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Morphological Factors and Forces Acting in Normal and Sickled Erythrocytes in Sickle Cell Anemia: A Mathematical Model

Omamoke Ekakitie [a*], Funakpo Isaac [a], Olugbenro Osinowo [b], Sylvester Chibueze Izah [c], Keneke Edwin Dauseye [d] and Bunonyo Wilcox Kubugha [e]

[a] Department of Mathematics, Bayelsa Medical University, Yenagoa, Bayelsa State, Nigeria.
[b] Department of Medicine and Surgery, Bayelsa Medical University, Yenagoa, Bayelsa State, Nigeria.
[c] Department of Microbiology, Bayelsa Medical University, Yenagoa, Bayelsa State, Nigeria.
[d] Department of Physics, Bayelsa Medical University, Yenagoa, Bayelsa State, Nigeria.
[e] Department of Mathematics, Federal University, Otuoke, Bayelsa State, Nigeria.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

We carried out a theoretical study that considers the morphological factors and forces acting on a normal and a sickled blood cell. Sickle cell disease is associated with vaso-occlusion which creates blood flow crises as a result of loss in shape memory of the normal red blood cell. Certain forces and chemical compositions acting

**Corresponding author: Email: ekakitieomamoke@gmail.com, omamoke.ekaitie@bmu.edu.ng;*

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on the cell could retain the shape memory. The problem of a second order partial differential equation modeled was solved to get the forces and chemical composition required to restore the sickled red blood cells back to its original shape. The results gotten showed that, increase in chemical reaction increased the RBC growth by creating a stretching force that causes the sickle cell to regain elasticity with improved oxygen.

Keywords: Blood viscosity; stretching force; chemical reaction; sickle cell; sickle cell disease; shear force.

Nomenclature

x, y	*: Coordinates position of the RBC*
r	*: Radius of the RBC*
A	*: RBC Surface area*
μ	*: Blood Viscosity*
μ_p	*: Internal Blood Viscosity*
ρ	*: RBC Density*
I	*: Energy stored in the Blood Cells*
E	*: Chemical reaction constant*
λ	*: Depth constant*
d	*: RBC Diameter*
a	*: RBC Thickness*
θ_i	*: Bending angle of the RBC*
d_o	*: Initial length/diameter of the RBC*
d_i	*: RBC increased length/diameter.*
A_i	*: Increased RBC Membrane cross sectional area*
L	*: Well-defined Erythrocyte Boundaries*

1 Introduction

Sickle cell disease (SCD) was discovered in the past 50 years as the first molecular disease [1]. In the United States, there are about 50,000 persons having SCD hospitalized regularly for sickle cell attacks. Sickle cell disease (SCD) was the reason an average of 75,000 persons were hospitalized between 1989 and 1993, with an annual cost of 475 million dollars while 600 African-American have been diagnosed with SCD in the United States [1]. Sickle cell anemia disease (SCD) also known as a molecular disease is the genetic hematological disorder that is genetically characterized by inhomogeneous or heterogeneous cell morphology, anomalous rheology of the red blood cell and crisis caused by vaso-occlusion or closure/blockage of the blood vessels.

The circulatory system of the human body supplies sufficient amount of nutrients and oxygen to the body cells and carry away waste from the cells through the blood transportation. The biological fluid called Blood is made up of proteins, plasma, platelets, and deformable cells. The hemoglobin in the RBC carries oxygen into the cell while in its normal state contains separate hemoglobin beads that maintain its protein quaternary structure. SCD is a genetic disorder that is autosomal recessive created when glutamic acid is substituted with valine in the β −subunit of the hemoglobin gene. The substitution creates the production of abnormal hemoglobin (HbS) [2]. A single substance change (β-globin mutation) causes the hemoglobin to form long rods which changes the red blood cell into a sickle shape [3, 4]. SCD is a disorder of a group of inherited blood which produces abnormally shaped RBCs in the body that is sickled in shape. The human RBCs when passing through a narrow blood vessel, under-goes repeated large elastic deformations. This flexibility of the RBCs which is large is attributed primarily to the cell membrane, since there is no organelles and filaments in the cell. The RBC membrane has a two – dimensional (2D) structure, which comprises of a cytoskeleton and lipid bilayer together. The lipid bilayer contains different types of cholesterol, phospholipids, sphingo-lipids and essential membrane proteins, such as band – 3 and glycophorin. Sickle cell has a shorter life span when compared to healthy red blood cells (RBCs). The natural life span of the RBC is 100 – 120 days; while the sickle cell is 10 – 20 days. The shortage of red blood cells known as anemia is causes fatigue, reduced breath and delay in the growth of children. Healthy RBCs have a biconcave shape while sickle cells are rigid sticky. These sickle cells come together and stick to the wall of the blood vessels creating an obstruction called vaso-occlusion events in the blood vessels, subsequently reducing the oxygen in the blood supplied to various organs. This creates and manifest periodic seasons of pains called crisis, which could last for hours or days and could result to the damage of the organs in the body such as the eyes (blindness), kidneys (renal failure), bones (avascular necrosis), lungs (pulmonary hypertension) and brain (strokes) [5]. Since the sickle cell has a short life span, the spleen then handles large numbers of RBCs and become enlarged and fibered. The immune function will decline, causing the body to become vulnerable to infections. In an attempt to compensate the lost RBC, more RBCs are produced by the bone marrow which grows larger causing weakened bones. Other signs include: jaundice (yellow skin or eyes) caused as a result of increased heme destruction. Healthy RBC has a shape that is biconcave, with a mean diameter of 7.8 mm. The lipid bilayer membrane has an associated cytoskeleton created by spectrin proteins interconnected by short actin filaments. The lipid bilayer is considered to be almost viscous with area-preserving membrane [6], while the elasticity of RBC is attributed to the spectrin network attached, just as the integrity of the entire RBC when subjected to severe deformations in the capillaries with a diameter of 3 mm. Under physiological conditions, the membrane of the RBC enfolds a viscous cytosol that is greater than the plasma of the blood. Both rheological and Mechanical characteristics of RBCs and its dynamics are influenced by the bending resistance, viscosity, elastic membrane and the viscosities of the internal or external fluid. RBC properties have been measured in a number of experiments such as micropipette aspiration [7, 8], RBC deformation by optical tweezers [9], optical magnetic spin cytometer [10] and three dimensional (3D) measurements of membrane thermal fluctuations [11]. The extremely small pipette inhalation and optical hand tool practical method will deform the membrane of the RBC, resulting to a visible shear modulus of the healthy RBC ranging between 2–12 mN/m. Optics magnetic spin cytometer and membrane thermal fluctuation measurement, probes locally for the membrane characteristics and furnishes the properties of the measurement of local rheology (e.g., the complex modulus). This experiment shows clearly, the viscoelastic mechanical response of the membrane [12].

The major component of RBCs is the hemoglobin which is responsible for the transportation of oxygen. Adult hemoglobin (HbA) consists of four protein hemoglobin chains; $2-\alpha$ chains and $2-\beta$ chains. The $\beta-$ subuinte contains the HBB gene. The HBB gene undergoes several mutations, responsible for sickle cell disease with individual having two copies of the HBB gene. The SCD is developed when both mutated producing abnormal β – globin is copied. The two copies could be mutated differently, creating two different kind of abnormal β - subunits. The combinations in these mutations, produces different kind of sickle cell disease (HbSs and HbSc disease; HbS/b-0 and HbS/b+ thalassemia). SCD is more severe and common and is caused by two copies of same mutation producing mutated HbS with each copy coming from a parent. The two parents carry each copy of this mutated gene but don't show any symptom. This pattern is called autosomal recessive inheritance [13]. At the early stage of sickle cell anemia (SCA), there is intracellular polymerization of sickle cell hemoglobin (HbS) under de-oxygenation conditions resulting to an increase in intracellular viscosity and stiffness causing great damage to the RBC membrane [14, 15, 16]. The HbS polymerization process at the molecular scale has been characterized by a double nucleation mechanism while at the cellular scale, sickle RBCs has a remarkable heterogeneity in density, rigidity and morphology [17]. At the micro-vascular scale, the HbS polymerization creates entrapment of the RBCs in capillaries [18, 19]. The HbS creating polymers under conditions of low oxygen is referred to as sickling (gelation). As these polymers fill the membrane, they destroy the cells into sickle shape. Apart from oxygen tension, other hemoglobin present will affect the sickling process. Normal adult hemoglobin decreases sickling whereby heterozygote parents which produce both mutated HbS and NHA do not develop the disease [20, 21]. Oxidative stress caused from little inflammation, severe intravascular hemolysis, unstable auto-oxidative sickle hemoglobin (HbS) and continuous ischemia reperfusion injury, all play a key role of the organ damage in sickle cell disease (SCD). Increases in the level of reactive oxygen species (ROS) causes accelerated hemolysis, hypercoagulability, damage of the endothelial and decrease in the nitric oxide (NO). Sickle red blood cell becomes depleted with potassium and then dehydrated and abnormally dense. Dense sickle cells have more severe membrane abnormalities than cells with normal hydration. High percentage of cells in dense fractions has lost their normal phospholipid asymmetry and display on the outer membrane leaflet, Phosphatidylserine (PS) [22]. Hemoglobin polymerization, which results to an increase in erythrocytes rigidity, is central and causes an onset episode of an induced sickle cell (SS) vaso-occlusion. The lack of relationship between percentage dense cells and incidence of sickle cell crisis [21] suggest that factors other than intracellular polymerization might be involved [23]. An Increase in the adhesion of sickle cells could be an added factor first demonstrated by [24] and confirmed later in both static and dynamic systems with cultured endothelial cells gotten from the human and other mammalian sources [25]. It has not yet been estimated in a living micro-vascular interconnection that the increase in adherence of sickle cells to the endothelium wall will contribute to vaso-occlusion. The erythrocytes in patients with SCD have heterogeneous density, morphological characteristics, and function but no demonstration for a congener donation of separate sickle cell class to adhesion and occlusive events in a perfused microvasculature. In a microcirculatory event, sickle cell vaso-occlusion, contributions from micro-vascular factors such as the topography, vessel wall features, and predominant rate of the wall shear, will be critical to the micro-vascular occlusion individual sickle cell class adhesion. No direct microcirculatory study has been performed to show specific sites of sickle cell adhesion and their topographical characteristics [26]. Nitric oxide (NO) reacts at rates with oxy-hemoglobin and deoxy-hemoglobin to create nitrate plus met-hemoglobin [27, 28] and iron-nitrosyl hemoglobin respectively [29] however, the rate of NO scavenging is reduced 1,000-fold by sequestering hemoglobin in the red cell membrane [30, 31, 32]. The amount of NO consumed by cell-free and intra-erythrocyte hemoglobin shows that when there is physically compartmentalization of hemoglobin within erythrocytes, Nitrogen Oxide (NO) produced by endothelial cells will reach concentrations within the smooth muscle that will activate Guanylate cyclase and cause vasodilation [33, 34]. This effect causes pulmonary and systemic hypertension [35], decreases organ perfusion [36, 37], esophageal (smooth muscle) and increased mortality, that happens after infusions of stroma-free hemoglobin in animals or humans as an oxygen-carrying, artificial blood substitute. Mutations of the Heme-pocket which reduces the hemoglobin–NO affinity, increase the effect of hypertension of cell-free hemoglobin. Furthermore, hemoglobin breaks up into dimers when released into plasma. These smaller species extravagated from the vascular lumen to positions between endothelial cells and smooth muscle, and may magnify NO scavenging [38, 39].

This sickle cell anemia/molecular disease is associated with certain hematological disorder inherited genetically leading to crises such as splenic sequestration, vaso-occlusion, hemolysis and others. In cell morphology, the shape structure, form and size of the cell changes as a result of the de-oxygenation of the RBC while in normal rheology, high viscosity of oxygenated blood. [1] did a proposal attributing the disease to an abnormal molecule of the hemoglobin within the erythrocytes. Hydrophilic amino acid called glutamic is replaced by hydrophobic amino acid called valine at the B-6 chain in the molecule of the sickled hemoglobin [40]. These intracellular sickled hemoglobin molecules become polymerized in the hypoxic condition which then alters the functioning of the membrane cell and micro-circulation [41]. SCD is characterized by heterogeneous and irregular cell morphologies, abnormal rheology and decreased cell deformability and finally vaso-occlusion crises which causes morbidity and mortality in patients with SCD. The double nucleation model characterizes the polymerization process of the sickled hemoglobin molecule that is caused by homogeneous nucleation of bulk solutions of the sickled hemoglobin molecule [42, 43]. As discussed by [44], groups of heterogeneous cell density in suspension of a sickled red blood cell is broken into four parts as a result of the concentrated intercellular mean corpuscular hemoglobin. These include sickled red blood cells 1 and 2 with average concentrated intercellular mean corpuscular hemoglobin is made up of reticulocyte and discocyte. The reticulocytes are slightly immature red blood cells with its count measuring the amount of cell in the blood while the discocyte is a discoid shape form of the RBC. Furthermore, sickled RBC 3 and 4 with high concentrated intercellular mean corpuscular hemoglobin is made of irreversible sickle cells and rigid discocytes in association with rigid heterogeneous cells [45, 46, 47] and abnormal blood rheology [48, 49, 50]. According to the study done by [51, 52, 53], hydroxyurea is a treatment drug applied on patients with SCD which is targeted at the intracellular sickle hemoglobin molecule polymerization process responsible for the vaso-occlusion crisis such that the fetal hemoglobin reduces the timing of the sickling process. Several researchers have used mathematical models to study the morphological changes associated with the Red blood cell leading to its sickling. The study done by [54] shows the multiple red blood cell deformation in the capillary with immersed boundary condition used for the interaction of the RBC and hyper-elastic model used for the RBC membrane. In the capillary flow the viscosity was more sensitive to the shear coefficient change of the cell membrane than the bending coefficient and dilation coefficient of the surface of the membrane while increased shear coefficient caused a drop in the pressure of the flow of blood through the capillaries resulting to constant rate of flux of the RBC. The study done by [55] showed the Single RBC deformation in a micro-vessel using numerical methods on a two-dimensional spring model representing the RBC membrane with the blood cells having different kind of motion and shape deformation. The deformation of RBC with a spherical shape in a pair beam optical stretcher was calculated by [56] using numerical method to impute the deformed morphology of the cell spherical in shape from the distribution of photonics stress past a membrane that is cellular. In the health care of children, with prevalence of sickle cell disease (SCD) over the past decades, this disease continues to be associated with morbidity and pre - mature mortality, with a 25 - to 30 - year loss of life expectancy [57, 58]. Bone marrow transplant is presently the known cure for the SCD. It requires the replacement of the disease stem cells in the bone marrow with healthy cells from a donor usually a relative. Others include the use of vaccinations, prophylactic antibiotic, pain medication, drugs to promote formation of hemoglobin F and blood transfusions. Early detection and treatment for complications is crucial for a sickle cell patient. Transfusion therapy reduces stroke and other complications with increased risk for transfusion infection, reactions, and iron overload [59]. Hydroxyurea increases the total hemoglobin concentration, reduces the vaso-occlusive complications of pain and acute chest syndrome, and attenuates mortality in adults [60]. However, less than 30% of patients are referred to take this drug but majority of the adults do not respond to treatment. A small and un-quantified risk of latent transformation to leukemia with long-term use remains a concern [61]. Furthermore, allogeneic HCT is currently another treatment therapy for SCD with an encouraging result in young patients (less than 16 years of age) with SCD, with an overall event-free survival (EFS) of approximately 85% and transplant-related mortality of less than 10% [62, 63, 64,65]. Recently, [66] studied mathematical modeling for improved flow of blood in patients with sickle cell anemia where mathematical modeling was used to model the blodd cell geometry with certain parameters restoring the memory of the sickle blood cell and improving blood flow while [67-72] did a study on blood flow through arteries.

Several approaches have been followed for the mathematical description and modeling of the SCD. In this study, we are proposing a mathematical model that describes the morphology of sickle cell disease. We are considering those factors that will lead to the loss in the shape of the normal red blood shape and its recovery. We are proposing a partial differential equation (PDE) that will combine both the forces and the chemical composition to keep the RBC in the normal shape and the extent where these forces or the chemical composition acting on the red blood will cause it to regain its shape.

2 Mathematical Formulation

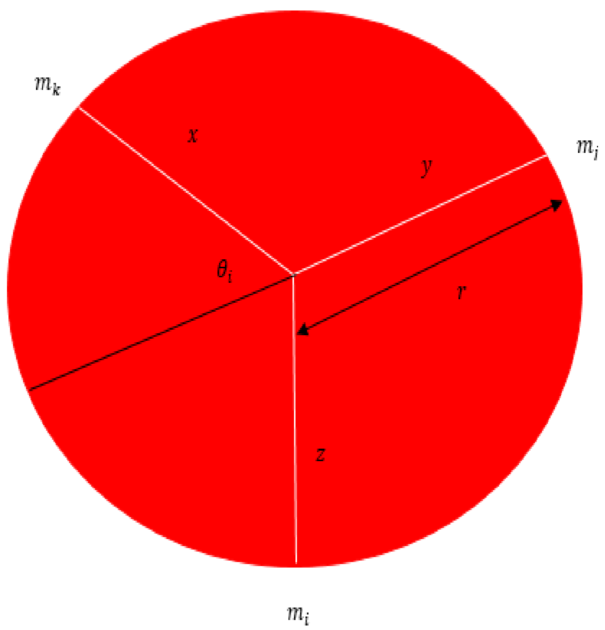

Fig. 1. Diagrammatic representation of the geometry of the Red Blood Cell Membrane

2.1 Mathematical modeling of the energy acting on the RBC membrane

There is a relationship between the acting force on the ith membrane and the energy of the red blood cells.

$$I = Fx \tag{1}$$

From Hooke's law

$$I = \frac{1}{2}kx^2 \tag{2}$$

The RBC elastic energy stored as a result of compression and stretching

$$x_{sk} = \left(\frac{d_i - d_o}{d_o}\right)^2 \quad (3)$$

$$I_{sk} = \frac{1}{2} k_{sk} \sum_{i=1}^{n} \left(\frac{d_i - d_o}{d_o}\right)^2 \quad (4)$$

Where $k_{sk} = 3 \times 10^{12} Nm$ is the Hooke's spring constant for compression and stretching.

The elastic energy stored in the RBC due to bending

$$x_b = tan^2\left(\frac{\theta_i}{2}\right) \quad (5)$$

$$I_b = \frac{1}{2} k_b \sum_{i=1}^{n} tan^2\left(\frac{\theta_i}{2}\right) \quad (6)$$

Elastic energy stored in the RBC due to the cross-sectional area

$$x_{sA} = \left(\frac{A_i - A_o}{A_o}\right)^2 \quad (7)$$

$$I_{sA} = \frac{1}{2} k_{sA} \sum_{i=1}^{n} \left(\frac{A_i - A_o}{A_o}\right)^2 \quad (8)$$

Where $k_{sA} = 3 \times 10^{12} Nm$ is the Hooke's spring constant for compression and stretching, $A_o = \pi(2.8 \times 10^{-6})^2 \times 0.55 m^2$ is the initial equivalent RBC membrane cross sectional area?

The total energy acting on the RBC membrane is expressed as

$$I = I_{sk} + I_b + I_{sA} \quad (9)$$

The forces acting on the ith membrane is expressed as

$$F_i = \frac{dI}{dx_i} \quad (10)$$

$$I = F_i x_i \quad (11)$$

This implies that the energy acting on the RBC membrane

$$I_{sk} + I_b + I_{sA} = F_i x_i \quad (12)$$

2.2 Mathematical modeling of the shape geometry of the RBC membrane

$$x = rcos\theta \quad (13)$$

$$y = rsin\theta \quad (14)$$

$$x^2 + y^2 = r^2 \quad (15)$$

$$cos^2\theta + sin^2\theta = 1 \quad (16)$$

$$cos^2\theta + sin^2\theta = \frac{x^2 + y^2}{r^2} \quad (17)$$

$$L = \frac{e^{\frac{x^2+y^2}{2r^2}}}{2\pi r^2} \ (Vivek\ et\ al., 65) \quad (18)$$

3 Governing Equation

The governing equation in non-dimensional form for the chemical reaction effect on the RBC morphology and shape recovery is expressed below as

$$\rho A\mu \frac{\partial^2 \varphi}{\partial x^2} + EI \frac{\partial^4 \varphi}{\partial x^4} = 0 \tag{19}$$

The blood viscosity in relation to blood hematocrit non-dimensional form is expressed below as

$$\mu = \mu_P(1 + 2.5H) \tag{20}$$

$$E = \frac{\sigma}{\varepsilon} \tag{21}$$

The blood density in relation to cross sectional area of the blood cell in non-dimensional form is expressed below as

$$\rho = \frac{Q}{A} \tag{22}$$

The energy acting on the red blood cell RBC due to bending, cross sectional area, stretching and compression non-dimensional form is expressed as

$$I = Fx \tag{23}$$

The governing equation for the depth of the sickling of the RBC and shape recovery is expressed below as

$$\frac{\partial^2 \delta}{\partial t^2} + \lambda x \frac{\partial^2 \delta}{\partial x^2} = 0 \tag{24}$$

$$\lambda = \frac{\sigma F x}{Q\mu\varepsilon} \tag{25}$$

4 First Method of Solution

The separation of variable method is used to solve the partial differential equation that models the dip, shear force and chemical composition for the memory and shape recovery.

$$\varphi = X_1 T_1 \tag{26}$$

$$\delta = X_2 T_2 \tag{27}$$

Boundary Conditions for the Erythrocytes

$$\varphi(0, t) = 0;\ \delta(0, t) = 0 \tag{28}$$

$$\varphi(L, t) = 0;\ \delta(L, t) = 0 \tag{29}$$

$$\varphi(x, 0) = 1;\ \delta(x, 0) = 1 \tag{30}$$

$$\varphi(x, \infty) = 0;\ \delta(x, \infty) = 0 \tag{31}$$

4.1 Solution to the governing equation

$$T_1 = B_1 e^{\left(\frac{k}{\sqrt{\rho A}}\right)t} + B_2 e^{-\left(\frac{k}{\sqrt{\rho A}}\right)t} \tag{32}$$

$$X_1 = B_3 \cos\left(\sqrt[4]{\frac{k^2}{EI}}\right)x + B_4 \sin\left(\sqrt[4]{\frac{k^2}{EI}}\right)x \tag{33}$$

Substituting equation (32) and (33) into equation (26), the chemical reaction effect on RBC is expressed as

$$\varphi(x,t) = \left(B_1 e^{\left(\frac{k}{\sqrt{\rho A}}\right)t} + B_2 e^{-\left(\frac{k}{\sqrt{\rho A}}\right)t}\right)\left[(B_3)\cos\left(\sqrt[4]{\frac{k^2}{EI}}\right)x + \left((B_4)\sin\left(\sqrt[4]{\frac{k^2}{EI}}\right)x\right)\right] \tag{34}$$

Applying the boundary conditions on equation (19), the chemical reaction effect on RBC growth is

$$\varphi(x,t) = \sum_{n=0}^{\infty}\left[\sin\frac{n\pi}{L}x\left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right)\left(e^{-\left(\left(\frac{n\pi}{L}\right)^2\left(\sqrt{\frac{\varepsilon I}{\rho A}}\right)\right)t}\right)\right] \tag{35}$$

where $B_1 = 0, B_3 = 0, B_2 = 1, B_4 = \left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right), L = \frac{e^{\frac{x^2+y^2}{2r^2}}}{2\pi r^2}$ [65]

$$T_2 = C_1 e^{kt} + C_2 e^{-kt} \tag{36}$$

$$X_2 = C_3\cos\left(\sqrt[4]{\frac{k^2}{\lambda}}\right)x + C_4\sin\left(\sqrt[4]{\frac{k^2}{\lambda}}\right)x \tag{37}$$

Substituting equation (36) and (37) into equation (27), the depth/growth of RBC is expressed as

$$\delta(x,t) = (C_1 e^{kt} + C_2 e^{-kt})\left[(C_3)\cos\left(\sqrt[4]{\frac{k^2}{\lambda}}\right)x + \left((C_4)\sin\left(\sqrt[4]{\frac{k^2}{\lambda}}\right)x\right)\right] \tag{38}$$

Applying the boundary conditions on equation (24) the solution for the depth of RBC is

$$\delta(x,t) = \sum_{n=0}^{\infty}\left[\sin\frac{n\pi}{L}x\left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right)\left(e^{-\left(\left(\frac{n\pi}{L}\right)^2(\sqrt{\lambda})\right)t}\right)\right] \tag{39}$$

Where $C_1 = 0, C_3 = 0, C_2 = 1, C_4 = \left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right), L = \frac{e^{\frac{x^2+y^2}{2r^2}}}{2\pi r^2}$ [65]

5 Second Method of Solution

From equation (19), we assume the solution to be

$$\varphi = \varphi_0 e^{iwt} \tag{40}$$

The expression for equation (19) will be given as

$$\rho A\mu w^2\varphi_0 e^{iwt} + EI\frac{\partial^4\varphi_0}{\partial x^4}e^{iwt} = 0 \tag{41}$$

Equation (41) is simplified and expressed as

$$\frac{\partial^4\varphi_0}{\partial x^4} + \beta^4\varphi_0 = 0 \tag{42}$$

$$\text{Where } \beta = \left(\frac{\rho A\mu w^2}{EI}\right)^{\frac{1}{4}} = \left(\frac{\mu k}{EI}\right)^{\frac{1}{4}} \tag{43}$$

$$w = \left(\frac{n\pi}{l}\right)^2\sqrt{\frac{EI}{\rho A\mu}} \tag{44}$$

$$\varphi_0 = A_1\cos(\beta y) + B_1\sin(\beta y) + A_2\cosh(\beta y) + B_2\sinh(\beta y) \tag{45}$$

$$\varphi_0(y,t) = [A_1\cos(\beta y) + B_1\sin(\beta y) + A_2\cosh(\beta y) + B_2\sinh(\beta y)\ ]e^{iwt} \tag{46}$$

Applying the boundary conditions in (28-29),

$$\varphi_0(l,t) = [A_1 \cos(\beta l) + B_1 \sin(\beta l) + A_2 \cosh(\beta l) + B_2 \sinh(\beta l)\ ]e^{iwt} \tag{47}$$

The equation of the sickle cell growth model on the deformed RBC becomes

$$\varphi_0(x,t) = \sum_{n=0}^{\infty}\left[\sin\frac{n\pi}{L}x\left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right)\left(e^{-\left(\left(\frac{n\pi}{L}\right)^2\left(\sqrt{\frac{\varepsilon I}{\rho A}}\right)\right)t}\right)\right] \tag{48}$$

where $B_1 = 0, B_3 = 0, B_2 = 1, B_4 = \left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right), L = \frac{e^{\frac{x^2+y^2}{2r^2}}}{2\pi r^2}$ [65]

Applying the same method of solution on equation (24), the equation of the sickle cell depth/growth model on the deformed RBC is expressed as

$$\delta(x,t) = \sum_{n=0}^{\infty}\left[\sin\frac{n\pi}{L}x\left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right)\left(e^{-\left(\left(\frac{n\pi}{L}\right)^2(\sqrt{\lambda})\right)t}\right)\right] \tag{49}$$

Where $C_1 = 0, C_3 = 0, C_2 = 1, C_4 = \left(\frac{2L}{n\pi}\left(1-\cos\frac{n\pi}{L}\right)\right), L = \frac{e^{\frac{x^2+y^2}{2r^2}}}{2\pi r^2}$ [65]

6 Graphical Results and Discussion

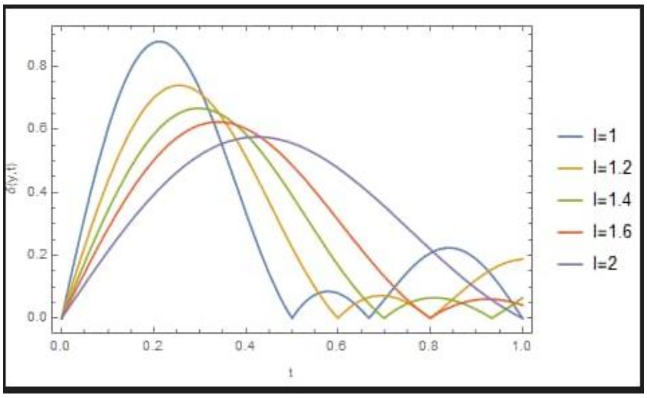

Fig. 2. Changes in shape geometry with effect on the deformed RBC

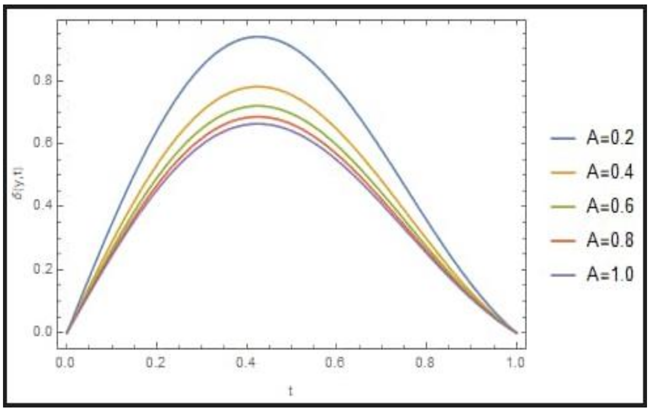

Fig. 3. Changes in cross sectional area with effect on the deformed RBC

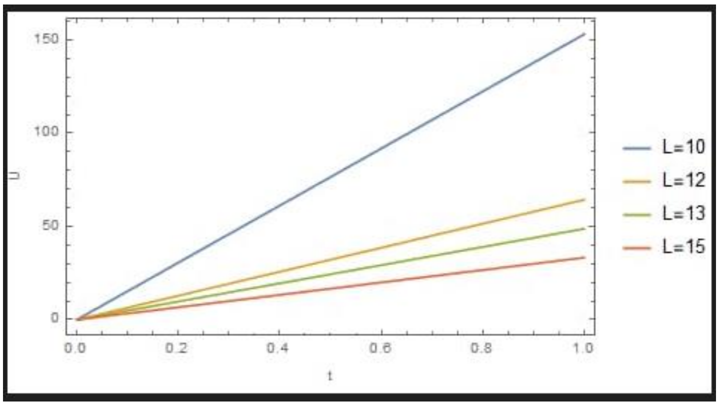

Fig. 4. Changes in cross sectional area with effect on the deformed RBC

From Fig. 2 it was observed that an increase in the geometry of the RBC increases the RBC growth reducing the deformability resulting to the restoration of the RBC. This is as a result of increased chemical reaction effect on the sickled RBC. Furthermore, the chemical reaction creates a stretching force which in turn affects the viscosity of the blood. The stretching force, forces the sickle cell to regain its elasticity, improves the oxygen level of the blood and reduces its stickiness helping it to recover its RBC shape depending on the amount of force applied which will affect the flow of the RBC. The increase in the shear force reduces the viscosity of the blood enabling improved flow with the shear force creating a correction on the sickled RBC reducing rigidity, stickiness and breaking the frictional forces which afterwards help to reduce viscosity. Prolonged exposure to chemical reaction would reduce oxygen in the RBC cell causing a turbulent flow.

From Fig. 3 it is observed that an increase in the cross-section area of the RBC causes an increase in the depth of the RBC due to the change in the radius of the RBC caused by the stretching force acting on the RBC. The long rods created in the hemoglobin to form a sickle shape are broken with the external forces acting on the sickle cell causing the shape to regain its memory and recover its original shape. The sickling is reduced as a result of the parent heterozygote producing both mutated Hbs and NHA which does not develop the sickle cell disease causing it to become normal adult hemoglobin.

From Fig. 4, it is observed that the increase in the boundary of the erythrocyte blood cells due to chemical reaction on the RBC and external forces acting on the wall of the blood vessels results in the decrease of the sickle cell growth, hence enabling it to regain its memory and reduce stickiness to each other and the wall of the blood vessel.

7 Conclusion

The following conclusion was gotten from the research:

I. An increase in chemical reaction increased the geometry/boundary of the RBC by increasing the stretching force, which in turn increases the growth of the RBC and reduce its deformability.
II. An increased cross-section area of the RBC, increases the RBC depth due to the change in the RBC radius caused by the stretching force which brakes the long rods created in the hemoglobin which forms a sickle shape. This creates improved oxygenation of the blood and reduces the stickiness of the cell.

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Competing Interests

Authors have declared that no competing interests exist.

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