In-Silico Medicine: Multiscale Modeling of Hematological Disorders

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Human red blood cells (RBCs) have remarkable deformability, squeezing through narrow capillaries as small as three microns in diameter without any damage. Several pathological conditions, including malaria, sickle cell disease (SCD), and diabetes can alter the shape and deformability of circulating RBCs. Recent work demonstrates how new computational and analytical models can reveal the ways in which tiny inter-endothelial slits in the spleen prevent or discard RBCs from re-entering the systemic circulation. A general computational multiscale framework for RBC modeling is essential in quantifying the altered morphological and biomechanical properties of RBCs in the aforementioned diseases. One can apply this computational framework to other blood pathogens, e.g., in patients with cancer or HIV.

Why Computational Models?

Blood is a non-Newtonian fluid. The movement of RBCs through and with plasma, which is closely associated with RBC deformability, determines blood’s rheological properties. Advances in experimental techniques have enabled accurate measurements of RBC deformability. However, while most of these techniques are suitable for RBC populations, i.e., measuring properties averaged over all RBCs in a blood sample, they do not account for the heterogeneity in shape or size differences within the RBC population. A major challenge for single-cell techniques is the need to obtain a realistic geometry, as experiments on small blood vessels require an especially careful vessel preparation, and in certain conditions, the precise determination of RBC membrane properties is difficult to achieve, in part due to resolution limitations. Hence, computational models, such as continuum-based and particle-based RBC models provide a promising means for tackling a broad range of dynamical and rheological blood-related problems [3].

Continuum-based RBC models treat the RBC membrane and intracellular fluids as homogeneous materials, and describe the model using constitutive relations for viscoelastic variables, such as velocity, density, and stress, with ordinary and partial differential equations often governing kinematics and dynamics. While continuum-based RBC models enable simulations of large-scale blood flow, they do not provide the detailed dynamics of local subcellular structures. RBC models based on particle methods, where mesoscopic particle-collision models are employed, fill this gap. Mesoscopic particle-based methods are coarse-grained analogs of the molecular dynamics method, and can be rigorously derived through the Mori-Zwanzig formalism [4]. Such RBC models are increasingly popular as a promising tool for modeling the structural, mechanical, and rheological properties of RBCs. Examples include dynamic deformability for various stages of Plasmodium falciparum-infected RBCs, (PfRBCs), and membrane flickering of human RBCs. These studies lead to better understanding of the microscopic function of RBCs in healthy and diseased states.

Why Two-component RBC models?

A normal RBC is a nucleus-free cell, it adopts a distinctive biconcave shape of about 8.0 µm in diameter and 2.0 µm in thickness. The membrane of a RBC consists of a lipid bilayer supported by an attached spectrin network (cytoskeleton); they are connected by transmembrane proteins, such as the spectrin-based RBC model. Membrane properties associated with the bilayer-cytoskeleton interactions strongly influence cell function and progression of RBC diseases. One-component RBC models cannot facilitate detailed whole-cell exploration of diverse biological and biomechanical problems involved in such cases. There is, hence, a compelling need to develop a more realistic RBC representation, e.g., to endow the spectrin-based RBC models with more accurate structure, thus considering the lipid bilayer and cytoskeleton separately but also including the transmembrane proteins. More recent efforts have focused on this approach, leading to a two-component composite model of the RBC membrane with explicit descriptions of lipid bilayer, cytoskeleton, and transmembrane proteins using coarse-grained molecular dynamics (CGMD) [2]. This CGMD membrane model has been successfully used to study membrane-related problems in RBCs, such as the multiple stiffening effects of nanoscale knobs on T-RBCs [8]. Recently, a two-component whole-cell model was also developed and implemented using dissipative particle dynamics (DPD) [5]. The DPD-based RBC model also separately accounts for the lipid bilayer and cytoskeleton but implicitly includes the transmembrane proteins; thus, it is computationally more efficient than the CGMD model for RBC modeling at the whole-cell level, which has been applied to investigate RBC response and dynamics in various blood flow conditions.

Why a Two-step Multiscale Framework for RBC Modeling?

Computational RBC models can predict properties beyond available experimental measurements [5, 8]. Modeling a small piece of cell membrane with the two-component composite model can sometimes evaluate modifications of the RBC membrane biomechanics, including bending rigidity and shear modulus. However, modeling only a portion of the RBC membrane does not efficiently depict the whole-cell characteristics strongly related to RBC biomechanics and biophysics. On the other hand, the lack of molecular details in the two-component whole-cell model may limit its predictive capacity in identifying key factors that cause the reorganization of the RBC membrane. Incorporating the necessary molecular information from a molecular-detailed composite membrane model into a more coarse-grained whole-cell model effectively addresses this problem. We have recently developed and validated a two-step multiscale framework for RBC modeling by interfacing the two-component CGMD and DPD models (see Figure 1). The only experimental input required is information about the structural characteristics of the RBC membrane. Then, we perform CGMD simulations to compute the shear modulus, bending stiffness and network parameters of a small RBC patch, which we use as input to DPD simulations to predict the stress field and morphology of defective RBCs.

In-silico Predictions

The human spleen acts primarily as a blood filter. By using the simplest one-component whole-cell model based on DPD, we present a recent mesoscopic computational study of physiological and pathological RBCs passing through the spleen that quantifies biophysical limits for splenic slit clear ance. A range of possible shapes and sizes allow RBCs to move through the splenic slits (see Figure 2); these closely match the normal ranges observed in healthy human RBCs, with surface areas ranging from 80 to 180 µm² and volumes ranging from 60 to 160 µm³. However, diseases such as malaria can significantly impact the size and shape of affected RBCs, causing them to be filtered by the spleen.

Using the two-step multiscale framework for RBC modeling, we studied the biomechanical characteristics of healthy RBCs (H-RBCs) and Pf-RBCs under tensile forcing, and examined the RBC stretching response to large deformation (Figure 3). Our results showed that both the axial and transverse diameters were in agreement with previous experimental measurements (see Figure 3, left). We also investigated the influence of knob density on RBC deformability and found a decrease in elongation index (EI) for Pf-RBCs at trophozoite (T-RBC) and schizont stages (S-RBC); the increase of knob density indicates that the rigid nanoscale knobs contribute to cell membrane stiffness.

Outlook

Our aforementioned simulation highlights demonstrate that stochastic multiscale modeling, based on particle methods...
to simulate RBCs at the protein level, can facilitate the effective study of longstanding biophysical questions not possible by other computational methods or experimental techniques. One can further extend the two-step computational framework to investigate the following problems related to pathological blood flow: (i) Development of hybrid models, which encompass all scales by combining continuum description for blood plasma with particle description for RBCs, for cost-effective simulations. Such simulations could shed light on the coupling of biology, chemistry, and mechanics (the “triple-point”). (ii) Development of predictive patient-specific models to describe heterogeneity-related issues in hematological disorders such as malaria, diabetes, or SCD. Perhaps, the most important extension is to connect such multiscale models to all the “omics” technologies (genomics, proteomics, metabolomics, etc.) to implement the vision of precision medicine advocated both in the U.S. and around the world.

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References

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