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EDITORIAL

Biomedical Modeling: The Role of Transport and Mechanics

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This volume is dedicated to the memory of Jerrold Marsden.

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This issue contains a series of papers that were invited following a workshop held in July 2011 at the University of Notre Dame London Center. The goal of the workshop was to present the latest advances in theory, experimentation, and modeling methodologies related to the role of mechanics in biological systems. Growth, morphogenesis, and many diseases are characterized by time dependent changes in the material properties of tissues—affected by resident cells—that, in turn, affect the function of the tissue and contribute to, or mitigate, the disease. Mathematical modeling and simulation are essential for testing and developing scientific hypotheses related to the physical behavior of biological tissues, because of the complex geometries, inhomogeneous properties, rate dependences, and nonlinear feedback interactions that it entails.

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The concepts of "functional adaptation" and "remodeling" controlled by cells sensing their environment were developed by Roux (1881) and Wolff (1892) in the late nineteenth century. While their hypotheses were visionary, the mathematical, computational, and experimental tools available to couple physics, chemistry, and biology were too crude at that time to fully explore these concepts in the way we understand them today. However, by the late twentieth century, researchers could effectively model and simulate the experimentally observed mechanical and physical behavior of tissues using finite element and finite difference computational techniques implemented on powerful computer clusters, and the biological processes could be modeled and predicted by phenomenological laws (Van Rietbergen et al. 1993; Mullender et al. 1994; Ruimerman et al. 2003). Today, simulations with increasing fidelity and mechanistic laws for both tissue and cellular behavior (Ruimerman et al. 2005) can be used to refine hypotheses involving individual growth factors and devise experiments to rigorously evaluate them. The papers in this issue demonstrate these capabilities in different biomedical fields and the role simulations play in testing hypotheses based on integrated modeling and experimental approaches.

At the Notre Dame London Center workshop, investigators discussed the state of the art in simulation of tissues, ranging from the sclera of the eye, to orthopedic tissues, and thrombus formation. Two key areas of focus were functional adaptation to loads, and exploitation of the natural adaptive mechanisms for use in tissue engineering or regenerative medicine. A third area highlighted was the role of altered tissue behavior in diseases, or a failure of the normal tissue function. As with healthy tissues, the goal of studying diseased tissues is to understand the biological mechanisms and events that give rise to abnormal tissue or structures. The workshop highlighted the broad range of biological and physical processes that must be addressed to fully model the behavior of physiological systems and their response to environmental inputs, from the intricate multiscale mechanical properties of bone to the complex balance of factors that result in normal—or abnormal—thrombus formation. This issue contains a number of papers addressing mathematical and computational methods for modeling physiological systems from the single cell level to tissue and organ level that were solicited based on the presentations and discussions during the workshop.

Contributors to this volume include participants of the workshop as well as other experts who were invited but unable to attend the workshop. The volume contains both research and review papers on predictive models in biomechanics, cell biology, physiology, and cancer. The papers describe some recent advances in the development of specific predictive multiscale and hybrid models, as well as parameter determination using existing experimental data. They provide examples of how theoretical modeling can generate novel biological hypotheses and suggest experiments to validate them.

Cell Level Simulations

At the cellular level, the papers by Buchanan et al., Weafer et al., and Suhail et al. demonstrate the power of modeling to refine hypotheses related to cellular mechanics and cell-cell interaction. In many tissues, the resident cells react to normal tissue

loading. Osteocytes and osteoblasts react to local deformation of bone in order to adapt the local architecture and density to resist loads (Huiskes et al. 1997; Huiskes et al. 2000; Smit et al. 2003; Schulte et al. 2013), endothelial cells alter their gene expression in response to altered shear stress on heart valves (Sucosky et al. 2009; Balachandran et al. 2011; Sun et al. 2012), and renal epithelial cells rely on and direct well-regulated fluid flow for their normal function (Weinbaum et al. 2010).

Suhail et al. study cell-cell communication based on a recently identified mode of intercellular transfer of molecules between cells that is important in many physiological and pathological contexts. The authors propose a mathematical model to explain the observed intercellular transfer of both membrane-bound and cytoplasmic biomolecules between cells through tunneling nanotubes (TNTs). The model suggests that increased stability of TNTs, and the frequency of TNT formation can decrease the significant size dependence of cytosolic transfer of biomolecules. Buchanan et al. use a mathematical model to show that the experimentally observed transport of the cytoplasm along the cytoskeletal tracks from the membrane to the nucleus in osteoblasts is more consistent with fixed velocity movement than diffusion. The model generates predictions of the concentrations of the Vitamin D_3 metabolite, and other compounds formed from D_3, such as protegerin, in various regions of the cell. Weafer et al. describe a model of actin cytoskeletal remodeling in response to both chemical and mechanical cues, and the resulting effects on the resistance to compressive loading in osteoblasts. The authors obtain good agreement with associated experiments, and provide a potential predictive model for changes in the actin cytoskeleton in response to loads and paracrine signaling. The framework developed should provide new methodologies to study the osteoblast, a cell for which mechanical cues are essential for normal function.

Physiology

Modeling physiological processes provides a means to aggregate existing data and to refine hypotheses related to physiological events. Models can range from the phenomenological models of muscle physiology based on length-tension and velocity-tension predictions of Hill (Brand et al. 1986; Goel et al. 1993) to those incorporating more detailed physiology of muscle contraction in response to electrophysiological waves (Hurtado and Kuhl 2012) or include detailed information on cytokine activity and cell aggregation.

Alonso et al. review the work in the area of simulating and analyzing scroll waves, vortices that occur in three-dimensional excitable media, from the first simulations in FitzHugh–Nagumo type models in the 1980s, to recent studies involving detailed ionic models of cardiac tissue. The disorganization of scroll waves into chaotic behavior is thought to be the mechanism for ventricular fibrillation.

Leiderman and Fogelson extend their previously developed spatial-temporal mathematical model of complex biochemical, biophysical, and biomechanical interactions during intravascular clot (thrombus) formation to include reduction of the advection and diffusion of the coagulation proteins in regions of the clot with high platelet number density. The effect of this reduction, in conjunction with limitations on fluid and

platelet transport through dense regions of the clot, can be profound. The results of the paper suggest a possible physical mechanism for limiting thrombus growth, and exploit modeling to test hypotheses regarding the interactions of proteins.

Cancer Research

Kim and Othmer determine conditions that can lead to progression of the ductal carcinoma comedo DCIS and, ultimately, the most common type of breast cancer, invasive ductal carcinoma. The authors further develop their mathematical model, which incorporates the cross-talk between stromal and tumor cells, and which can predict how perturbations of the local biochemical and mechanical state influence tumor evolution. They then study a hybrid model for the interaction of cells with the tumor microenvironment (TME), in which epithelial cells are modeled individually while the extracellular matrix (ECM) is treated as a continuum, and show how these interactions affect the early development of tumors.

Daub and Merks present a novel modeling study of the cellular self-organization resulting from the ECM-coordinated migration of the endothelial cells during angiogenesis, the formation of new blood vessels sprouting from existing ones during tumor growth. Simulations show that a set of biologically-motivated cell behavioral rules, including chemotaxis, haptotaxis, haptokinesis, and ECM-guided proliferation, suffice for forming sprouts and branching vascular trees.

Tissue Mechanics

Whole tissues are the interface at which biological systems transduce many environmental signals, especially forces in the musculoskeletal system. The cells in musculoskeletal tissues are generally entombed in lacunae within the tissue or on endothelial surfaces. As such, mechanical signals are modulated by the surrounding tissue and there is general agreement that cellular adaptation in skeletal tissues seeks to maintain the signal within a range. Thompson, in a review of the state of the art in tendon and ligament mechanobiology, makes a case for coupled, multiscale models incorporating complex geometrical and microstructural information as well as time-based descriptions of cellular activity and response. The author describes existing data already available for such model development, including tissue structure and biomechanics, cell biomechanics, and current understanding of tendon function in health and disease.

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