



A TWO COMPONENT RED BLOOD CELL MODEL FOR SINGLE CELL MECHANIC

Ida Laila Ahmad^{1,2} and Mohd Ridzuan Ahmad¹

¹Micro-Nano Mechatronics Research Group, Department of Control and Mechatronics Engineering, Faculty of Electrical Engineering, Universiti Teknologi Malaysia, Johor Bahru, Johor, Malaysia

²Department of Electronic Engineering, Faculty of Electrical and Electronic Engineering, Universiti Tun Hussein Onn Malaysia, Batu Pahat, Johor, Malaysia

E-Mail: ida@uthm.edu.my

ABSTRACT

This work presents the deformation of red blood cell (RBC) as it travels in a microchannel using a theoretical model. The developed model predicts the deformation experienced by the RBC when exposed to shear stresses (fluid) as a function of mechanical properties. RBC is known to be a biconcave disk and is modeled as a liquid enclosed with a solid membrane. Therefore it is appropriate to model the RBC as a two component models consists of membrane and cytoplasm. The membrane, assumed to behave as a nearly incompressible material shows hyperelastic response to bending and shearing while the cytoplasm exhibits homogeneous Newtonian fluid properties. The model parameters were determined from the experimental measurements and comparison was made. Agreement in terms of hyperelasticity, deformation rate and stress distribution were found with previous researches.

Keywords: red blood cell, theoretical model, membrane, cytoplasm, hyperelasticity.

INTRODUCTION

Red blood cell (RBC) is known for delivering oxygen throughout the microcirculation system in a human body. The efficacy of such transportation mechanism heavily determines by the ability of RBC to undergo large deformation and pass through smaller capillaries relative to its size (Xu *et al.* 2012, Li *et al.* 2014, Tomaiuolo *et al.* 2009). Researches made from several decades have looked into the trends and to understand this unique phenomenon possess by RBC. The emergence of advance technological instruments enabled the rapid investigation on mechanical properties of RBC.

RBC mechanical properties measurements

Numerous experimental approach can broadly be classified into two main groups uses direct measurement or indirect measurement on RBC mechanical properties. Direct measurement treats RBC in population means either RBC in suspension or diluted RBC will give high throughput; however do not address on size heterogeneity. Some of the techniques include rheometer (Tran-Son-Tay *et al.* 1984), laser cavitation bubbles (Quinto-Su *et al.* 2011), microfiltration (Turmezei *et al.* 2003) and ektacytometry (Bessis *et al.* 1980, Liu *et al.* 2007).

On the other hand, the indirect measurement employ single cell approach overcomes several problems faced by the former techniques. Several techniques namely optical tweezers (Mills *et al.* 2004, Dao *et al.* 2005, Rancourt-Grenier *et al.* 2010, Huruta *et al.* 2014, Hénon *et al.* 1999, Bronkhorst *et al.* 1995, Brandão *et al.* 2003), micropipette aspiration (Evans 1973, Evans 1983, Hochmuth 2000, Artmann *et al.* 1997), atomic force

microscopy (Kuznetsova *et al.* 2007) and recent movements using microfluidic platforms (Sakuma *et al.* 2014; Quinn *et al.* 2011; Tomaiuolo *et al.* 2009; Luo *et al.* 2014; Yaginuma *et al.* 2011). Further reading on single cell mechanical properties measurements can be found from (Ahmad and Ahmad 2014) while more facts on RBC were discussed in details by (Kim *et al.* 1979) and (Tomaiuolo 2014).

RBC related diseases

As a living entity, RBC should withstand the changes attributed not only from its environment but also due to mechanical stimuli. Nevertheless, pathological alterations on RBC due to diseases have been discussed by many (Maciaszek *et al.* 2011, Williamson *et al.* 1985, Park *et al.* 2010, Hosseini and Feng 2012, Sleep *et al.* 1999) and can be found from comprehensive review by (Tomaiuolo 2014). Table-1 below signifies the evidence that RBC will experience mechanical alterations whenever a disease incurred.



Table-1. RBC mechanical properties alterations due to diseases.

Disease	RBC conditions
Malaria	<ul style="list-style-type: none"> RBC stiffened according to stages of infection Less deformable Increased adhesion bond (Glenister <i>et al.</i> 2002, Herricks <i>et al.</i> 2009, Cooke <i>et al.</i> 2000, Bow <i>et al.</i> 2011, Shelby <i>et al.</i> 2003)
Sickle cell	<ul style="list-style-type: none"> RBC stiffened Change of shape and increased rigidity (Brandão <i>et al.</i> 2003)
Cancer	<ul style="list-style-type: none"> RBC more softer and deformable (Lekka <i>et al.</i> 1999, Guck <i>et al.</i> 2005, Byun <i>et al.</i> 2013, Cross <i>et al.</i> 2007)
Diabetes	<ul style="list-style-type: none"> RBC stiffened, lower deformability (Tsukada <i>et al.</i> 2001)

MECHANICAL MODEL OF RBC

To further elucidate the general concept of modelling a cell, one needs to understand the divisions of mechanical models available. A good review was provided by (C T Lim *et al.* 2006) explained on most of the mechanical models have been developed either using continuum or nano-structural approach. Continuum means cell is represented by a continuum material whereby the associative constitutive material model will be properly defined using appropriate parameters. By doing so, less computational time will be required and hence give a more straightforward approach. On the other hand, the nano-structural approach treated cytoskeleton as the main structural components and thus limit the model only to cytoskeletal related investigation especially for adherent cell. Various researchers' works spanned from as early as 1980s and to date covers wide area of mechanical models as given in Figure-1 below.

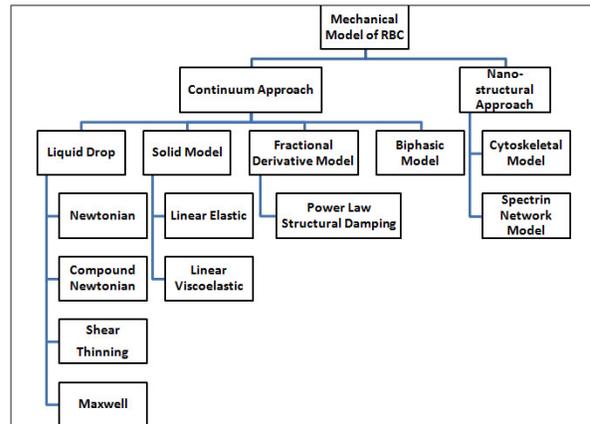


Figure-1. Mechanical model of RBC excerpted from (C T Lim *et al.* 2006).

There are three critical domains to be addressed on whenever a cell model is proposed which are; the structural heterogeneity of cells, appropriate constitutive relations for each subcellular regions and components and active forces acting on cell. Several mechanical models have been developed by previous researchers according to the type of cell. Different cells react differently towards applied stimuli and these helped to setting up requirements for mechanical model. Table-2 below depicts the requirements needed for mechanical model based on cell type.

Table-2. Proposed mechanical model based on cell types.

Cell type	Mechanical model
Suspended cell	Cortical shell-liquid core (Liquid drop)
Adherent cell	Solid model (Elastic, Viscoelastic)
Adherent cell	Fractional Derivative Model (Power-Law structural damping)
Musculoskeletal	Biphasic model

METHODOLOGY

The RBC is a cell with no nucleus and so it has the form of a microcapsule that contains a cytoplasm. In this model, RBC is represented by two components consists of membrane and cytoplasm. Using continuum approach for mechanical model, the Newtonian Liquid Drop Model was adopted. The cytoplasm is treated as an incompressible Newtonian fluid with hydraulic fluid model within fluid filled cavity. It is surrounded by a thin viscoelastic membrane, which consist of a lipid bilayer and a protein cytoskeleton.

When a suspension of RBCs is subjected to flow, viscous stresses are exerted on the RBCs and this may lead



to large deformations. The mechanical properties of the membrane are highly important due to control of the resistance towards the applied stresses. Since the membrane thickness is small compared to the cell dimensions, the membrane may be considered as a two-dimensional solid with viscoelastic properties. Moreover, changes in the cell due to the load applied can be divided into: membrane area uniform (isotropic) dilation, shear deformation (with no area change or bending), bending (with no area change or shearing).

Frequently, the RBC is associated with hyperelasticity governed by either Neo Hookean or Mooney Rivlin strain energy potential. A Neo-Hookean model is a hyperelastic material model that can be used for predicting the stress-strain behavior of materials, and the model is similar to Hooke's law. For general materials, the relationship between applied stress and strain is initially linear, but at a certain point the stress-strain curve changes to nonlinear. A Neo Hookean model is one of the simple model and the strain energy density function for an incompressible Neo-Hookean material as given by (Abaqus 2013) is:

$$W = C_1(\bar{I}_1 - 3) \quad (1)$$

Where C_1 is a material constant and I_1 is the first invariant of the left Cauchy-Green deformation tensor. ABAQUS/ CAE Version 6.12 require that the Neo-Hookean material parameters be expressed in terms of C_{10} and D_1 . These parameters can be obtained from the shear modulus (μ) and the bulk modulus (κ) by (Abaqus 2013) based on the following expressions:

$$C_{10} = \mu / 2 \quad (2)$$

$$D_1 = 2 / \kappa \quad (3)$$

This model adopted isotropic hyperelasticity with Neo Hookean strain energy potential.

Geometrical design

The finite element modeling and simulation works were carried out using ABAQUS/ CAE Version

6.12. The RBC was recreated using shell to allow for two components model (membrane and cytoplasm). Figure-2 shows the geometrical parameters used for the RBC model. It closely resembles the dimensions of a healthy RBC reported from previous literatures. The thickness of the membrane is generally 200nm.

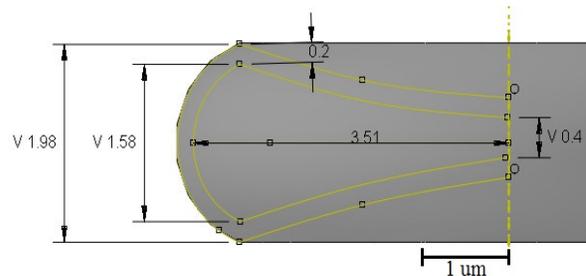


Figure-2. Dimensions of the proposed RBC model.

RBC model considerations

Several assumptions were made prior to the RBC modeling are listed below:

- Fluid surrounding the RBC is considered to be incompressible therefore allowing RBC to keep constant volume.
- RBC material behaviour is anisotropic therefore there is possibilities of tilting/rotating during measurements.
- RBC membrane is hyperelastic therefore defines a material which can recover its original shape following a finite deformation.
- Plane symmetry of RBC allowing for smaller model to be designed to reduce computational complexity.

During the design stage, important parameters summarized in Table-3 were used to model the healthy RBC.

**Table-3.** Simulation parameters.

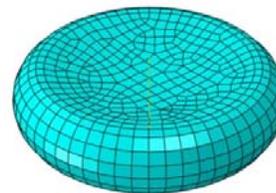
Parameter (unit)	Healthy RBC
Volume (μm^3)	89.4 ± 17.6
Surface area (μm^2)	113.8 ± 27.6
Cytoplasmic viscosity (mPa/s)	6.07 ± 3.8
Cytoplasm density (kg/m^3)	1050
Shear Elastic Modulus($\mu\text{N}/\text{m}$)	5.5 ± 3.3
Bending Elastic Modulus ($\times 10^{-19}$ Nm)	1.15 ± 0.9
Relaxation time constant (s)	0.17 ± 0.08
Area compressibility Modulus (mN/m)	399 ± 110
Young's Modulus (kPa)	26 ± 7
Mass density (kg/m^3)	1139 ± 3.0
Poisson Ratio	0.4999
Membrane thickness (μm)	0.2
Membrane shear modulus ($\mu\text{N}/\text{m}$)	$3.7 \sim 9.0$
Bending stiffness ($\times 10^{-19}$ J)	$1.8 \sim 7.0$
Initial shear modulus ($\mu\text{N}/\text{m}$)	7.6
Initial membrane shear modulus ($\mu\text{N}/\text{m}$)	$1 @ 5 \times 7.6$
Initial bending modulus ($\times 10^{-19}$ J)	2.6

RBC model materials definitions

The model was developed using ABAQUS/ CAE Version 6.12. In order to successfully model two components RBC, two different types of shell elements were used. The outer surface of the cell, depicting the membrane employed S4R shell elements (4-node doubly curved shell finite membrane strains elements). While, the inner surface of the cell was composed of F3D4 shell elements (4-node linear 3-dimensional quadrilateral hydrostatic fluid element), which represented the cytoplasm. This is to mimic the fluidic property of the cytoplasm.

RBC model meshing requirements

As mentioned previously, the shell elements were used while meshing the proposed RBC model. 2964 elements were generated from S4R shell (membrane) and 3000 elements for F3D4 (cytoplasm). Figure-3 shows the meshing.

**Figure-3.** Mesh of two components RBC model.

Simulation settings for RBC stretching

For the purpose to reduce computational complexity, the loading and boundary conditions for the simulation were set in the direction as in Figure-4. The applied force was intended to stretch the RBC in the predefined directions as the displacement in terms of transverse and axial diameter was observed. Furthermore, the flexibility of RBC corresponds to the force applied will indirectly provide hints towards mechanical properties such as bending moduli and health status.

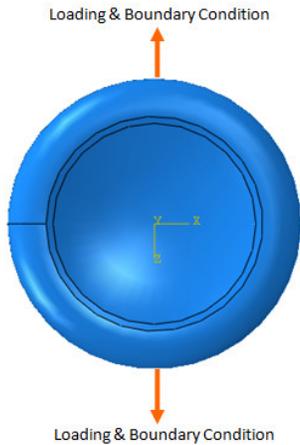


Figure-4. Simulation settings for stretching experiment.

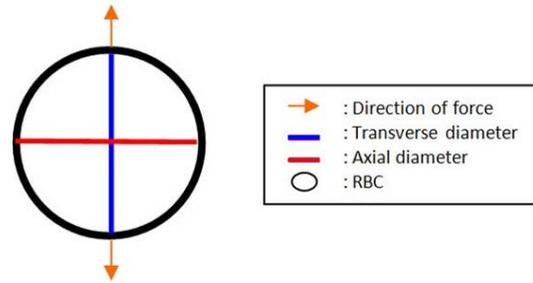


Figure-6. Schematic of stretching experiment.

RESULTS AND DISCUSSIONS

RBC hyperelasticity

Figure-5 below shows the hyperelastic curve derived from the Neo-Hookean parameters using ABAQUS/ CAE Version 6.12. The stress and strain were expressed in terms of nominal values. In general, these values were in agreement with biological materials (cells) behaviour during compression and tension experiments.

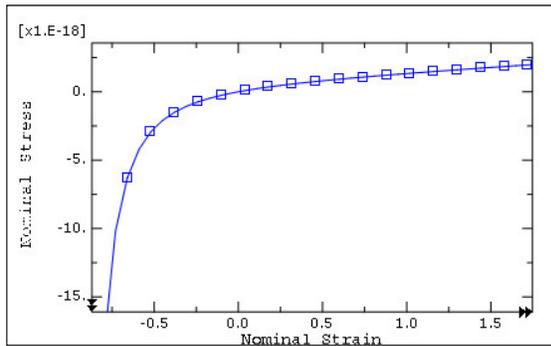


Figure-5. Neo-Hookean RBC Hyperelasticity curve.

RBC stretching simulation measurements

The schematic of measurements during stretching simulation is given by Figure-6 below. It can be seen that the measurements were taken with respect to the direction of cell's elongation. The elongation with respect to horizontal axis is known as axial diameter, while the elongation along the vertical axis is known as transverse diameter.

RBC stretching simulation results

The following Figures 7 (a)-(d) were the examples of simulation results at different tensile force. Greater elongation was observed when larger force was applied. These observations were tabulated and the resultant graph can be seen from Figure-8.

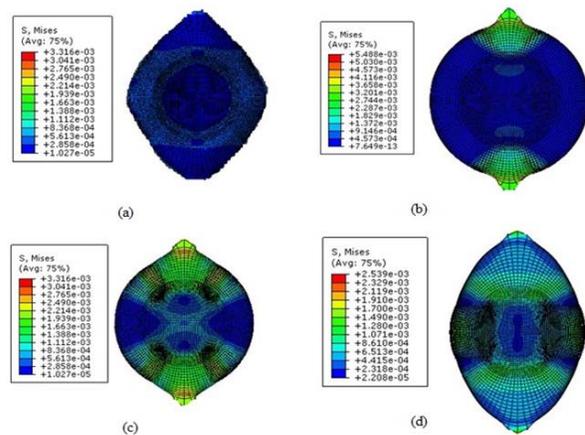


Figure-7. Stretching of RBC when (a) 10pN (b) 20pN (c) 40pN (d) 60pN.

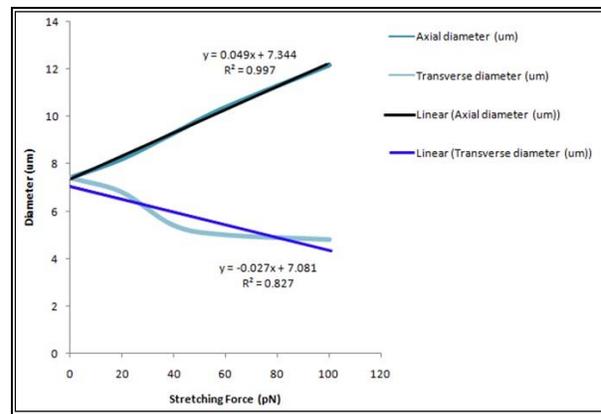


Figure-8. Axial and transversal diameter measurement when applied to various stretching force ($\mu_0 = 7.6 \mu\text{N/m}$).



From the graph, it is worthwhile to note that for a given external force applied, the degree of deformation depends largely on the specified initial shear modulus. Furthermore, the coupling between solid membrane and fluidic cytoplasm in this model helps to eliminate the problem concerning accurate prediction for the axial and transverse measurements. The predefined cytoplasm properties in this model also show that cytoplasm viscosity plays important role in terms of deformation of RBC under loading. Previously, most of researchers neglect this fact in order to simplify computational complexity by assuming the small and insignificant role of cytoplasm viscosity. Another improvement in terms of replicating the actual experimental conditions also can be achieved via this model. An agreement with experimental data coming from (C.T. Lim *et al.* 2006; Dao *et al.* 2005) were obtained. Hence, the fluid-interactions model adopted in this paper were able to provide better estimation of RBC deformation as comparable to the experimental approach.

RBC in a microconfined channel

To further investigate the deformability limit of the developed RBC model, a microchannel was used. It is equally important to visualize the RBC behaviour when undergone a deformation under laminar flow. A constricted hyperbolic microchannel was designed to have the following dimensions (height, width, length) of $5\mu\text{m}$, $3\mu\text{m}$ and $10\mu\text{m}$ respectively on the constriction area as shown in Figure-9.

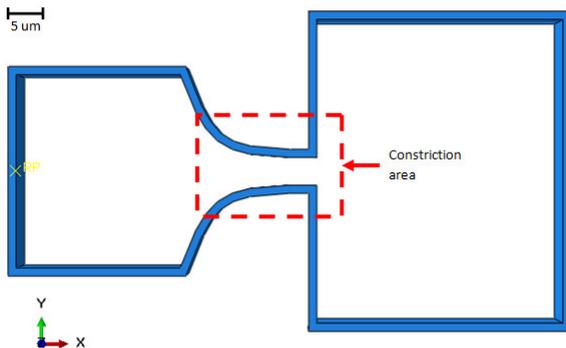


Figure-9. Hyperbolic microchannel with constriction area.

As suggested by Figure-10, the ability of RBC to recover its original shape was demonstrated via the simulation. During the simulation, the normal biconcave shaped RBC underwent a severe shape transition from the entrance until an ellipsoidal RBC was observed. Once the RBC exiting the constriction area, RBC slowly recovers its original shape. This natural phenomenon explains the capability of RBC to travel within blood capillaries with diameter as small as $3\mu\text{m}$.

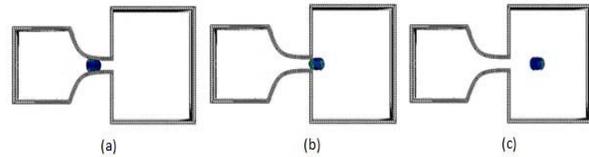


Figure-10. Recoverability of RBC model in microchannel (a) at the channel entrance, (b) exiting the channel and (c) full recovery.

Furthermore, Figure-11 below depicts stress distribution in terms of mises experienced by the RBC when travelling in the microchannel. The intensified area (red shaded) normally are due to greater stress experienced with respect to smaller constriction and the edges. With the proposed RBC model, the recoverability rate is improved due to cytoplasm influence which is previously neglected. Theoretically, the averaged value of cytoplasm viscosity is mainly contributed from haemoglobin concentration. It is also temperature dependent (Chee *et al.* 2008).

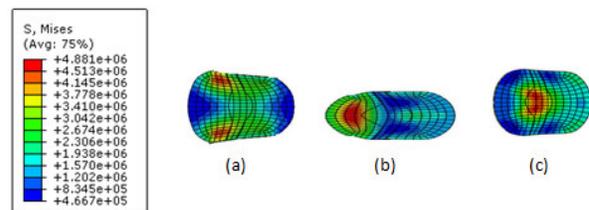


Figure-11. Von Mises Stress of RBC model in microchannel (a) at the channel entrance, (b) exiting the channel and (c) full recovery.

CONCLUSIONS

We proposed a two components model of RBC consisting of membrane and cytoplasm adapting Neo-Hookean strain energy potential. The model was carefully evaluated in terms of hyperelasticity and stretching behaviour when subjected to applied force. Next, the model was integrated into a microchannel in order to demonstrate the recoverability and in order to achieve better understanding of RBC mechanics. The advantages of the proposed model are: firstly, more accurate stretching simulation results that is comparable to experimental works and secondly, improved recovery rate since RBC uses its own elastic energy with the aid of cytoplasm viscosity. Altogether, the presented results show that the developed RBC model may serve as a quantitative tool for estimating RBC mechanical properties.

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