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Atomistic–continuum model for probing the biomechanical properties of human erythrocyte membrane under extreme conditions

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Abstract

A precise first attempt is performed to quantify the biomechanical properties of human erythrocyte membrane subjects to extreme temperature and loading conditions. An improved three-dimensional (3D) atomistic–continuum model based on the Cauchy–Born rule is proposed to investigate the elastic properties and biomechanical responses of the erythrocyte membrane. A membrane rigidity model is developed to estimate the membrane elastic properties over an extreme temperature range. Our computational results reveal that the membrane is able to sustain large strains up to a certain limit; beyond which, mechanically induced hemolysis may occur as exponential stress increment, fluctuations and multiple peaks were observed in the stress–strain curves. Additionally, we found that the overall deformability of the erythrocyte membrane significantly decreases as temperature increases. It is concluded that the observed increase in membrane rigidity may be attributed to the denaturation, structural remodeling and cross-linking of membrane cytoskeletal proteins.

Keywords: Erythrocyte membrane deformability; Large strains and deformation; Multiscale Cauchy–Born framework; Elastic properties; Temperature effect

1. Introduction

The ability of erythrocytes or red blood cells (RBCs) to undergo a wide range of deformations while traversing vessels during microcirculation is crucial to the sustenance of life. Erythrocytes are undoubtedly a very important component of human blood, as they account for approximately 99% of the particulate matter in the blood and occupy between 40% and 45% of blood volume. This suggests that the properties and states of the cells determine the overall behavior of the blood. Some recent studies have also concluded that the development and progression of some blood-related hereditary diseases—such as sickle cell anemia, spherocytosis and elliptocytosis, and non-hereditary diseases

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like malaria—can be attributed to changes in the properties of the erythrocyte membrane. It is also well known that erythrocytes, owing to their highly flexible and elastic membrane structure, can readily pass through blood vessels with diameters smaller than the cell diameter by transforming from their original biconcave shape into a bullet-like shape.

The erythrocyte membrane structure comprises of three important components namely, the phospholipid bilayer, transmembrane proteins and an underlying triangular spectrin protein network or cytoskeleton that is attached to the cytoplasmic side of the bilayer through short actin filaments or junction complexes [1]. These junction complexes can be visualized as a network of nodes that are connected by the spectrin tetramers or links, with the number of links originating from each node fluctuating from five to seven but mostly numbering six. The spectrin links are convoluted with an end-to-end distance of around 70 nm, which can extend to a full contour length of about 200 nm [2]. Of all these components, the spectrin network plays the most dominant role in maintaining the integrity of the membrane and it is responsible for the highly elastic nature of the membrane since the lipid bilayer behaves like a fluid when loaded [3].

Several experimental approaches have been used to study the elastic properties and deformability of healthy and infected RBC membrane. These include micropipette aspiration [4], atomic force microscopy [5], optical tweezers [6], microfluidics [7], ektacytometry [8,9] and flicker microscopy [10]. The use of numerical and computational modeling techniques has also been explored. Discher et al. [11] examined the elastic properties of the RBC spectrin network by means of stress-free, prestress and condensed models. A two-layer, coupled finite element approach for modeling the nonlinear elastic and viscoelastic behavior of RBC was proposed by Klöppel and Wall [12]. Dao, Lim, and Suresh [13] studied the deformation behavior of a single RBC by simulating the optical tweezers experiment using the finite element method. Over the years, the use of particle-based methods, such as the coarse-grained molecular dynamics related approach [14], dissipative particle dynamics [15,16], the moving particle method [17–19], the lattice Boltzmann method [20] and the smoothed particle hydrodynamics (SPH) method [21,22] for various studies on RBC properties has been greatly explored. More recently, an atomistic–continuum hyperelastic constitutive modeling approach [23,24], which combines the advantages of atomistic simulation with those of continuum modeling, was proposed for blood cell related studies.

Wang et al. [25] introduced the concept of chirality (or the chiral angle), similar to that found in graphene sheets and studied its effect on the large deformation properties of the RBC membrane. However, the 2D atomistic–continuum modeling technique presented in Refs. [23,24] suffers from certain drawbacks. In order to study the deformability of a three-dimensional (3D) erythrocyte membrane, the 2D atomistic–continuum modeling approach requires the numerical approximation of the geometry from a 2D planar sheet. This process leads to increased complexity of solution procedure and computational cost as well as loss of accuracy due to problem domain approximation. To overcome these limitations, Ademiloye and co-workers in Ref. [26] extended the standard Cauchy–Born rule to account for a 3D reference configuration, which was then used to explore the biomechanical properties of healthy [27,28] and malaria-infected [29–31] RBCs. They concluded that the standard Cauchy–Born rule is sufficient for RBC related studies, hence avoiding the increased computational cost associated with computing the second derivatives of the meshfree shape function.

The previous studies reviewed above mainly focus on understanding the biomechanical behavior of RBCs under normal temperature and loading conditions. Typically, whole blood (WB) is separated by centrifugation into its components prior to storage. WB and RBC units are both refrigerated at below 6 °C for a maximum permitted storage period of 35 and 42 days. To extend their shelf lives up to ten years, frozen red cells are usually cryopreserved and stored at about −80 °C [32,33]. Furthermore, before stored RBCs can be used in blood transfusion, they must be warmed at room temperature or heated in a water bath at a temperature up to 60 °C. Sometimes, RBCs may be overheated during this process, which may result in evident or concealed damage to them, as reported by Hirsch et al. [34]. Although, cryopreservation and reheating are widely accepted practices, the effect of such extreme storage conditions and reheating processes on the deformability and biomechanical properties of the erythrocyte membrane remain unclear. The current study is an attempt to fill this knowledge gap by means of numerical experiments.

Lovelock [35] concluded that hemolysis in human RBCs occurs due to a concentration of electrolytes within the cell and the removal of water in the form of ice when the temperature varies between 20 °C and −40 °C. At −79 °C, hemolysis of RBCs due to the loss of a considerable portion of the membrane bilayer lipids has also been reported [36]. Shen et al. [37] experimentally studied the effect of heating on human RBCs at varying temperatures up to 65 °C and observed abnormal morphological changes in the RBCs, leading to hemolysis of the cells. It has also been reported