

MULTISCALE CO-SIMULATION IN THE CARDIOVASCULAR SYSTEM: INTEGRATION FROM MOLECULES TO ORGANS

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The increasing need for quantitative understanding of complex biological systems, in parallel with rapid developments in modern computers, has made computational simulations an integral part of biological research. Biological phenomena typically encompass a range of time and length scales whose intrinsically complex interactions are critical to system function. For example, in the study of arterial disease, one needs to understand how the entire cardiovascular system responds to a variety of external factors that impact local flow characteristics. The fluid dynamic and solid stresses experienced by the vascular wall tissues lead to a cascade of critical biological events, which may contribute to disease progression. At the cellular level, these stresses produce deformations of the cytoskeletal network, the cell membrane, and the nuclear envelope, which lead, in turn, to conformational changes in individual proteins that elicit the biological response. Computational simulations provide a powerful tool for understanding such complexities inherent in biological systems. We present multi-scale models of cardiovascular function as related to arterial disease.

A coarse-grained model of the cardiovascular system is developed which provides a method for determining velocity and pressure boundary conditions for more refined, local simulations at smaller scales to study the relation between local characteristics of flow dynamics and arterial wall stresses and disease initiation/progression in human carotid bifurcation. Arterial disease is characterized as focal, and thus its distribution is believed to be influenced by localized shear stresses acting on the endothelial cells and cellular deformation. It is, hence, essential to understand the biological events at a single cell level. A continuum mechanics model is next presented to examine the distribution of stresses within a cell monolayer. These intracellular stresses are in turn transmitted through the cell via a complex 3-D network of protein filaments. Force-induced conformational changes in proteins may play a critical role in initiating and controlling cell signaling pathways. To understand mechanotransduction at the molecular level, a detailed analysis is performed of protein molecular conformational changes that occur in response to forces.

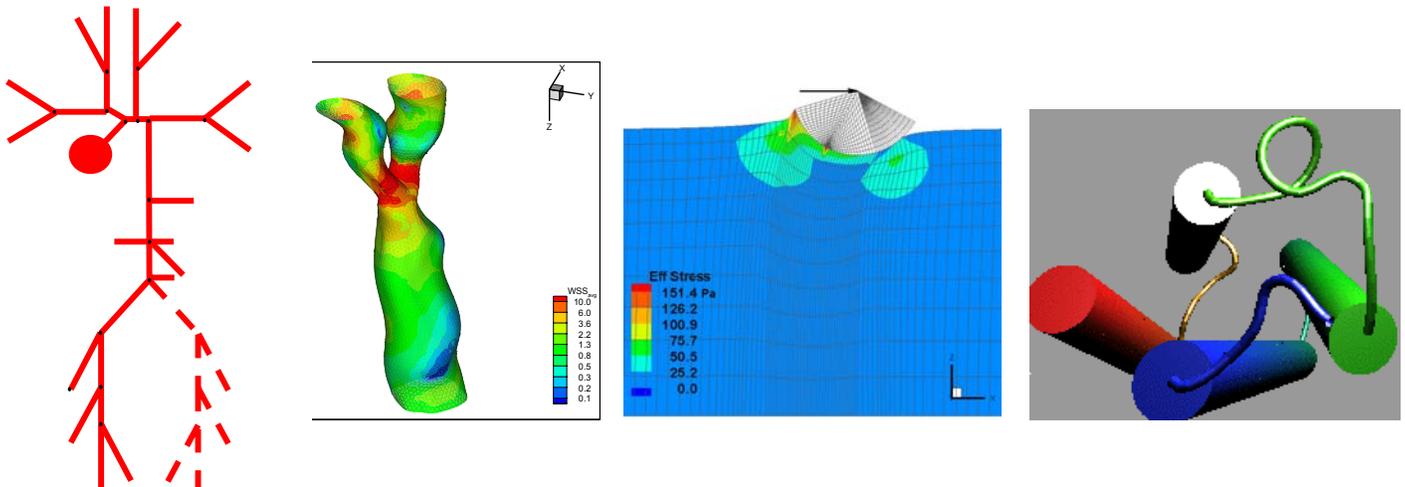


Fig. 1: (a) Distributed cardiovascular network model, (b) Wall shear stress (WSS) distribution in a diseased carotid bifurcation, (c) Effective stress distribution in a cell monolayer during magnetocytometry experiments, (d) Molecular conformation of a focal adhesion targeting region of focal adhesion kinase during a steered molecular dynamic simulation.