Lecture Notes in Mathematics 2167
CIME Foundation Subseries

Pasquale Ciarletta · Thomas Hillen
Hans Othmer · Luigi Preziosi
Dumitru Trucu

Mathematical Models and Methods for Living Systems

Levico Terme, Italy 2014

Luigi Preziosi · Mark Chaplain
Andrea Pugliese *Editors*

Springer

Lecture Notes in Mathematics 2167

More information about this series at http://www.springer.com/series/#304

Fondazione C.I.M.E., Firenze

C.I.M.E. stands for *Centro Internazionale Matematico Estivo*, that is, International Mathematical Summer Centre. Conceived in the early fifties, it was born in 1954 in Florence, Italy, and welcomed by the world mathematical community: it continues successfully, year for year, to this day.

Many mathematicians from all over the world have been involved in a way or another in C.I.M.E.'s activities over the years. The main purpose and mode of functioning of the Centre may be summarised as follows: every year, during the summer, sessions on different themes from pure and applied mathematics are offered by application to mathematicians from all countries. A Session is generally based on three or four main courses given by specialists of international renown, plus a certain number of seminars, and is held in an attractive rural location in Italy.

The aim of a C.I.M.E. session is to bring to the attention of younger researchers the origins, development, and perspectives of some very active branch of mathematical research. The topics of the courses are generally of international resonance. The full immersion atmosphere of the courses and the daily exchange among participants are thus an initiation to international collaboration in mathematical research.

C.I.M.E. Director (2002 – 2014)
Pietro Zecca
Dipartimento di Energetica "S. Stecco"
Università di Firenze
Via S. Marta, 3
50139 Florence
Italy
e-mail: zecca@unifi.it

C.I.M.E. Director (2015 –)
Elvira Mascolo
Dipartimento di Matematica "U. Dini"
Università di Firenze
viale G.B. Morgagni 67/A
50134 Florence
Italy
e-mail: mascolo@math.unifi.it

C.I.M.E. Secretary
Paolo Salani
Dipartimento di Matematica "U. Dini"
Università di Firenze
viale G.B. Morgagni 67/A
50134 Florence
Italy
e-mail: salani@math.unifi.it

CIME activity is carried out with
the collaboration and financial support
of INdAM (Istituto Nazionale di Alta
Matematica)
For more information see CIME's homepage:
http://www.cime.unifi.it

Pasquale Ciarletta • Thomas Hillen • Hans Othmer •
Luigi Preziosi • Dumitru Trucu

Mathematical Models and Methods for Living Systems

Levico Terme, Italy 2014

Luigi Preziosi • Mark Chaplain • Andrea Pugliese
Editors

Springer

FONDAZIONE CIME ROBERTO CONTI
CENTRO INTERNAZIONALE MATEMATICO ESTIVO
INTERNATIONAL MATHEMATICAL SUMMER CENTER

Authors
Pasquale Ciarletta
Politecnico di Milano
Dip. Matematica
Milano, Italy

Thomas Hillen
Mathematical & Statistical Sciences
University of Alberta
Edmonton
Alberta, Canada

Hans Othmer
School of Mathematics
University of Minnesota
Minneapolis
Minnesota, USA

Luigi Preziosi
Mathematical Sciences
Politecnico di Torino
Torino, Italy

Dumitru Trucu
Dept. of Mathematics
University of Dundee
Dundee, United Kingdom

Editors
Luigi Preziosi
Mathematical Sciences
Politecnico di Torino
Torino, Italy

Mark Chaplain
School of Mathematics and Statistics
University of St. Andrews
St. Andrews, United Kingdom

Andrea Pugliese
Department of Mathematics
Università di Trento
Povo, Italy

ISSN 0075-8434 ISSN 1617-9692 (electronic)
Lecture Notes in Mathematics
ISBN 978-3-319-42678-5 ISBN 978-3-319-42679-2 (eBook)
DOI 10.1007/978-3-319-42679-2

Library of Congress Control Number: 2016950724

Mathematics Subject Classification (2010): 92Cxx

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland

Preface

Understanding the mechanisms used by cells to move, to self-organise and to develop in tissues is not only fundamental in embryogenesis but is also relevant in tissue engineering and in other environmental and industrial processes involving the growth and homeostasis of biological systems, e.g. biofilm growth. Growth and organisation processes are also important in many diseases and tissue degeneration and regeneration processes, such as tumour growth, tissue vascularization, heart and muscle functionality and cardiovascular diseases.

In the last decade there has been a burst in the development of mathematical models aimed at studying the behaviour of such biological systems. In doing that, the most difficult point to be taken care of is that by definition biological systems are alive which means that, for instance, they do not respond in a passive way to external chemical and mechanical stimuli, but react actively. They are also able to modify their internal state according to the surrounding environment. Modelling this aspect requires to deeply question and re-analyse whether the classical tools used to model inert matter are proper enough to describe active behaviours. For instance, in continuum mechanics, the concept of evolving natural configurations was proposed to describe the active behaviour of cells, cell ensembles and entire tissues, e.g. muscle and heart (see, for instance, Chap. 4).

In some cases, it is necessary to link mathematical techniques that appear very different. For instance, the study of networks describing chemical reactions occurring inside the cells is interlinking more and more with kinetic theories and continuum mechanics. In fact, more in general what happens at a certain spatial scale, i.e. subcellular, cellular or tissue scale, is logically and functionally linked with what happens at other scales (see, for instance, Chap. 5). For instance, the behaviour of a cell depends on the one hand on the interaction it has with the surrounding environment (see, for instance, Chap. 3) and on the other hand on the chemical reactions occurring inside it (see, for instance, Chap. 1). The two aspects are then related through feedback loops, so that describing a phenomenon without considering what happens at a smaller or at a larger scale results in a strong oversimplification. From the mathematical point of view, this leads to the need of

using multiscale methods and upscaling techniques to connect phenomena occurring at different scales, like the diffusive limits described in Chap. 2.

Keeping this in mind, the aim of the C.I.M.E.-C.I.R.M. summer school on Mathematical Models and Methods for Living Systems was to give an introduction to several mathematical models and methods used to describe the behaviour of living systems. In more detail, then

- Chapter 1, authored by Hans Othmer, deals with models of cell motion starting from the reaction networks occurring at the cytoskeleton level to end with the motion of cell aggregates. In particular, the chapter gives an overview of how chemical and mechanical signals are integrated, how spatial differences in signals are produced and how propulsive and adhesive forces are controlled.
- Chapter 2, authored by Thomas Hillen and Amanda Swan, having in mind the modelling of cell motion, deals with transport models and their relations with individual-based random walk models and reaction-diffusion equations. The model is then applied to bacterial movement, amoeboid movement of cells and the spread of metastasis in anisotropic tissues like the growth of glioblastoma in the brain.
- Chapter 3, authored by Luigi Preziosi and Marco Scianna, focuses on the interaction of cells with the surrounding environment, taking into account several phenomena occurring at the cellular level, such as the role of the nucleus stiffness and the adhesion mechanisms between cells and the fibre network forming the extracellular matrix. With this aim in mind, several mathematical models are introduced, e.g. age-structured models, cellular Potts models and continuum mechanics models.
- Chapter 4, authored by Pasquale Ciarletta and Valentina Balbi, deals with a continuous chemomechanical approach to morphogenesis. The basic evolution laws for both volumetric and interfacial processes are derived and then applied to the study of pattern formation in biological systems treated either as fluids or as solids.
- Chapter 5, authored by Dumitru Trucu, Pia Domschke, Alf Gerisch, and Mark A.J. Chaplain, deals with a multiscale model of cancer invasion. The main focus of the modelling is how the molecular processes occurring at the level of individual cells (micro-scale) and the processes occurring at the tissue level (cell population or macro-scale) are connected and affect each other. Initially a single tissue scale model of cancer invasion is presented based around a system of non-local partial differential equations where the specific roles of cell-cell adhesion and cell-matrix adhesion are explored. This leads naturally to the development of a general spatio-temporal-structured cell population modelling framework which considers the role of cell-receptor dynamics in cancer invasion. Finally, a multiscale moving boundary modelling framework for cancer invasion is developed. In each case, computational simulations are presented which all aim to predict how far cancer cells can invade into healthy normal tissue.

As a concluding remark, we express our deepest gratitude to all the people that have contributed to the success of this C.I.M.E.-C.I.R.M. summer school: the

lecturers, the authors that have contributed to this volume, the participants and all the persons in charge of the organisation. We thank both C.I.M.E. and C.I.R.M. for their financial support, without which the school and therefore this lecture note would have never been possible.

St. Andrews, UK — Mark Chaplain
Torino, Italy — Luigi Preziosi
Povo, Italy — Andrea Pugliese

Acknowledgements

CIME activity is carried out with the collaboration and financial support of INdAM (Istituto Nazionale di Alta Matematica) and MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca).

Contents

Chapter 1
Cell-Based, Continuum and Hybrid Models of Tissue Dynamics

Hans G. Othmer

Abstract Movement of amoeboid cells is involved in embryonic development, wound repair, the immune response to bacterial invasion, and tumor formation and metastasis. Individual cells detect extracellular chemical and mechanical signals via membrane receptors, and this initiates signal transduction cascades that produce intracellular signals. These signals control the motile machinery of the cell and thereby determine the spatial localization of contact sites with the substrate and the sites of force-generation needed to produce directed motion. The coordination and control of this complex process of direction sensing, amplification of spatial differences in the signal, assembly of the motile machinery, and control of the attachment to the substratum involves numerous molecules whose spatial distribution serves to distinguish the front from the rear of the cell, and whose temporal expression is tightly controlled. How chemical and mechanical signals are integrated, how spatial differences in signals are produced, and how propulsive and adhesive forces are controlled are issues that are amenable to mathematical modeling. An overview of some approaches to these complex problems is the subject of this chapter.

1.1 Introduction

Cell and tissue movement is an integral part of many biological processes, such as large-scale tissue rearrangements or translocations that occur during embryogenesis, wound healing, angiogenesis, the immune response, and axon growth and migration. Individual cells such as bacteria migrate toward better environments by a combination of taxis and kinesis, and macrophages and neutrophils use these same processes to find bacteria and cellular debris as part of the immune response. Our understanding of signal transduction and motor control in flagellated bacteria such as *E. coli* that move by swimming and bias their movement by control of their run lengths is quite advanced [2, 93, 108] compared with our understanding of how amoeboid cells such as macrophages crawl through tissues. Some basic issues in the

Supported in part by NSF Grants DMS-0817529 & -1311974 and by NIH Grant GM 29123.

H.G. Othmer (✉)
School of Mathematics, University of Minnesota, Minneapolis, MN 55455, USA
e-mail: othmer@math.umn.edu

L. Preziosi et al. (eds.), *Mathematical Models and Methods for Living Systems*,
Lecture Notes in Mathematics 2167, DOI 10.1007/978-3-319-42679-2_1

latter context include how directional information is extracted from the extracellular signals, how cells develop and maintain polarity, how cells exert traction on their environment, and how adhesion to substrates or other cells is controlled.

Many eukaryotic cells can detect both the magnitude and direction of extracellular signals using receptors embedded in the cell membrane. When the signal is spatially nonuniform they may respond by directed migration either up or down the gradient of the signal, a process called taxis. When the extracellular signal is a diffusible molecule the response is chemotactic, and when it is an adhesion factor attached to the substrate or extracellular matrix (ECM) the process is called haptotaxis [1]. Cells frequently must integrate several signals downstream of the respective receptors, but the mechanisms for doing this are not well understood [45]. Chemotaxis controls the migration of single-celled organisms such as the slime mold *Dictyostelium discoideum* (Dd hereafter), toward a source of cyclic AMP (cAMP), and the movement of leukocytes toward attractants released by bacteria in a tissue. Movement toward a chemoattractant involves directional sensing and orientation, assembly of the motile machinery, polarization of the cell, and control of the attachment to the substratum or ECM. Many eukaryotic cells share common mechanisms, to be described shortly, for sensing and responding to chemoattractant gradients via G-protein-coupled receptors (GPCRs), and to adhesion gradients via integrins or their homologs.

At sufficiently high densities a cell's movement is strongly influenced by that of its neighbors. In some cases cells repeatedly form contacts with neighbors to gain traction, and then break them, only to re-attach to other nearby cells. Examples occur in the streaming and slug stages of the slime mold Dd, to be described later. In other cases cells remain attached to one another, and movement involves massive, coordinated rearrangements of entire tissues, such as folding of the neural plate to form a tube [26, 103]. Movement in both cases involves the same processes as for individual cells, with the addition of more-or-less tight coupling between the movement of neighboring cells, and we refer to both cases as tissue movement.

The classical description of amoeboid cell movement—which roughly speaking is 'crawling' movement that involves cell deformation and protrusions of various types—involves at least four different stages: protrusion, attachment to the substrate, translocation of the cell body, and detachment of the rear (Fig. 1.1) [71, 88]. (1) Cells first extend directed protrusions (lamellipodia, filopodia, or pseudopodia) at the leading edge. The force for this results from localized actin polymerization (discussed later) into cross-linked networks of filaments in lamellipodia or bundles of filaments in filopdia or pseudopodia. Behind the protrusion there is a region of actin disassembly, where filaments are disassembled, crosslinks broken and actin monomers recycled to the site of active polymerization [1]. (2) To persist, protrusions must anchor to the substrate, the extracellular matrix (ECM), or another cell via adhesive complexes, which serve as sites for molecular signaling and force transmission [91, 92]. In mesenchymal motion such as in fibroblasts, the adhesive complexes at the leading edge grow into larger focal adhesions that serve as traction 'pads' over which the cell body moves [33, 90]. (3) Next, depending on the cell type, actomyosin filaments contract at the front, in the perinuclear region, or at the

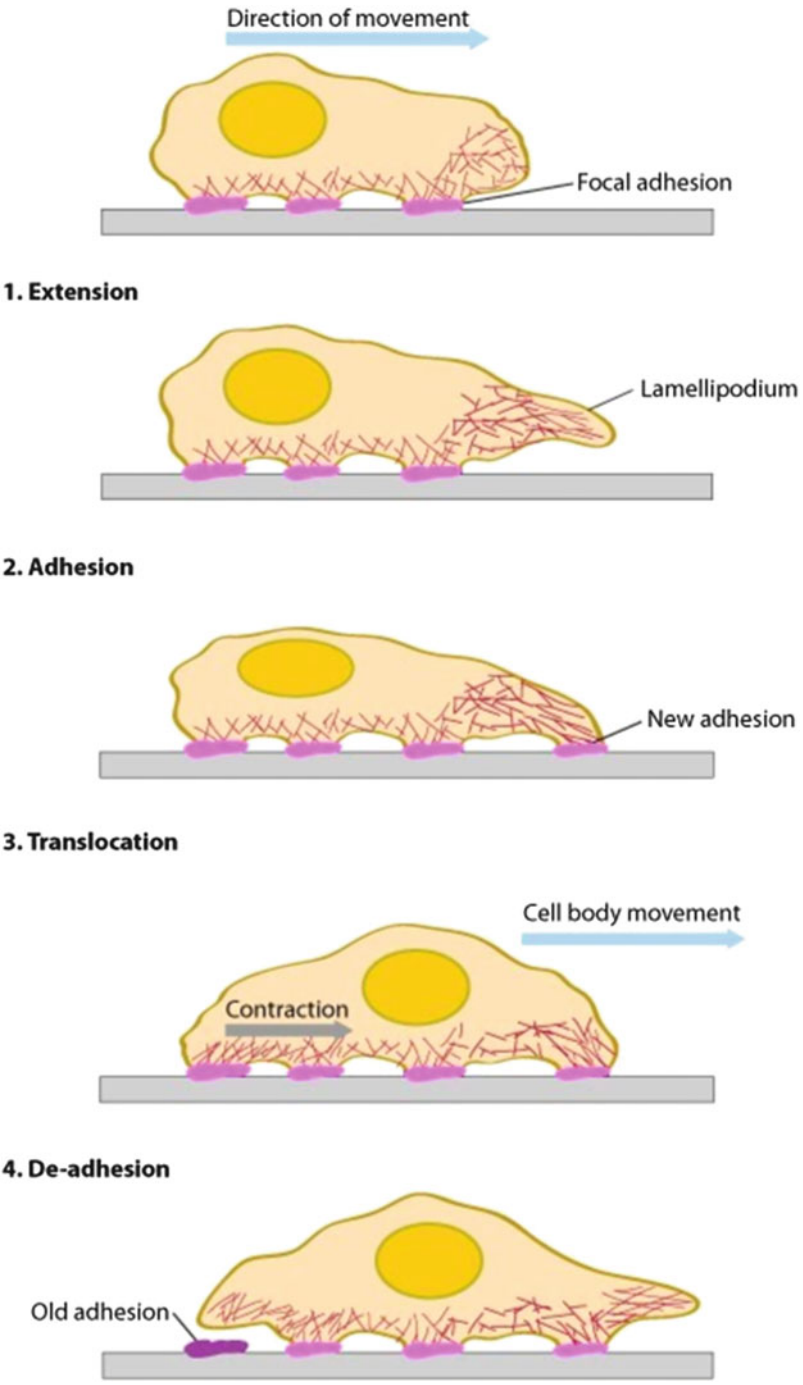

Fig. 1.1 The four stages of eukaryotic cell motion. From [3]

rear, to move the cell body forward. (4) Finally, cells release attachments at the rear [80]. In Dd or keratocytes the adhesion is weak and cells move rapidly, whereas in fibroblasts it is strong and cells move slowly.

The cytoplasm in many amoeboid cells has been characterized as a viscoelastic material whose properties are dominated by actin filaments, intermediate filaments and microtubules, collectively termed the cytoskeleton [54]. The controlled deformation and remodeling of the cytoskeleton that are involved in the shape deformations and protrusions are essential for movement. Its stress/strain response can be varied from that of a solid to that of a liquid by controlled assembly, cross-linking, and disassembly of its components. Thus the cytoskeleton is a dynamically-reorganizable nanomachine. The biochemical control processes, the microstructure of the cytoskeleton, and the formation and dissolution of adhesion sites are coordinated at the whole-cell level to produce the forces needed for movement [5, 8, 61]. Much is known about the biochemical details of the constituent steps in signaling and force generation, and the focus is now shifting to understanding whole-cell movement. For this one needs a mathematical model that links molecular-level behavior with macroscopic observations on forces exerted, cell shape, and cell speed because the large-scale mechanical effects cannot be predicted from the molecular biology of individual steps alone. However, how to formulate a multiscale model that integrates the microscopic steps into a macroscopic model is poorly understood in this context. What is needed are successively more complex model systems that will enable one to test the major modules in an integrated model sequentially. Some of these components are discussed later, and in the following section we begin with actin dynamics. However we first introduce a model system that is widely-used for both experimental and theoretical studies.

1.1.1 Dictyostelium Discoideum as a Model System

The cellular slime mold *Dictyostelium discoideum* is an important system for the study of many developmental processes, including intercellular communication, chemotaxis and differentiation. In a favorable environment the free-ranging individual amoeba feed on bacteria and divide by binary fission, but if the food supply is exhausted an elaborate developmental program is initiated (Fig. 1.2). After a period of starvation the cells attain relay competence and can respond to an external cyclic AMP signal by synthesizing and releasing cyclic AMP. This is called the relay response. The fraction of relay competent cells in a population increases with time after starvation, and at 10 h post-starvation almost all cells are relay competent [43]. At about 8 h post-starvation the cells begin aggregating in response to periodic waves of cyclic AMP initiated by randomly-located pacemaker cells. The proportion of autonomously-signaling cells in an aggregation field rises from zero at about 7 h post starvation and saturates at a small fraction of the total population within 21 h [82]. At the end of aggregation the cells form a cylindrical slug or grex which may migrate on the substrate for some time. Following migration the slug forms a fruiting

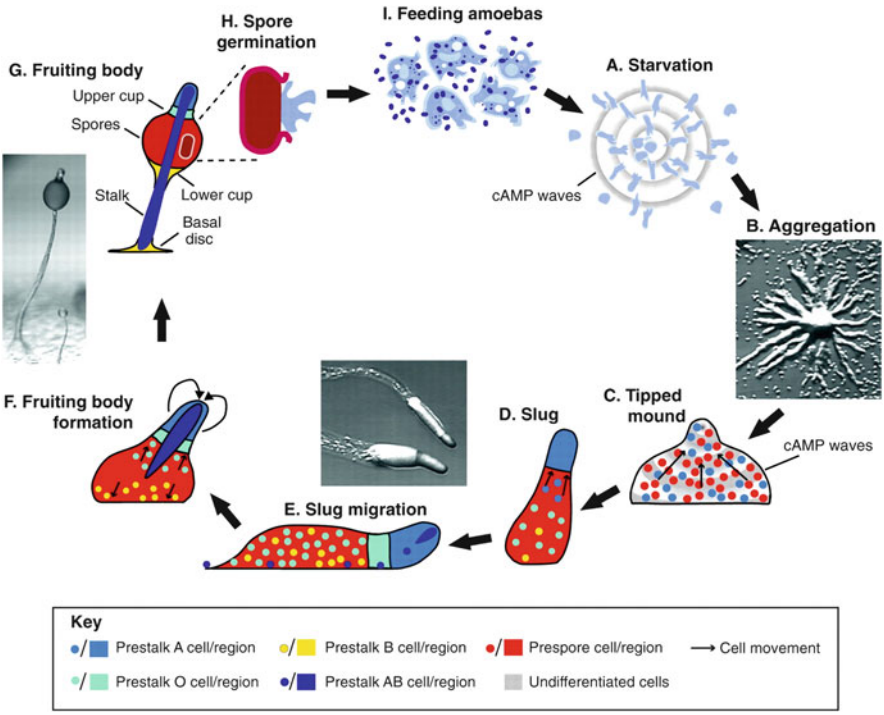

Fig. 1.2 (**a**)–(**i**) The life cycle of Dictyostelium. From [86] with permission

body, which consists of an erect stalk that supports a spherical cap containing spores. Under favorable conditions of temperature and humidity the spores are released and can germinate, and the cycle begins anew [6].

Many biological networks that occur in higher organisms first appeared in lower organisms such as Dd, and thus Dd has been widely-used for studying signal transduction, chemotaxis, and cell motility. Dd uses adenosine 3',5'-monophosphate (cAMP) as a messenger for signaling by randomly-located pacemaker cells that emit cAMP periodically in time to control cell movement in various stages of development [74]. The production by pacemakers and relay of cAMP pulses by cells that are excitable but not oscillatory, leads to cAMP waves that propagate outward from a pacemaker, and this coupled with chemotactic movement toward the source of cAMP, facilitates the recruitment of widely-dispersed cells (Fig. 1.3). In early aggregation the cells move autonomously, but in late aggregation and in the slug stage they interact strongly and the collective motion is tissue-like [74]. In the absence of cAMP stimuli Dd cells extend protrusions called pseudopods in random directions. Aggregation-competent cells respond to cAMP stimuli by suppressing existing pseudopods and rounding up (the 'cringe response'), which occurs within about 20 s after the initial stimulus and lasts about 30 s [20]. Under uniform elevation of the ambient cAMP this is followed by extension of pseudopods in various directions, and an increase in the motility [44, 101, 105]. A localized

Fig. 1.3 Spiral cell density waves observed in aggregation. From [89] with permission

application of cAMP elicits the cringe response followed by a localized extension of a pseudopod near the point of application of the stimulus [95]. How the cell determines the direction in which the signal is largest, and how it organizes the motile machinery to polarize and move in that direction, are major questions from both the experimental and theoretical viewpoint. Since cAMP receptors remain uniformly distributed around the cell membrane during a tactic response, receptor localization or aggregation is not part of the response [55]. Well-polarized cells are able to detect and respond to chemoattractant gradients with a 2 % concentration difference between the anterior and posterior of the cell [76]. Directional changes of a shallow gradient induce polarized cells to turn, whereas large changes lead to large-scale disassembly of motile components and creation of a new 'leading edge' directed toward the stimulus [37].

The first step in developing models for the movement of individuals and population-level aggregation patterns is to identify the distinct processes involved in

producing the different types of response. What a cell must do can be summarized as follows.

- Some cells (or small groups of cells) must become pacemakers. It is known from theoretical studies that a single cell suffices to create an aggregation wave [29], but this has not been demonstrated experimentally.
- A cell must detect the external cAMP and transduce it into an internal signal. A model of this process is discussed later.
- It must choose a direction in which to move and rebuild the cytoskeleton if needed to exert the necessary forces for movement.
- Cells must amplify and relay the signal, and adapt to the ambient signal.
- They must respond to an oncoming wave but not to a receding wave (this is the 'back-of-the-wave' problem), and they must move for an appropriate length of time.
- Eventually a cell interacts with its neighbors and moves collectively, first in pairs, then in streams, then in the slug and finally in the erection of the fruiting body.
- Slightly later it has to 'decide' what type of cell to become in the final fruiting body. This is a collective decision reached by the community (absent cheaters!).
- The entire aggregate has to stop migrating and erect the fruiting body.

The central theme in this chapter can be summarized in the question 'how do we model and analyze these behaviors, and what do we learn from that process?' Since there are many processes involved we approach these steps individually, and for the description of single cell behavior we modularize it as shown in Fig. 1.4.

1.2 Actin Dynamics

1.2.1 The Basic Biochemistry

Actin is a cellular protein that exists either in the globular, monomeric form, called G-actin, or in the polymeric two-stranded filament form, called F-actin. In solution G-actin can self-assemble into long filaments, into bundles, and into higher-dimensional structures. The filaments are long and flexible in vitro, and buckle easily, but in vivo cells create a dense dendritic network of short, branched filaments by tightly coupling nucleation, branching, and cross-linking of filaments in the lamellipodium, a thin (0.1–0.2 μm), sheet-like protrusion at the leading edge of a moving cell [21, 94]. Figure 1.4 shows the processes and some of the auxiliary molecules involved in vivo, and suggests the complexity of models to describe this. Table 1.1—revised from [80]—gives representative concentrations of G- and F-actin, and various auxiliary molecules.

The stiffness of the network enables new filaments to exert force on the membrane and provides the structural basis for polymerization-driven protrusion. The type of structure formed is tightly controlled by extracellular mechanical