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► **To cite this version:**

Arnaud Chauvière, Luigi Preziosi, Claude Verdier. Cell Mechanics. From single scale-based models to multiscale modeling. Chapman & Hall/CRC. Taylor & Francis Group CRC Press, pp.456, 2010, Mathematical and computational Biology Series. hal-00565645

HAL Id: hal-00565645

<https://hal.science/hal-00565645>

Submitted on 14 Feb 2011

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CELL MECHANICS. FROM SINGLE SCALE-BASED MODELS
TO MULTISCALE MODELING

Arnaud Chauvière, Luigi Preziosi and Claude Verdier

April 6, 2009

Preface

This book is the result of years of collaboration between different teams interacting in the framework of a European Research and Training Network on “Modeling, Mathematical Methods and Computer Simulation of Tumour Growth and Therapy”. Throughout this Network, the collaboration between groups has brought new insight and motivated research leading to mechanical, mathematical, physical and biological approaches all related to the simulation of the behavior of cells and, in particular, of tumor cells.

While looking at the phenomena from different points of view, it became soon clear that multiscale problems are ubiquitous and fundamental in cell mechanics as illustrated in figure 1. For instance, such problems naturally emerge from the description of situations involving cell adhesion, migration, invasion, intravasation and extravasation, mitosis, cell-cell interactions, etc. Modeling the role of mechano-transduction in the behavior of the cell, its fate (duplication, survival, or death) or even its differentiation, or how the internal dynamics of actin and microtubules determine the migratory characteristics of the cells, leads also to a combination of intrinsically coupled scales. These aspects are, of course, not only of major interests to describe the growth of tumors, but also in embryogenesis, in the description of physiological and pathological states of all tissues, and nowadays in tissue engineering, in tissue remediation and regeneration. It is our motivation here to present non exhaustive tools which will help graduate students, researchers, and professors in their research and teaching activity.

The book is a pluridisciplinary collective effort which contains reviews or articles interesting for students and researchers from different disciplines such as the ones presented above.

Some of the collected works were presented in a European Workshop on “Multiscale approaches in cell mechanics” (January 7-10, 2008) which took place in Autrans (France) and was organized by Arnaud Chauvière (TU Dresden - Germany) and Claude Verdier (CNRS, Grenoble - France). Several other works from experts in the field were also included in order to get a more general overview of the subject. At the moment, it appears that solving such multiscale problems is still a difficult task to achieve.

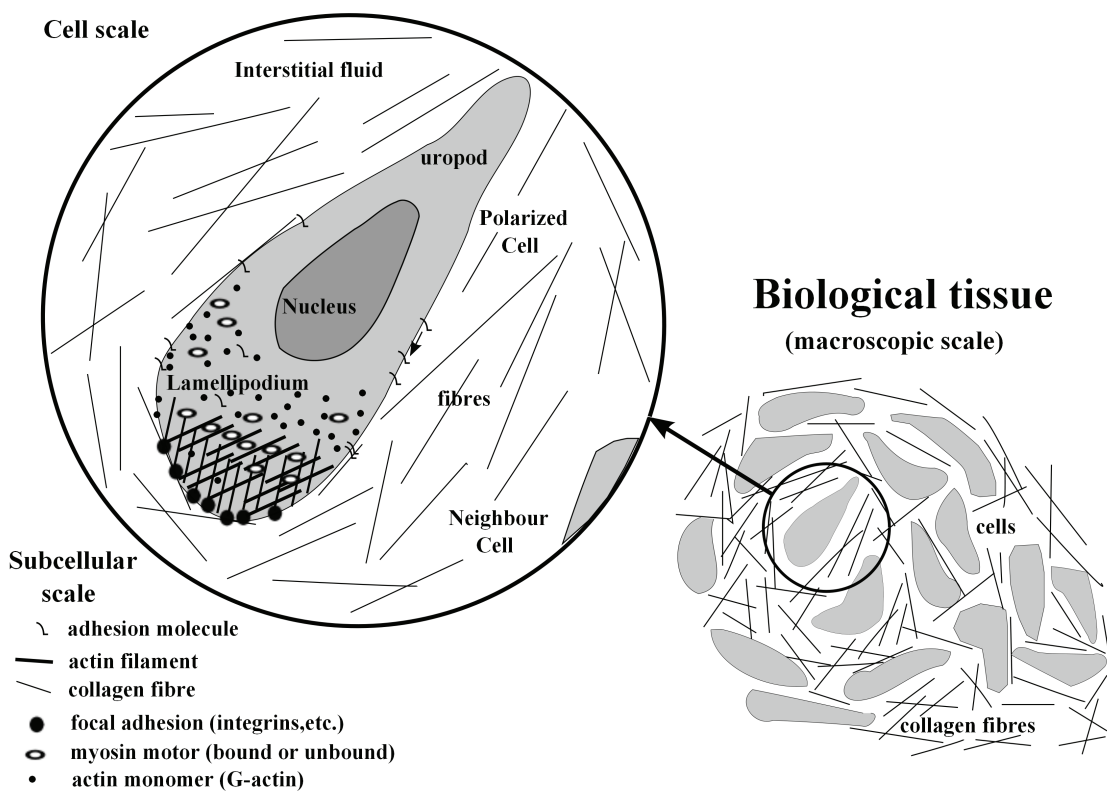


Figure 1: Multiscale view of cell mechanics. A biological tissue is made of several components including cells and the extracellular matrix. A zoom allows to identify a single cell embedded in the extracellular matrix and surrounded by neighboring cells. Details illustrate the configuration at the cellular scale. At the microscopic scale, various elements interact to create cell motion (actin filaments, adhesion molecules within focal adhesions). At the nanoscale, cell sub-elements combine to create actin filaments generating forces through the acto-myosin complex.

Throughout this textbook, various approaches and methods are presented in order to highlight how phenomena happening at various scales can be modeled and coupled to account for multiscale aspects. It is also our purpose here to show the existing tools available, and

by default to bring the need to carry on new approaches. In the spirit of the Workshop mentioned above, efforts have been made to propose, in some chapters, both experimental and theoretical aspects of the same topic. In some other ones, experiments and theories are discussed separately in order to provide a deeper insight of, either biological aspects in the first case, or complex modeling in the second one.

The book is divided into four parts. In the first part, some subcellular and cellular aspects, and their links, are presented. Microrheology (Chapter 1) is shown to be a powerful tool for the investigation of cell mechanical properties. Links between length scales are properly identified in a unified concept. Chapter 2 presents multiphysics and multiscale approaches to investigate intra-cellular mechanisms involved in cell motility. Minimal ingredients are used to explain how the actin polymerization can take place and trigger forces to generate motion. This approach is very promising for further investigations and understanding of cell motion. The last chapter of the first part discusses how subcellular effects involving certain genes can play a role to induce cell motility, in the particular context of cancer. The multiscale approach is explained within the concept of sophisticated experiments.

In the second part, cell migration is considered. The basic ingredients which have been proposed earlier ¹ are revisited through three different models respectively based on physical (chapter 4), mathematical (chapter 5) and computational (chapter 6) approaches. All of them introduce and develop tools to account for the description of the complex interplay between cell adhesion molecules and the dynamic evolution of the cell cytoskeleton. They underline the ubiquity of multiscale aspects when one aims to understand the complex interaction between molecules at the nanometer scale, and their combination to create motion at the cellular scale (i.e. micron scale).

The third part is devoted to the study of cells interaction with the environment, in particular the role of external mechanical forces and their effects on cell behaviour. In the first chapter (chapter 7), a model approach is considered to see how a flow field (involving shear stresses mainly) can affect the dynamic behavior of a cell (a bead here) in close contact to a wall. Such a motion is very important when considering the rolling motion of leukocytes on the vessel wall, but may also be relevant when cancer cells interact with the endothelium

¹D. A. Lauffenburger, and A. F. Horwitz (1996) Cell migration: a physically integrated molecular process. *Cell* **84**:359–369.

of blood vessels to intravasate or extravasate. The next two chapters (8 and 9) consider the role of a substrate on the adhesion of a cell and the exerted traction forces. In particular, the role of rigidity of the substrate is very important and affects mechano-transduction (chapter 8) as well as the development of stable or unstable focal adhesions. Another related aspect is the corresponding forces which are exerted by cells on a rigid substrate (chapter 9) which depend on its rigidity. Such features are important when considering many cells in their natural environment, for example when in contact with a soft tissue. Mechano-transduction is also reported in chapter 10 in an attempt to see how external mechanical forces can lead to calcium fluxes, and then to biochemical responses at the cell level.

In the last part, models of multicellular systems are presented. A substantial review of innovative models developed in the context of cancer has been presented before ², but some recent developments are now available and can be considered complementary. This is the aim of this last part to propose such new approaches. Chapter 11 investigates the collective amoeboid motion of cells within the extracellular matrix (i.e. collagen in a real tissue). This problem is important in particular when looking at cancer cell migration ³. The next three chapters present applications of population models to developmental biology and cancer (chapter 12), embryogenesis (chapter 13) and cancer invasion (chapter 14). Finally a new approach based on Delaunay-Object-Dynamics is considered (chapter 15) to study the behaviour of highly motile cells involved in certain tissues.

Of course, there is still a large gap between the acceptance of multiscale models and their effectiveness in predicting accurate pathologies, or their import towards real medical applications. Nevertheless, we have tried here to collect, among others, some new methods to apply to cells and tissues, through a multiscale concept.

The editors wish to thank warmly all the authors who contributed to this book. Special thanks are also given to all participants of the Marie Curie RTN Network (2004-2008) for bringing into play such challenging scientific efforts. We are also indebted to N. Sunil at CRC Press for his helpful advices.

²Cancer Modelling and Simulation, Chapman & Hall/CRC Mathematical and Medicine Series, Ed Luigi Preziosi, 2003.

³P. Friedl and Wolf K. (2003) Tumour-cell invasion and migration: diversity and escape mechanisms, *Nature*, **3**:362–374

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