattice . . . . . 67 |
| $L_i, i = 1, \ldots, d$ | number of cells in space direction $i$ . . . . . 68 |
| $\mathtt{M}$ | shuffling (mixing) operator . . . . . 115 |

| | | |
|---|---|---|
| $\mathrm{n}(r) \in \{0, \ldots, \tilde{b}\}$ | total number of particles present at node $r$ | 72 |
| $\mathcal{N}_b$ | neighborhood template | 68 |
| $\mathcal{N}_b^I$ | interaction neighborhood template | 70 |
| $\mathcal{N}_{bo}^I$ | outer interaction neighborhood template | 70 |
| $\mathtt{P}$ | propagation operator | 77 |
| $q \in \{0, \ldots, L\}$ | (discrete) wave number | 93 |
| $q^s$ | wave number observed in simulation | 220 |
| $q_* \in Q^c$ | dominant critical wave number | 96 |
| $Q^c$ | set of critical wave numbers | 96 |
| $Q^+, Q^-$ | subsets of critical wave numbers | 96 |
| $r \in \mathcal{L}$ | spatial coordinate, cell, node, site | 67 |
| $(r, c_i)$ | channel with direction $c_i$ at node $r$ | 72 |
| $\mathtt{R}$ | reactive interaction operator ("Turing" model) | 212 |
| $\mathcal{R} : \mathcal{E}^v \to \mathcal{E}$ | cellular automaton rule | 73 |
| $s(r) \in \mathcal{E}$<br>$s : \mathcal{L} \to \mathcal{E}$ | state value at node $r$ | 71 |
| $\boldsymbol{s} = (s(r_i))_{r_i \in \mathcal{L}} \in \mathcal{S}$ | global configuration | 71 |
| $\boldsymbol{s}_\mathcal{M} = (s(r_i))_{r_i \in \mathcal{M}}$,<br>$\mathcal{M} \subset \mathcal{L}$ | local configuration | 72 |
| $\mathcal{S} = \mathcal{E}^{\lvert\mathcal{L}\rvert}$ | state space | 72 |
| $W : \mathcal{E}^v \to [0, 1]$ | time-independent transition probability | 74 |
| $X_\sigma$ | particle of "species" $\sigma$ | 78 |

*Cellular Automaton Modeling of Biological Pattern Formation*

# Part I

## General Principles, Theories, and Models of Pattern Formation

# 1

# Introduction and Outline

"*Things should be made as simple as possible, but not any simpler.*"
(A. Einstein)

This book deals with the problem of biological pattern formation. What are the mechanisms according to which individual organisms develop and biological patterns form? Biological organisms are characterized by their genomes. The letters of the genetic alphabet (the nucleotides), their precise arrangement in selected organisms (the gene sequence), and the molecular structure of a huge number of encoded proteins are public today. However, analysis of single gene and protein function is not sufficient to explain the complex pattern formation which results from the collective behavior of interacting molecules and cells. In the beginning of embryological development all cells are identical—equipped with basically the same set of genes. Accordingly, collective phenomena brought about by the interaction of cells with themselves and their surroundings are responsible for the differentiation and pattern formation characterizing subsequent developmental stages. It has become clear that mathematical modeling is strongly needed to discover the self-organization principles of interacting cell systems (Deutsch et al. 2004). But what are appropriate mathematical models, how can they be analyzed, and which specific biological problems can they address?

This chapter provides the motivation for the book. The basic problems are introduced and the connection between biological pattern formation and mathematical modeling is emphasized. An outline presents the book's structure and specific suggestions on how to read the book depending on the reader's background.

**Principles of Biological Pattern Formation.** The *morphogenesis* of multicellular organisms (fig. 1.1) as the development of characteristic tissue and organ arrangements, but also as the establishment and maintenance of life cycles distinguishing unicellular microorganisms (e.g., the slime mold *Dictyostelium discoideum* or myxobacteria; fig. 1.2) are manifestations of biological pattern formation.

Pattern formation is a *spatio-temporal* process: characterization of its principles therefore depends on the underlying space and time concept. In a *static* Platonian

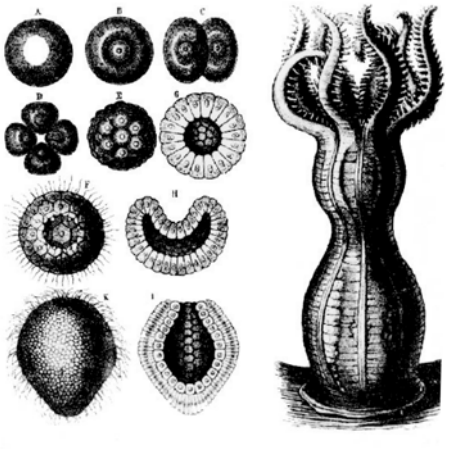

**Figure 1.1.** Morphogenesis of the coral *Monoxenia darwinii* (drawing by E. Haeckel). Left: from fertilized egg (top left) to gastrula stage (bottom right); right: adult stage. Courtesy of Ernst-Haeckel-Haus, Jena.

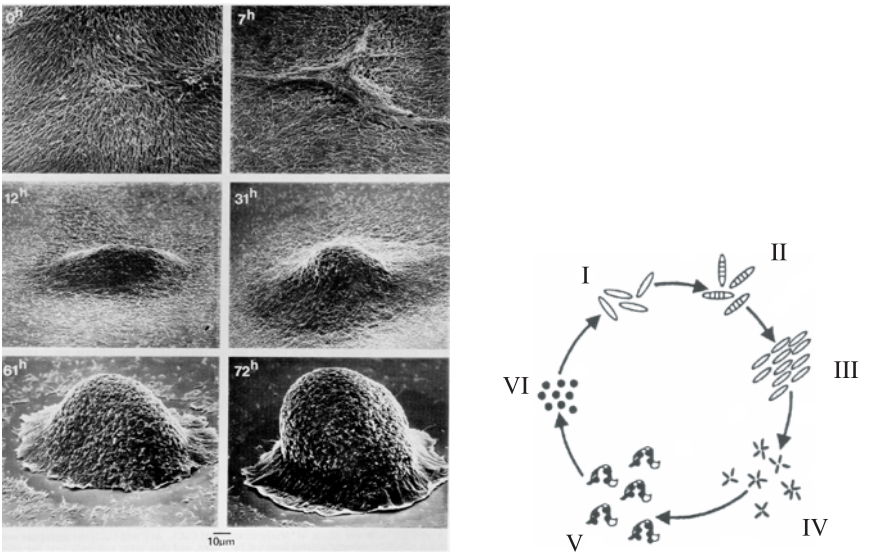


**Figure 1.2.** Pattern formation of unicellular organisms: myxobacteria. Left: fruiting body formation of *Myxococcus xanthus*. A developmental time series in submerged culture is shown. Initially asymmetric aggregates become round and develop intro three-dimensional fruiting bodies. Right: schematic sketch of myxobacterial life cycle. Rod-shaped vegetative cells (I) undergo cell division (II) and are able to migrate on suitable surfaces. Under certain conditions (e.g., starvation) cells cooperate, form streets (III), aggregate (IV), and develop fruiting bodies (V). Within these fruiting bodies cells differentiate into metabolically dormant myxospores (VI).

**Figure 1.3.** Preformed homunculus; inside a human spermatozoan a sitting "homunculus" was assumed which merely uncoils and grows during embryogenesis. Similar "homunculi" were expected to occupy the female egg (after Hartsoeker, 1694).

world view, any form (including biological forms) is regarded as *preformed* and static: the world is fixed (and optimal) without time, motion, or change. This concept only allows recycling of existing forms (see also fig. 1.3). In a *dynamic* Aristotelian world view, the need for epigenetic principles is emphasized to account for *de novo* pattern formation (fig. 1.4).

Life is characterized by an inherent small *ontogenetic* and a larger *phylogenetic* time scale, which define individual morphogenesis and evolutionary change, respectively (fig. 1.5). Darwin realized the importance of space (spatial niches) and time (temporal changes of varieties), which can result in different survival rates for organismic varieties. He contributed to an understanding of the *evolutionary change* of biological organisms with his theory of selection (Darwin 1859). But how do varieties develop during their individual lifetimes? At the end of the nineteenth century, developmental dynamics, i.e., *ontogenetic change,* became a target of experimentally oriented research. It was discovered that embryos do not contain the final adult form

**Figure 1.4.** Aristotelian *epigenetic* view of development from a uniform distribution to a structured embryo (after Rueff 1554).

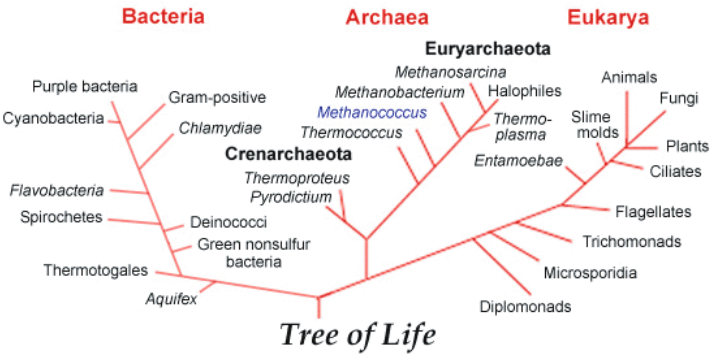


**Figure 1.5.** The tree of life or phylogenetic tree traces the pattern of descent of all life over millions of years into three major branches: bacteria, archaea, and eucarya. There is a controversy over the times at which archaea diverged from eubacteria and eukaryotes. One proposal is that eubacteria and archaea diverged around the time that eukaryotic cells developed, about 1.5 billion years ago.

in a mosaic prepattern and that all cells within an organism carry essentially the same genetical information. The need for *epigenetic principles* (e.g., regulation) became evident. Otherwise, cell differentiation and *de novo* formation of complex structures from a single cell in every new generation can not be explained.

**The Problem.** Even though a unified theory of morphogenesis comparable to Darwin's selection theory of evolution is still missing, one can address principles of biological pattern formation. Morphogenesis results from a limited repertoire of cellular activities: in particular, cells can change their shape, grow, divide, differentiate, undergo apoptosis, and migrate. It is the core of biological morphogenesis that cells do not behave independently of each other. To the contrary, cellular activities are intertwined and strongly rely on cooperative dynamics of *cell–cell interaction*, which may induce changes in cellular properties and activities.

Cells can interact directly (locally) or indirectly even over large distances. Local interaction of cells comprises interaction with their immediate environment, in particular other cells and the extracellular matrix. The importance of direct cell-cell interactions, in particular *adhesion*, became evident in tissue growth regeneration experiments (Holtfreter 1939, 1944; Townes and Holtfreter 1955). For example, phenomena of tissue reconstruction (e.g., sorting out) can be explained on a cell-to-cell basis by *differential adhesion* (Steinberg 1963). Further examples of direct cell interactions with their immediate surroundings are alignment, contact guidance or contact inhibition, and haptotaxis. In contrast, indirect cell interaction is mediated through long-range mechanical forces (e.g., bending forces) or chemical signals that propagate over large distances. Chemotaxis is a particularly well-studied example. Hereby, cells orient towards local maxima of a chemical signal gradient field.

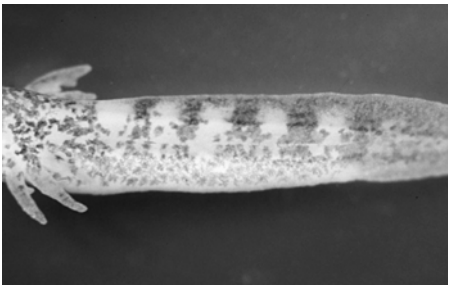

**Figure 1.6.** Axolotl pigment pattern. The barred (or transverse band) pigment pattern of an *Ambystoma mexicanum* larva. An albino-black larva (stage 40; 9.5 mm long) lacking maternal pigment granules is shown. Lateral aspect, head to the left outside. Melanophores (dark transverse bands) and xanthophores (bright areas in between) alternate along the dorsal trunk. The periodic pattern has no resemblance at the individual cell level; it is a *collective phenomenon* brought about by interactions of the axolotl cells (courtesy of H. H. Epperlein, Dresden).

A *morphogenetic system* provides an example of self-organization. The system is composed of many individual components, the cells, that interact with each other implying qualitatively new features on macroscopic scales, i.e., scales that are far bigger than those of the individual cells (e.g., formation of a periodic pigment cell pattern, see fig. 1.6). The question is, What are essential cell interactions and how do corresponding cooperative phenomena influence organismic morphogenesis? Possible answers can be found by means of *mathematical modeling*, which allows one to abstract from specific component behavior and to analyze generic properties.

**Mathematical Modeling.** Starting with D'Arcy Thompson (1917), principles of morphogenesis have been studied with the help of mathematical models. In particular, Thompson considered the shapes of unicellular organisms and suggested the minimization of surface tension as a plausible hypothesis, which he analyzed by studying corresponding equations. Another pioneer was A. Turing, who contributed with the idea of *diffusive instabilities* in reaction-diffusion dynamics (Turing 1952). The *Turing instability* can explain pattern formation in disturbed spatially homogeneous systems if (diffusive) transport of *activator-inhibitor morphogens* is coupled to appropriate *chemical kinetics*. In order to develop, e.g., a (periodic) pattern it is necessary that the diffusion coefficients of activator and inhibitor species differ drastically. Reaction-diffusion systems have become paradigms of nonequilibrium pattern formation and biological self-organization (Britton 1986; Murray 2002).

Meanwhile, there exists an established arsenal of *macroscopic models* based on continuum equations to analyze cellular interactions in reaction-diffusion systems (Chaplain, Singh, and McLachlan 1999; Maini 1999; Meinhardt 1992; Othmer, Maini, and Murray 1993). While the continuum assumption is appropriate in systems dealing with large numbers of cells and chemical concentrations, it is not adequate in systems consisting of a small number of interacting *discrete cells*. The problem arises

of how to design appropriate *microscopic models*, which allow the identification of individual cells.

**Cellular Automaton Models.** Interest in microscopic models, i.e., *spatial stochastic processes*, has grown lately due to the availability of "individual cell data" (genetic and proteomic) and has triggered the development of new cell-based mathematical models (for a recent review, see Drasdo 2003). Cell-based models are required if one is interested in understanding the organizational principles of interacting cell systems down to length scales of the order of a cell diameter in order to link the individual cell (microscopic) dynamics with a particular collective (macroscopic) phenomenon. Cell-based models, particularly cellular automata (CA), allow one to follow and analyze the spatio-temporal dynamics at the individual cell level.

Cellular automata are *discrete dynamical systems* and may be used as models of biological pattern formation based on cell–cell, cell–medium, and cell–medium–cell interactions. The roots of cellular automata can be traced back to the time when the origin of the genetic code was discovered (Watson and Crick 1953a, 1953b). Cellular automata were introduced by John von Neumann and Stanislaw Ulam as a computer model for self-reproduction, a necessary precondition for organismic inheritance (von Neumann 1966). Intensive research within the last few decades has demonstrated that successful model applications of cellular automata go far beyond self-reproduction. Since cellular automata have no central controller and are rule-based discrete dynamical systems, they can also be viewed as models of massively parallel, noncentralized computation. Cellular automata have become paradigms of self-organizing complex systems in which collective behavior arises from simple interaction rules of even more simple components. The automaton idea has been utilized in an enormous variety of biological and nonbiological systems. Accompanying the availability of more and more computing power, numerous automaton applications in physics, chemistry, biology, and even sociology have been studied extensively (Casti 2002; Hegselmann and Flache 1998; Mitchell 2002; Wolfram 2002).

Are there microscopic cellular automaton rules that can model the mechanisms of cell interaction? An important insight of complex system research is that macroscopic behavior is rather independent of the precise choice of the microscopic rule. For example, it was shown that simple collision rules can give rise to the intricate structures of hydrodynamic flow as long as the rules conserve mass and momentum (lattice-gas cellular automaton; Frisch, Hasslacher, and Pomeau 1986; Kadanoff 1986). Could it be that likewise in biological systems basic rules of cellular interaction are underlying complex developmental pattern formation? Contrary to differential equations representing a well-established concept, cellular automaton models of biological pattern formation are in a rather juvenile state. In particular, morphogenetic automaton classes have to be defined that allow for an analytic investigation. In this book, we introduce cellular automaton models in order to analyze the dynamics of interacting cell systems. We show how appropriately constructed stochastic automata allow for straightforward analysis of spatio-temporal pattern formation beyond mere simulation.

**Outline of the Book.** The book starts with a historical sketch of static and dynamic space-time concepts and shows how these concepts have influenced the understanding of pattern formation, particularly biological morphogenesis (ch. 2). Corresponding morphogenetic concepts are based on preformation, topology, optimization, and self-organization ideas. Furthermore, experimental approaches to the investigation of developmental principles are presented.

Ch. 3 introduces mathematical modeling concepts for analyzing principles of biological pattern formation. In particular, partial differential equations, coupled map lattices, many-particle systems, and cellular automata can be distinguished. In addition, *macroscopic* and *microscopic* modeling perspectives on biological pattern formation and their relations are discussed.

The cellular automaton idea is elaborated in ch. 4, starting from the biological roots of cellular automata as models of biological self-reproduction. We focus on the definition of deterministic, probabilistic, and lattice-gas cellular automata. Furthermore, routes to the linear stability (Boltzmann) analysis of automaton models are described. Stability analysis of the corresponding Boltzmann equation permits us to analyze the onset of pattern formation. It is demonstrated how particular cell interactions can be translated into corresponding automaton rules and how automaton simulations can be interpreted. It is also shown how to proceed from the (microscopic) automaton dynamics to a corresponding macroscopic equation.

An overview of cellular automaton models for different types of cellular interactions is presented in chs. 5–11. As a first example, the *interaction-free* (linear) automaton is introduced (ch. 5); this automaton can be viewed as a model of random cell dispersal. Stability analysis shows that all modes are stable and, accordingly, no spatial patterns can be expected. *Growth processes* are analyzed in ch. 6. In particular, probabilistic and lattice-gas automaton models for simple growth processes are proposed.

*Adhesive interactions* are the focus of ch. 7. Here, we consider adhesive interactions in systems consisting of a single cell type and two cell types, respectively. The underlying microdynamical equations of the proposed cellular automaton models are no longer linear. Stability analysis of the linearized Boltzmann equation indicates that the dominant (diffusive) mode can become unstable, implying spatial pattern formation visible as clustering and sorting out behavior (in the two-cell-type model). In particular, the two-cell-type system allows us to model and simulate a *differential adhesion* dynamics that is essential in key phases of embryonic development.

A cellular automaton based on *orientation-dependent (alignment) interaction* serves as a model of cellular alignment (swarming; see ch. 8). Cellular swarming is visible, e.g., in the formation of streets (rafts) of similarly oriented cells in certain microorganisms (e.g., myxobacteria). With the help of stability analysis it is possible to identify an "orientational mode" that indicates the swarming phase and that can destabilize. This behavior allows us to characterize the onset of swarming as a phase transition.

Ch. 9 takes up the problem of cellular pigment pattern formation. These patterns are easy to observe and evolve as the result of complex interactions between pigment cells and their structured tissue environment. Now, modeling has to incorporate both

interactions between cells and interactions between cells and the extracellular matrix. An automaton model of pigment pattern formation is introduced that is based on solely local interactions (adhesive interaction as well as contact guidance) without including long-range signaling. Simulations are shown which exhibit the development of vertical stripes that are found in axolotl embryos (cp. fig. 1.6). However, the cellular automaton model can be modified to simulate other cellular pigment patterns (e.g., horizontal stripes) that arise in salamanders and fish.

Cellular automata can also be used to simulate the implications of long-range signaling, in particular chemotaxis. Chemotaxis is an example of long-range cellular interaction mediated by diffusible signal molecules. In ch. 10 it is demonstrated how *chemotaxis* may be modeled with cellular automata. Furthermore, we present a model for *contact inhibition*. By combining of model modules (e.g., chemotaxis, contact inhibition, adhesion, etc.) simple models of tissue and tumor growth can be constructed (see ch. 10).

The study of Turing systems and excitable media has contributed enormously to a better qualitative and quantitative understanding of pattern formation. In ch. 11 we introduce and analyze cellular automaton models for Turing systems and excitable media based on microscopic interactions. The analysis allows us to characterize heterogeneous spatial (Turing) and spiral patterns, respectively, and sheds light on the influence of fluctuations and initial conditions.

Ch. 11 summarizes the results presented throughout the book. Cellular automata can be viewed as a discrete dynamical system, discrete in space, time and state space. In the final chapter, we critically discuss possibilities and limitations of the automaton approach in modeling various cell-biological applications, especially various types of morphogenetic motion and malignant pattern formation (tumor growth). Furthermore, perspectives on the future of the cellular automaton approach are presented.

The chapters of the book can be studied independently of each other, depending on the reader's specific interest. Note that all models introduced in the book are based on the cellular automaton notation defined in ch. 4. The model of pigment pattern formation presented in ch. 9 and the model of tumor growth in ch. 10 use model modules explained in earlier chapters (chs. 7 and 8). Readers interested in the principles of the mathematical modeling of spatio-temporal pattern formation should consult chs. 2 and 3. In addition, it is highly recommended to study the "Further Research Projects" sections at the end of the individual chapters (for additional problems, see also Casti 1989; Wolfram 1985). Readers requiring an introduction to a specific modeling problem should concentrate on elementary interactions, especially those derived in chs. 5 and 6. Ch. 9 can serve as a good introduction on how to construct a complex model by combining individual model modules.

The book has greatly benefitted from various inputs by many friends and colleagues. Special thanks go to E. Ben-Jacob (Tel-Aviv), L. Berec (Ceske Budejovice), U. Börner (Dresden), D. Bredemann (Dresden), L. Brusch (Dresden), H. Bussemaker (Amsterdam), D. Dormann (Dundee), H. Dullin (Loughborough), H.-H. Epperlein (Dresden), A. Focks (Osnabrück), S. Gault (Montreal), A. Greven (Erlangen), M. Kolev (Warsaw), M. Lachowicz (Warsaw), A. Lawniczak (Toronto), H.