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Advances in Cell Mechanics

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With 147 figures, 54 of them in color

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Preface

During the past decade, molecular and cellular biophysics has emerged as one of the most active and exciting areas at the frontier of scientific research. It is a multi-disciplinary field that has many important applications in medicine, health care, life science and biology in general. In essence, the origins of many diseases and illness are rooted at the cellular level. Like molecular and cellular biology, molecular and cellular biophysics is also an indispensable part of the very foundation of contemporary medical and life sciences. In fact, cellular biophysics not only provides a theoretical foundation toward understanding biological processes such as the function of organs, tissues and their interactions, but also provides practical answers to medical treatment and pathology including molecular mechanism of diseases and infections. Because of rapid development of nano-science and nano-technologies, molecular and cellular biophysics not only offers a practical means but also the promise to treat and cure many diseases with which we as a human society are still struggling with. However, unlike molecular cellular biology, molecular and cellular biophysics, in particular molecular and cellular biomechanics, is still a field at its infancy. It is precisely because of this that makes cellular mechanics a promising and exciting research field to study and to work.

In this book, we have selected nine research works at the forefront of molecular and cellular biomechanics to be introduced to our readers. It is our opinion that these works represent the current trend and future directions of cellular biomechanics research. By compiling these different topics into one volume, a unique perspective is provided on the current state of cell mechanics research and what lies in the future.

Among these contributions, Romero and Arribas presented their groundbreaking work on three-dimensional cell model, cell growth dynamics algorithm, and associated large-scale finite element simulation through Chapter 1. In Chapter 2, Zeng, Li, and Kohles presented their work on multiscale simulations of soft contact and adhesion of stem cells. In this work, a soft matter model has been developed to model the mechanical mechanism of the mechanotransduction of stem cells. Focusing on molecular mechanics and genetic mechanism of cellular biology, Wu, Wang, and Cohen presented their molecular dynamics modeling of proteins in Chapter 3. More specifically, they employed a molecular dynamics and principal component analysis (MD-PCA) approach studying sickled hemoglobin-hemoglobin interaction, which is the main cause of sickle cell anemia. In Chapter 4, Qin, Chou, Kreplak, and Buehler presented their latest work on atomistic and coarse-grain modeling and simulations of cellular intermediate filaments. They not only presented their own work, but also provided a detailed tutorial on modeling and simulations of intermediate filament networks. Complementary to Qin et al's work, in Chapter 5, Hatami-Marbini and Mofrad give a tutorial overview of

cytoskeletal mechanics and rheology, and the topics that they have touched on are from mechanics of intermediate filament, rheology of cytoskeleton network, experimental measurements and techniques, to computation and simulation approach. To capture the complexity of cell's constitutive behaviors, in Chapter 6, Vernerey presented a multiphase mixture cell model and its application to cell-substrate interactions. In the proposed multiphase cell model, it combines the continuum description of the stress fiber, mass transport, cytosol fluid motion, and G-actin monomer motion, etc. Not only does the multiphysics model couple and combine several different aspects of cell biology, but the author has also applied the latest extended finite element method (X-FEM) and level-set method to simulate cell contact and adhesion with an extracellular substrate. This has demonstrated how applied and computational mechanics can solve complex problems in cell mechanics. To investigate mechanotransduction of cells through a purely thermodynamic approach, Sarvestani presented his analytical cell adhesion model in Chapter 7 that takes into account the effects of substrate stiffness and how it affects the growth of nascent adhesion areas. In Chapter 8, Kohles provided a detailed account on the experimental biomechanics of a single cell, in which he has discussed a state-of-the-art opto-hydrodynamics technique for measuring isolated cellular mechanical properties. Finally, in Chapter 9, Shen discussed his nonlocal shell model to simulate the buckling of microtubules inside a cell. This is a good example that clearly shows how non-classical continuum mechanics can contribute to the understanding of cellular biology.

Finally, it is our hope that this volume will disseminate much useful information in cellular biomechanics to a larger community outside the area of applied mechanics, while arousing public interest in cell mechanics research and applications. Ultimately, we envision that these works would promote more in-depth study and research in cell mechanics and cellular biophysics.

Shaofan Li and Bohua Sun
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Chapter 1 Modeling and Simulations of the Dynamics of Growing Cell Clusters

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Abstract: A phenomenological discrete model for the dynamics of growing cell clusters is presented. Each cell is modeled as a growing deformable solid which can interact mechanically with its neighbors by means of adhesion and repulsion forces. By defining simple behavior rules based on the age and the mechanical state of the cells, simple cluster dynamics can be reproduced. The framework is far from complete, but describes the essential features required for more complete mechanical simulations of cell ensembles.

Keywords: cell mechanics, finite elements, population dynamics, cellular automata

1.1 Introduction

The study of cell cluster dynamics is fundamental for understanding biological phenomena such as embryology, tissue repair, and most importantly, solid tumors. Up to now, biochemistry has been the main discipline employed to study such processes, with undeniable success. There is, however, growing awareness that mechanics also plays a crucial role in these dynamical processes and new avenues to research and analysis are now opened.

Since the classical work of Young[1] and later Eaves[2], the mechanical effects on tumors have been widely studied. For example, in the key work of Helmlinger et al.[3] experimental evidence was provided to support the idea that the growth of multicellular tumor spheroids is controlled by pressure. More surprisingly, their findings are demonstrated *"... regardless of host species, tissue of origin, or differentiation state."* These, and similar ones[4,5] motivate the study of single cell mechanics, multiple cell mechanical interactions, and their effect on the global dynamics of growing ensembles.

Several approaches have been investigated to understand the mechanics of

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growing cell clusters, cancer in particular[6]. The oldest models employ partial differential equations that treat tumors as continua with deterministic growth (see [7] and references therein). While these approaches allow of the study of complete tumors, they can not provide enough details of the mechanical effects at the micro scale, since cells are smeared out and are not represented.

The second type of approaches employed for studying cell population dynamics is based on cellular automata (see [8-10] among many others). These methods represent individual cells and their behavior, so they allow much richer resolution than smeared models. In an effort to keep the computational cost low, many of the geometrical/mechanical details are often ignored. Some cellular automata include sophisticated discrete evolution laws, and even some crude mechanical behavior.

The computational model that is presented in the current work advocates the use of individual entities to represent each cell in the cluster, just as cellular automata. However, in contrast with the latter, the proposed models have sufficient mechanical and geometrical details so as to replicate, at least qualitatively, the most important phenomena that seem to be at the heart of their mechanical behavior. The underlying motivation is to provide a testbed for the mechanical response of cell clusters based on first principles and as few ad hoc evolution rules as possible. This environment will allow test hypothesis on the effect of mechanical variables on growth or elimination of cell colonies while providing very high definition pictures of the geometry and internal variables of the ensembles.

The basic mechanical features that are represented in the model are: deformation, material response, growth, adhesion, and repulsion. To replicate *in silico* all these effects, a nonlinear finite element model is employed. In it, every single cell is defined as a Deformable solid of ellipsoidal shape capable of following complex deformation modes. The material for each body is homogeneous and isotropic whose constants are chosen so as to qualitatively match experimental results. Growth, an attribute that most cellular automata do not incorporate, is described in a mechanically sound manner, whose rate is predetermined based on each cell's age. A key ingredient of the model is the numerical treatment of cell-to-cell interation forces. The computational cost of a molecule-based, membrane-to-membrane interaction model is prohibitive. Thus, a macroscopic model is incorporated into the finite element computations using standard penalty constraints and surface-to-surface potentials. Finally, a decision tree is employed to capture the most basic events of the life cycle of each cell. At each instant, a cell might be divided or die depending on random decisions whose probability function depends on the cell's age and its mechanical stresses.

The model described in the current article still fails to become predictive.