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A multiscale Cauchy–Born meshfree model for deformability of red blood cells parasitized by *Plasmodium falciparum*

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ABSTRACT

In normal physiological and healthy conditions, red blood cells (RBCs) deform readily as they pass through the microcapillaries and the spleen, however, upon invasion by the malaria parasite, the host RBC membrane begins to lose their deformability. In spite of the progress in understanding malaria pathogenesis, the primary mechanism responsible for the loss of deformability remains unclear. In this paper, we examine the effects of *Plasmodium falciparum* infection and maturation on the deformability of parasitized or infected red blood cells (iRBCs) by means of a three-dimensional (3D) multiscale red blood cell (RBC) framework. This multiscale framework is developed based on the Cauchy–Born rule and the meshfree IMLS-Ritz method. The atomistic scale strain energy density function of the RBC membrane was computed using a selected representative cell based on the membrane spectrin network. The results obtained from our numerical simulations affirm that the presence of malaria infection significantly increases the rigidity of RBC membrane. It was observed that in the trophozoite and schizont infection stages, biconcave cell geometry leads to better prediction than nearly spherical geometry in comparison with experimental studies. Furthermore, we confirm that increase in temperature also results to increased stiffening of the cell membrane. Lastly, the observed decrease in the deformability of iRBC membrane may be primarily due to the structural remodeling and changes in the microstructure of the membrane rather than the change in cell shape.

1. Introduction

Despite the huge volume of research works devoted to elucidating the primary cause of reduction in red blood cell (RBC) membrane deformability upon the invasion of malaria parasite, it is still unclear whether the increased rigidity of RBC membrane is due to changes in the RBC membrane, presence of malaria parasites within the cell or both. The interest in malaria infection is justified due to ravaging impacts of this infectious disease. Statistically, malaria is the most important parasitic disease of humans and it claims the lives of more children worldwide than any other infectious disease. According to the World Malaria Report 2015 published by the World Health Organization (WHO), approximately 214 million new cases of malaria (range 149–303 million) and 438,000 malaria deaths (range 236,000–635,000) were reported worldwide in 2015, with the African region accounting for most global cases (up to 88%). This is distantly followed by the Southeast Asia region (with around 10%) and the Eastern Mediterranean region with approximately 2% (World Health Organisation, 2015). A lot of

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efforts have been put in place to curb the number of annual deaths due to malaria infection; however, the rapid increase in antimalarial drug and mosquito insecticide resistance, as well as inadequate access to quality treatment in the remote areas, remain major challenges to be overcome.

Of all four known species of malaria parasite that infect humans, *Plasmodium* (*P.*) *falciparum* has been identified as the most prevalent and lethal malaria parasite (Udeinya et al., 1981). *P. falciparum* is a protozoan parasite transmitted by the female Anopheles mosquito. They are usually released into human's blood from the mosquito salivary gland during feeding; thereafter they invade the liver cells and undergo asexual reproduction, producing countless merozoites. These merozoites causing malaria invade the healthy red blood cells (hRBCs) in three stages: contact, attachment, endocytosis, and they develop over a 48 hours period through the ring, trophozoite and schizont stages with changing attributes, effects and degrees of influence on the cell properties. These different intraerythrocytic developmental stages of the *P. falciparum* parasite are subsequently referred to as *Pf*-rRBC (ring stage), *Pf*-tRBC (trophozoite stage) and *Pf*-sRBC (schizont stage). It is worthy of note that a small percentage of asexual parasites, which do not cause disease, changes to gametocytes that are crucial for spreading the infection to others by means of female anopheles mosquitoes.

Following the invasion by merozoites, hRBCs that are originally biconcave in shape with a diameter of around 7.82 μm, remain biconcave with a slight reduction in diameter and are embedded with a thin ring-shaped malaria parasite of diameter 2–3 μm (Hanssen et al., 2010). This stage of infection is followed by the trophozoite stage, which is characterized by a change in shape, further reduction in size and an increase of approximately 17% in volume occurs (Esposito et al., 2010; Hanssen et al., 2010); additionally, the merozoite becomes more rounded and its size increases to about 4 μm. In the final (schizont) stage, the *Pf*-sRBC is nearly spherical in shape with around 18% reduction in its surface area compared to the hRBC (Esposito et al., 2010; Hanssen et al., 2010). The merozoite produces daughter merozoites through mitosis and occupies up to ~50% of the *Pf*-sRBC volume (Hosseini and Feng, 2012).

The outcome of this multifaceted dynamic invasion process that is accompanied by gradual changes in the shape, size, and mechanical properties of the cell, is the bursting of the RBCs. This cause anemia since the bone marrow cannot compensate for this damage resulting to further reduction in oxygen delivery in addition to the dehydration and hypovolemia the individuals infected with malaria experiences (English et al., 1996). Upon the rupture of iRBCs, the hemozoin wastes produced cause cytokine release that is typically associated with increased production of lactic acid by parasites and results to syndromes of respiratory distress (Miller et al., 2002), chills and fever (Roberts and Janovy, 2008). The RBCs with increased rigidity induces blockade in the blood circulation process, resulting in the dysfunction of several tissues and organs such as the brain in the human body. The presence of malaria infection results in altered antigenicity and rearrangement of normal RBC membrane proteins (Cooke et al., 2004) even though the overall architecture of the RBC membrane skeleton does not change.

In the past decades, numerous researchers have concluded that the decreased deformability of iRBC membrane can be linked to the direct and indirect interactions between the parasite proteins such as, knob-associated histidine-rich protein (KAHRP), *P. falciparum* erythrocyte membrane protein (*Pf*EMP) 1 and 3, etc. and the membrane cytoskeleton proteins (Deitsch and Wellems, 1996; Glenister et al., 2002; Newbold et al., 1999) as well as their increased sphericity, stiffness and viscosity (Cranston et al., 1984). The mature form of *P. falciparum* changes the structural, biochemical and mechanical properties of hRBCs, resulting in the sticking of iRBCs to blood vessel walls, the vascular endothelium and other RBCs (Cooke et al., 2004; Cowman et al., 2012). The iRBCs membrane progressively loses their deformability as well as the ability to recover their biconcave shape as the merozoites mature, resulting in a significant increase in shear modulus, rigidity and cell viscosity (Suresh, 2006). RBC membrane dynamics and biomechanical responses are also significantly altered by proteins released from the *P. falciparum* to the lipid bilayer-spectrin network binding sites (Glenister et al., 2002). Loss of deformability at the ring stage was found to be more severe at the febrile temperature (41°C) than at the physiological temperature (37°C) (Park et al., 2008).

Fedosov et al., (2010) employed a dissipative particle dynamics (DPM) simulation approach, which is capable of simplifying the spectrin level model reported by Li et al., (2005), to investigate the large deformation behavior of healthy and infected cells. In order to access the increased stiffening of the iRBC membrane, the shear modulus has been the sole means of measurement until Pan et al., (2010) proposed a low-dimensional RBC model to fit the values of Young's modulus of the hRBC and iRBC membrane. The changes in the mechanical response and adhesive properties of the iRBC membrane has been attributed to the remodeling of spectrin cytoskeleton and the formation of nanoscale knobs on the membrane surface, based on observations from the optical tweezers experiments (Suresh et al., 2005) and coarse-grained molecular dynamics (CGMD) RBC membrane model (Fedosov et al., 2011b; Zhang et al., 2015a).

In more recent studies, Ademiloye and his co-workers proposed a 3D multiscale RBC model for numerical computation of the elastic properties (Ademiloye et al., 2016b), biomechanical responses (Ademiloye et al., 2016a) and large deformation behaviors (Ademiloye et al., 2016b) of healthy RBC membrane. This approach was proposed in order to circumvent numerical and computational errors associated with the problem domain approximation procedure employed in the earlier developed 2D atomistic-continuum model based on the higher-order Cauchy–Born rule (Ademiloye et al., 2015; Wang et al., 2014). Meshfree simulation and analysis of the effects of temperature on the deformability of healthy RBC membrane in normal physiological conditions have also been investigated (Ademiloye et al., 2016c).

As mentioned earlier, the primary reason(s) for the increased stiffening of the iRBC membrane remain unclear. The work presented in this paper is aimed at investigating the deformability of iRBC membrane as the malaria parasite matures by means of a 3D multiscale meshfree framework. The multiscale RBC model proposed in this study is computationally efficient