Using Mathematical Modeling to Design Effective Regenerative Medicine Strategies for Orthopaedics

Douglas D. Robertson, MD, PhD
Gulshan B. Sharma, PhD, MBA
Barbara D. Boyan, PhD

From the Department of Radiology and Imaging Sciences, Division of Musculoskeletal Imaging, Emory Orthopaedics and Spine Center, Emory School of Medicine, Emory University, and the Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology College of Engineering, Atlanta, GA (Dr. Robertson), the Department of Mechanical and Manufacturing Engineering, University of Calgary, Calgary, Alberta, Canada (Dr. Sharma), and Virginia Commonwealth University, School of Engineering, Richmond, VA (Dr. Boyan).

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The acceleration of scientific discovery in orthopaedic regenerative medicine and its transformation into bedside application require a paradigm shift in computational methods and strategies. Computational modeling must move from static simulations to adaptive methods that predict integrative physiology and physics from the molecular scale to human body scale. Computational methods have been extensively used to study musculoskeletal systems and go hand in hand with experimental studies. However, computational methods have primarily modeled a moment in time and not the adaptive response to altered environments produced by mechanical or biologic intervention. Computational strategies must be developed that integrate biologic remodeling rules and predict how musculoskeletal systems will respond over time. As we better understand musculoskeletal systems, such as those of the knee, from an organic perspective, models incorporating bone, cartilage, ligament, and muscle must be multiscale. They must integrate physiology and physics principles as well as multibody conditions to predict response at the molecular, cellular, tissue, organ, body, and population levels.

Recent work has shown progress using such methods. Adaptive (predictive) bone remodeling simulations have been applied to arthroplasty and drug intervention.[1,2] Modeling of articular and fibrocartilaginous structures has improved our understanding of the mechanical conditions and tissue responses created by physiologic and pathologic loading.[3,4] Muscle and ligament modeling has provided insight into muscle loads and ligament strains in traumatic and atraumatic conditions.[5] Combined multibody knee simulations incorporating bone, cartilage, muscle, and ligament have been used to evaluate structural and functional adaptation produced by joint pathology and surgical intervention.[6,7]

Adaptive multiscale computational methods and strategies are complex and vary depending on what is being studied. These simulations produce large data-rich sets, which must be manipulated and analyzed. The efficient use of these data are aided by principal component analysis and machine learning approaches, such as support vector machines or neural networks.[8] This integrative analysis environment can be used to create patient-specific evaluations and treatments,[9] including rapid prototyping and manufacturing for custom orthopaedic devices[10] and personalized rehabilitation protocols that include advanced sensor technology (eg, inertial sensors) for specific feedback.[11]

The importance of multiscale modeling is highlighted by the formation in 2003 of the Interagency Modeling and Analysis Group Multiscale Modeling Consortium. This coalition of 10 government agencies in the United States and Canada, includes the National Institutes of Health, the National Science Foundation, the Department of Energy, and the Food and Drug Administration and promotes the development and funding of biomedical systems, with a particular emphasis on multiscale modeling.[12] The mission of the consortium is to develop accurate methods and algorithms to cross the interface between multiple spatio-temporal scales and to disseminate the models and insights derived from the models to the larger biomedical research communities. To share ideas among national and international research groups, the Multiscale Modeling Consortium organized a special journal issue on "Multi-scale Modeling and Simulation of Biological Systems,"[13] and the Orthopaedic Research Society (ORS) sponsored a workshop, "Multi-scale Adaptive Remodeling Simulations in Musculoskeletal Regenerative Medicine."[14]

Adaptive multiscale computational methodologies and strategies are required to address the complexity of orthopaedic disease and its prevention and treatment. Together with experimental studies the new modeling strategies provide a framework to significantly advance orthopaedic medicine, improve quality of life and outcomes, and reduce healthcare costs.

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