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Special Collection: Multiscale Modeling and Analysis in Biophysics

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INTRODUCTION

The unprecedented technological advancements seen in recent years have propelled the field of biophysics to the forefront of biological and medical research. More advanced analytical tools are needed to translate increasingly detailed biophysical information made available by these technologies into new scientific knowledge and improved medical care.

It is well understood that the dynamic integration across multiple scales of three-dimensional organization in biological systems is critical to their robust physiological function. The focus of biophysics research is to build tools and analyses that integrate structurally across physical scales (from molecules to populations) and link biochemical and biophysical processes across multiple time scales. The need for multiscale, multiphysics modeling and analysis to advance medicine cannot, therefore, be overstated. Although patients' symptoms manifest at the tissue, organ, or whole body scales, current medical therapies target specific molecules, cellular processes, or operate on single organs without integrating critical cell-cell, cell-tissue, cell-organ, and organ-organ couplings. Multiscale modeling is contributing to advanced knowledge of biophysical mechanisms and thus to the development of novel technologies like, for instance, 3D bioprinting[1] and model-derived clinical diagnostics[2] that will lead to improved medical treatments and innovative therapies. This Special Topic is a collection of studies on multiscale modeling and analyses of biological systems that can advance medical science.

SUMMARY OF AREAS COVERED

The papers in this Special Topic cover a wide range of research topics like cardiac biomechanics,[3–5] tissue mechanics,[6–8] cerebral periarterial fluid flow,[9] cell mechanics[10] and electroporation,[11] protein modeling,[12] and molecular fluorescence microscopy.[13]

The synchronization of the activation of calcium (Ca) release channels that initiates cardiac muscle contraction is investigated in Ref. 3. A mathematical model that uses a weakly lumped Markov chain and an Ising model is proposed to describe Ca spark activation as a system transition from a metastable to an absorbing state. The spark activation threshold predicted by the model is validated numerically and agrees with experimental observations. A parametric sensitivity analysis shows that spark activation threshold decreases with increasing Ca sensitivity of ryanodine receptors' (RyRs) activation and cluster size.

In Ref. 4, a multiscale computational modeling framework is proposed to study the action of 2′-deoxy-adenosine triphosphate (dATP) on the sarcoendoplasmic reticulum calcium-ATPase (SERCA) pump during cardiac relaxation. Combined Gaussian accelerated molecular dynamics simulations and Brownian dynamics simulations show that dATP increases calcium (Ca) association rate constants to SERCA and binds to apolipoprotein (apo) SERCA more rapidly than ATP. A compartmental ordinary differential equation that models human cardiomyocyte excitation-contraction coupling is further proposed and used to show that the increased Ca association rate constants accelerate the rates of Ca transient decay in agreement with published experimental observations.

A new model of fibrous atrial tissue is proposed in Ref. 5 that incorporates information about cellular structure and conduction in fibrotic areas. A trial tissue remodeled by fibroblasts is simulated with the Potts model. The wavefronts predicted by the model generate a dynamic heterogeneity of the tissue that causes the

migration and pinning of spiral waves and ultimately the formation of microreentries in the cardiac tissue that underlie atrial fibrillation.

A novel mathematical model of the actin-myosin interaction that controls muscle contraction is presented in Ref. 6. A jump-diffusion stochastic partial differential equation for the actin–myosin interaction is proposed to address the fact that jump-diffusion models available in the literature are not compatible with the principles of thermodynamics. The proposed model is not only able to successfully describe muscle contraction on various time scales but is also compatible with thermodynamic principles. Good agreement between model predictions and experimental data on fast and slow time scales is reported.

The lack of scaling laws for comparison of experimentally observed wrinkling features in biologically relevant fiber-reinforced bilayers inspired the work in Ref. 7. The paper studies the mechanical behavior of a uniaxially compressed bilayer made of a thin elastic film bonded on a hyperelastic fiber-reinforced substrate. The onset of wrinkling is investigated theoretically and numerically. Novel scaling laws for the critical strain and wavenumber at the onset of wrinkling for fiber-reinforced highly mismatched hyperelastic bilayers are further derived using asymptotic laws for neo-Hookean bilayers. Also, good agreement with finite element (FE) simulations is observed.

A multiscale model describing arterial wall active mechanics is proposed in Ref. 8. The model incorporates biochemical signaling and fiber networks and thus can link microscale contractility signaling to a macroscale, tissue-level response. The model's predictions of contractility at both cell and tissue scales agree with published experimental observations.

A reduced-order mathematical model of directional fluid flow in cerebral periarterial networks is proposed in Ref. 9 to understand how peristaltic pumping induces a directional flow within physiological regimes. Under certain physical assumptions, lubrication theory and regular perturbation methods are used to find closed-form analytical expressions for the net flow for simple network configurations. These expressions are used to show that, within specific physiological regimes, vasomotion pulsatility could induce net pial periarterial flow velocities of the order of a few to tens of microns/s and a threefold flow increase during sleep.

In Ref. 10, a multiscale mathematical model is described that links nanoscale integrin dynamics and whole-cell adhesion mechanics. Coupled molecular dynamics simulations of integrin stretching and FE simulations of whole-cell adhesion mechanics highlight how certain molecular mechanisms (fibronectin unfolding and residue binding/unbinding) contribute to the whole-cell integrin adhesion dynamics. Some results agree with experimental observations reported in the literature.

In Ref. 11, the COMSOL Multiphysics suite is used for studying cellular electroporation at various length scales and in the presence of complex geometries. Results are presented for voltage pulse driven electroporation in a Jurkat cell with mitochondria (nanoscale effects dominate) and in a *Bacillus* cluster (characterized by collective effects and mutual interactions). The predictions for Jurkat cells are in good agreement with published data. The field attenuation and shielding predicted in *Bacillus* clusters suggest non-uniform field distributions and, thus, the need for better electrodes.

Protein modeling is investigated in Ref. 12 using a flexible language-model-based deep learning approach. The model is built on an attention neural network that includes transformer and graph convolutional architectures in a causal multi-headed graph. It is shown that the model can predict protein solubility and sequencing tasks, and, when trained on inverse tasks, can design proteins with specific features. The model is validated on case studies yielding designs of proteins for various materials.

The vectorial theory of light is used in Ref. 13 to study the field–dipole interaction under polarization light-sheet fluorescence microscopy. By modeling the molecule as a radiating electric dipole in a polarized electric field, a system point spread function (PSF) analysis is performed for different orientations of the dipole. The results show that at a high numerical aperture (NA) of the objective lens the field spreads gradually along the polarization axis, while at low NA the field is more isotropic and homogeneous. Also, the distinct frequency spectrum observed for random and fixed dipoles highlights the importance of dipole orientation in a light-sheet field.

CONCLUSIONS

The papers in this Special Topic cover a wide range of research topics and highlight the essential role that multiscale modeling and analysis in biophysics play in the advancement of medical science. We hope that readers will find these studies informative and be inspired by them.

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