

# Mathematical Models for Red Blood Cell

Tianrui Xu<sup>\*</sup> and  
Advisor: Charles S. Peskin

<sup>\*</sup>Applied Math Summer Undergraduate Research Experience (AM-SURE), Courant Institute of Mathematical Sciences, New York University, New York, New York, United States of America  
<sup>\*</sup>tx392@nyu.edu

## Abstract

The red blood cell has a unique biconcave shape because this shape minimizes the bending energy of the membrane. In this study, we want to find the simplest discrete model to generate this shape. We use a triangulated surface to approximate a smoothly continuous surface and re-define curvature on our discrete surface. We formulate an evolution equation involving bending energy  $E$ , volume  $V$ , and area  $A$ , and use it to produce a biconcave shape that simulates red blood cell.

## 1 Introduction

The cell membrane is a very important part of the cell. It not only protects the cell from extreme environments and virus invasions, but also connects the cell with the outer world. Nutrients are transported into the cell through the membrane and waste is transported out. These transports happen through different channels on a cell's membrane and the exocytosis and endocytosis processes. Armed with such functions, a cell's membrane helps the cell to communicate with the outer environment, although this communication is done without words [1].

Due to the importance of the membrane, we would like to present a mathematical model that can generate a cell's membrane with the right shape. Among all types of cells, the red blood cell has one of the most interesting shapes, which is biconcave. This special shape motivates us to build a model for the red blood cell to show how the biconcave shape naturally emerges. Although there are many past studies on models of red blood cell, the goal of this project is to find the simplest model, and to use discrete differential geometry to generate a biconcave cell membrane from a perfect sphere. This model can be further generalized to other membranes and surfaces that have unique shapes.

## 2 Mathematical Modeling

### 2.1 Initial Condition

To get a biconcave cell, we start from a sphere. Then, we gradually pump out volume and simultaneously let the bending energy to alter the initial shape such that the bending energy can be minimized on the surface. Our model reversely mimics the experiment of putting the red blood

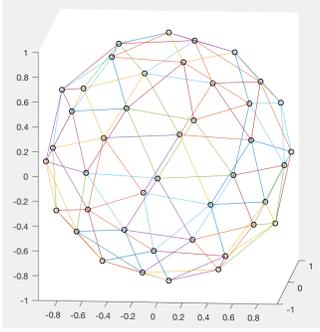


Figure 1(a)

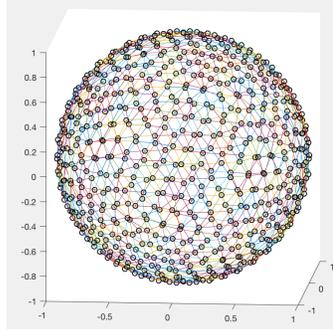


Figure 1(b)

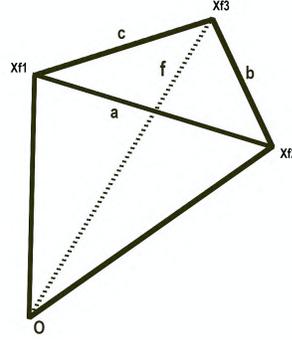


Figure 2(a)

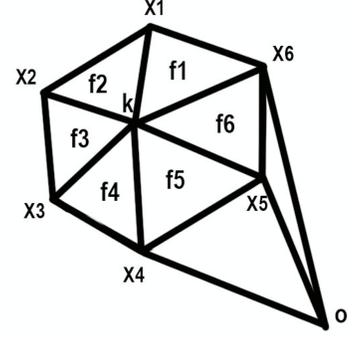


Figure 2(b)

Figure 1(a)-(b) are examples of using triangulated surface to model a sphere. (a) has a total of 42 points and 80 faces and (b) has a total of 1280 points and 642 faces. The more flat triangles we use, the more smooth the surface is. Figure 2(a) shows the three vertices with their coordinates  $\mathbf{X}_{f_1}$ ,  $\mathbf{X}_{f_2}$ , and  $\mathbf{X}_{f_3}$ , along with the tetrahedron  $T_f$  associated with the face  $f$ . Figure 2(b) shows the six tetrahedrons  $T_{f_1}$ ,  $T_{f_2}$ ,  $T_{f_3}$ ,  $T_{f_4}$ ,  $T_{f_5}$ , and  $T_{f_6}$  around the vertex  $k$ , associated with the faces  $f_1$ ,  $f_2$ ,  $f_3$ ,  $f_4$ ,  $f_5$ , and  $f_6$ .

cell in dilute solutions. When placed in dilute solutions, the biconcave red blood cell will become spherical [6]. Therefore, transforming the cell from a sphere to a biconcave shape is experimentally feasible. To get the initial shape of our model, we discretize the sphere as a faceted triangulated surface. The more triangles we use, the more smooth the surface is [2], see figures 1(a) and 1(b). After triangulating the surface, we track the coordinates of the points which are vertices of the triangles.

We use 642 vertices and 1280 faces. We give a unique index to every point and every face. We store a point by assigning its coordinates to its unique index, and we store a face by assigning the indexes of the three vertices of this triangle to the index of the face. In this work,  $\mathbf{X}_k$  refers to the Cartesian coordinates of the  $k$ -th point.

## 2.2 Model Setup

After initiating the cell membrane as a sphere, we want it to bend to a biconcave shape. According to Canham's discovery in 1970 [4], the reason a red blood cell is in a biconcave shape is that the biconcave shape requires the least amount of bending energy. If we allow the membrane of a cell to move freely, it will eventually bend to the biconcave shape to minimize its membrane's bending energy. Therefore, to obtain the shape of a red blood cell, we want our initial model, the sphere, to change its shape over time, and during this process, we reduce the volume  $V$  and minimize the bending energy  $E$ , while keeping its surface area  $A$  constant. To minimize the bending energy  $E$ , we want to minimize

$$Q = \frac{dE}{dt} + \frac{1}{2} \sum_k \frac{d\mathbf{X}_k}{dt} \frac{d\mathbf{X}_k}{dt},$$

where  $t$  refers to time. Minimizing  $dE/dt$  gives us the direction that decreases  $E$  as quickly as possible. To get a finite velocity we penalize speed by adding the second term  $\sum_k \frac{d\mathbf{X}_k}{dt} \frac{d\mathbf{X}_k}{dt}$  on the right hand side of the equation for  $Q$ .

In addition, we want to impose area and volume constraints. To preserve basic property of the cell membrane, we want to keep the surface area  $A$  constant. This gives us  $dA/dt = 0$ . Given a fixed surface area, the shape with the largest volume is a sphere. Since we start from a sphere and want to keep surface area constant, we have to force volume  $V$  to decrease. This gives us the

second constraint  $dV/dt = dV_0/dt$ , where  $V_0(t) = V_{\min} + (V_{\max} - V_{\min})e^{-at}$  is a given function with negative slope ( $V_{\max}$  refers to the initial volume,  $V_{\min}$  refers to the final volume, and  $a$  is a positive constant).

In summary, we would like to minimize  $Q$ , subject to  $dV/dt = dV_0/dt$  and  $dA/dt = 0$ . Solving this problem, we translate it into the following system of ordinary differential equations (ODEs):

$$\frac{d\mathbf{X}_k}{dt} = -\frac{\partial E}{\partial \mathbf{X}_k} - \lambda \frac{\partial V}{\partial \mathbf{X}_k} - \mu \frac{\partial A}{\partial \mathbf{X}_k}, \quad \text{subject to} \quad \frac{dV}{dt} = \frac{dV_0}{dt} \quad \text{and} \quad \frac{dA}{dt} = 0, \quad (1)$$

where  $\lambda$  and  $\mu$  are Lagrange multipliers for the constraints.

## 2.3 Calculation

After setting up the ODE equation, we would like to show how to calculate the volume  $V$  enclosed by the faceted surface, the area  $A$  of the faceted surface, the bending energy  $E$ , and the multipliers  $\lambda$  and  $\mu$ . The 1280-sided polyhedron we construct to approximate a sphere is partitioned into tetrahedrons. For each tetrahedron  $T_f$  (see figure 2(a)), its four vertices are the three vertices of the triangle  $t_f$  and the origin  $O$ . Face  $t_f$  represents the  $f$ -th triangle face on the membrane's surface. Then the total volume  $V = \sum_f V_f$ , where  $V_f = \frac{1}{6} \mathbf{X}_{f1} \cdot (\mathbf{X}_{f2} \times \mathbf{X}_{f3})$  is the volume of the tetrahedron  $T_f$ . Note that  $V_f$  is a signed quantity, and it is important that the vertices of each triangle are numbered in counterclockwise order when viewed from outside the surface. This makes  $V_f$  positive if the origin is within the region enclosed by the surface, but the formula is correct in any case. When the origin is outside of the enclosed region, some of the  $V_f$  are positive and some are negative and their sum is still the correct enclosed volume.

The total surface area  $A$  is the sum of areas of all surface triangles and can be written as  $A = \sum_f a_f$ , where  $a_f$  represents the area of the  $f$ -th triangle. We use Heron's formula  $a_f = \sqrt{s(s-a)(s-b)(s-c)}$ , where  $s = (a+b+c)/2$ , see figure 2(a).

Bending energy  $E$  is defined as  $E = \int H^2 da$  on a smooth surface, where  $H$  and  $a$  represent mean curvature and area, respectively. By first variation of area, we can interpret mean curvature  $H$  of a surface as the rate of change of its area, per unit area, when this surface is moving in the normal direction to itself [5]. Therefore, we would like to apply this definition on our discrete surface to define  $h_k$  as the mean curvature of the vertex  $k$ , see figure 2(b). Then,  $E = \int H^2 da \approx \sum_k h_k^2 a_k$  [3], where  $k$  refers to index of vertices. We now focus on defining surface area  $a_k$  and mean curvature  $h_k$  for the  $k$ -th vertex. Vertex  $k$ 's area is defined as the third of the sum of areas of faces around vertex  $k$ . In other words, vertex  $k$ 's area  $a_k = \sum_{i \in F(k)} \|\mathbf{A}(i)\| / 3$ , where  $F(k)$  is the set of indices of faces that meet at the  $k$ -th point and  $\mathbf{A}(i)$  is the surface normal of the  $i$ -th triangle. For the  $f$ -th face in figure 2(a),

$$\begin{aligned} \mathbf{A}(f) &= \frac{1}{2} (\mathbf{X}_{f1} - \mathbf{X}_{f3}) \times (\mathbf{X}_{f2} - \mathbf{X}_{f3}) \\ &= \frac{1}{2} (\mathbf{X}_{f1} \times \mathbf{X}_{f2} + \mathbf{X}_{f2} \times \mathbf{X}_{f3} + \mathbf{X}_{f3} \times \mathbf{X}_{f1}). \end{aligned}$$

Then  $h_k$  should be the gradient of vertex  $k$ 's area, divided by its area, when vertex  $k$  is moving in the direction that maximizes the rate of change of vertex  $k$ 's area. In other words,  $h_k = \|(da_k/d\mathbf{X}_k)\| \cdot a_k^{-1}$ . Then we are finally able to calculate  $E$ .

The lagrange multipliers  $\lambda$  and  $\mu$  are functions of time that ensure that the volume and area constraints in equation 1 are followed. To calculate  $\lambda$  and  $\mu$ , we write the two constraints as

$$\begin{aligned}
\frac{dV}{dt} &= \sum_k \frac{dV}{d\mathbf{X}_k} \cdot \frac{d\mathbf{X}_k}{dt} \\
&= \sum_k \frac{dV}{d\mathbf{X}_k} \cdot \left( -\frac{\partial E}{\partial \mathbf{X}_k} - \lambda \frac{\partial V}{\partial \mathbf{X}_k} - \mu \frac{\partial A}{\partial \mathbf{X}_k} \right) \\
&= -\sum_k \frac{dV}{d\mathbf{X}_k} \cdot \frac{\partial E}{\partial \mathbf{X}_k} - \lambda \sum_k \frac{dV}{d\mathbf{X}_k} \cdot \frac{\partial V}{\partial \mathbf{X}_k} - \mu \sum_k \frac{dV}{d\mathbf{X}_k} \cdot \frac{\partial A}{\partial \mathbf{X}_k} \\
&= \frac{dV_0}{dt},
\end{aligned}$$

$$\begin{aligned}
\frac{dA}{dt} &= \sum_k \frac{dA}{d\mathbf{X}_k} \cdot \frac{d\mathbf{X}_k}{dt} \\
&= \sum_k \frac{dA}{d\mathbf{X}_k} \cdot \left( -\frac{\partial E}{\partial \mathbf{X}_k} - \lambda \frac{\partial V}{\partial \mathbf{X}_k} - \mu \frac{\partial A}{\partial \mathbf{X}_k} \right) \\
&= -\sum_k \frac{dA}{d\mathbf{X}_k} \cdot \frac{\partial E}{\partial \mathbf{X}_k} - \lambda \sum_k \frac{dA}{d\mathbf{X}_k} \cdot \frac{\partial V}{\partial \mathbf{X}_k} - \mu \sum_k \frac{dA}{d\mathbf{X}_k} \cdot \frac{\partial A}{\partial \mathbf{X}_k} \\
&= 0.
\end{aligned}$$

This gives the system of equations

$$\begin{bmatrix} \sum_k \frac{dV}{d\mathbf{X}_k} \cdot \frac{\partial V}{\partial \mathbf{X}_k} & \sum_k \frac{dV}{d\mathbf{X}_k} \cdot \frac{\partial A}{\partial \mathbf{X}_k} \\ \sum_k \frac{dA}{d\mathbf{X}_k} \cdot \frac{\partial V}{\partial \mathbf{X}_k} & \sum_k \frac{dA}{d\mathbf{X}_k} \cdot \frac{\partial A}{\partial \mathbf{X}_k} \end{bmatrix} \cdot \begin{bmatrix} \lambda \\ \mu \end{bmatrix} = \begin{bmatrix} -\frac{dV_0}{dt} - \sum_k \frac{dV}{d\mathbf{X}_k} \cdot \frac{\partial E}{\partial \mathbf{X}_k} \\ -\sum_k \frac{dA}{d\mathbf{X}_k} \cdot \frac{\partial E}{\partial \mathbf{X}_k} \end{bmatrix}.$$

## 2.4 Refinement

Since we are using a discrete method to study a continuous problem, it becomes important to keep the surface smooth. Smoothness is important to our model, not only because irregular surface can produce errors, but also because the cell membrane has shear resistance. Therefore, to restrict changes in the shape of the triangular facets of our model, we impose a penalty to our ODE equation. Instead of solely minimizing  $E$ , we minimize  $E + \alpha \sum_{e=1}^{\# \text{ of edges}} l_e^2$ , where  $l_e$  represents the length of the  $i$ -th edge and  $\alpha$  is the penalty's weight. The weight  $\alpha$  is chosen to balance  $\sum_e l_e^2$  and  $E$ . Suppose that each triangle is equilateral, then  $\sum_e l_e^2 \approx 4a_f \cdot n_e / \sqrt{3} = 4a_f \cdot 3n_t / 2\sqrt{3} \approx 2\sqrt{3}A$ , where  $n_e$  is the number of edges and  $n_t$  is the number of faces. Then  $\alpha$  should be  $1/(2\sqrt{3})$ . By minimizing  $E + \sum_e l_e^2 / 2\sqrt{3}$ , we limit the possibility that one edge will get extremely long compared to other edges, and therefore limit the possibility that triangles will get deformed. Then our ODE equation 1 becomes

$$\frac{d\mathbf{X}_k}{dt} = -\frac{\partial E}{\partial \mathbf{X}_k} - \frac{1}{2\sqrt{3}} \frac{\partial (\sum_e l_e^2)}{\partial \mathbf{X}_k} - \lambda \frac{\partial V}{\partial \mathbf{X}_k} - \mu \frac{\partial A}{\partial \mathbf{X}_k}. \quad (2)$$

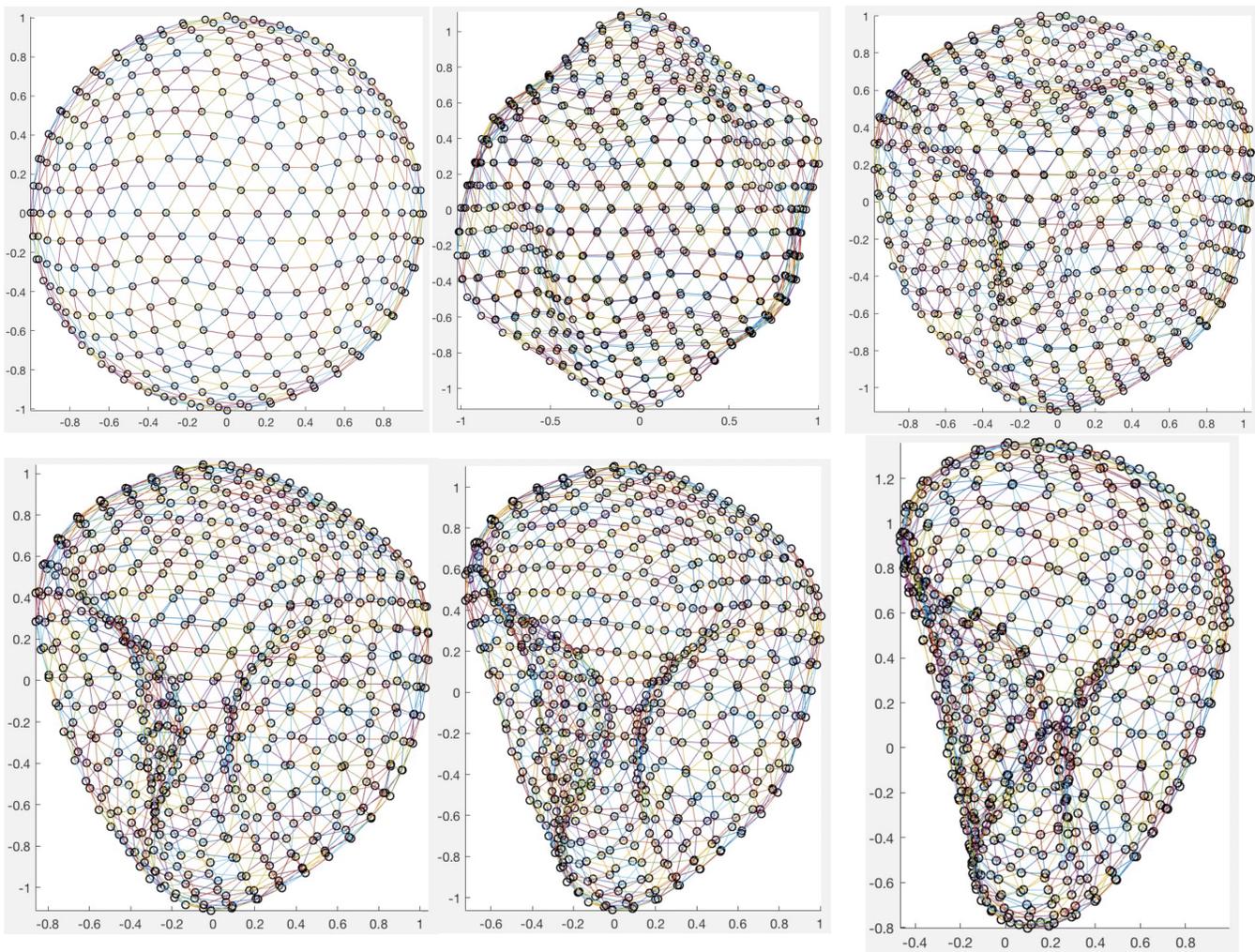
## 2.5 Solving ODEs

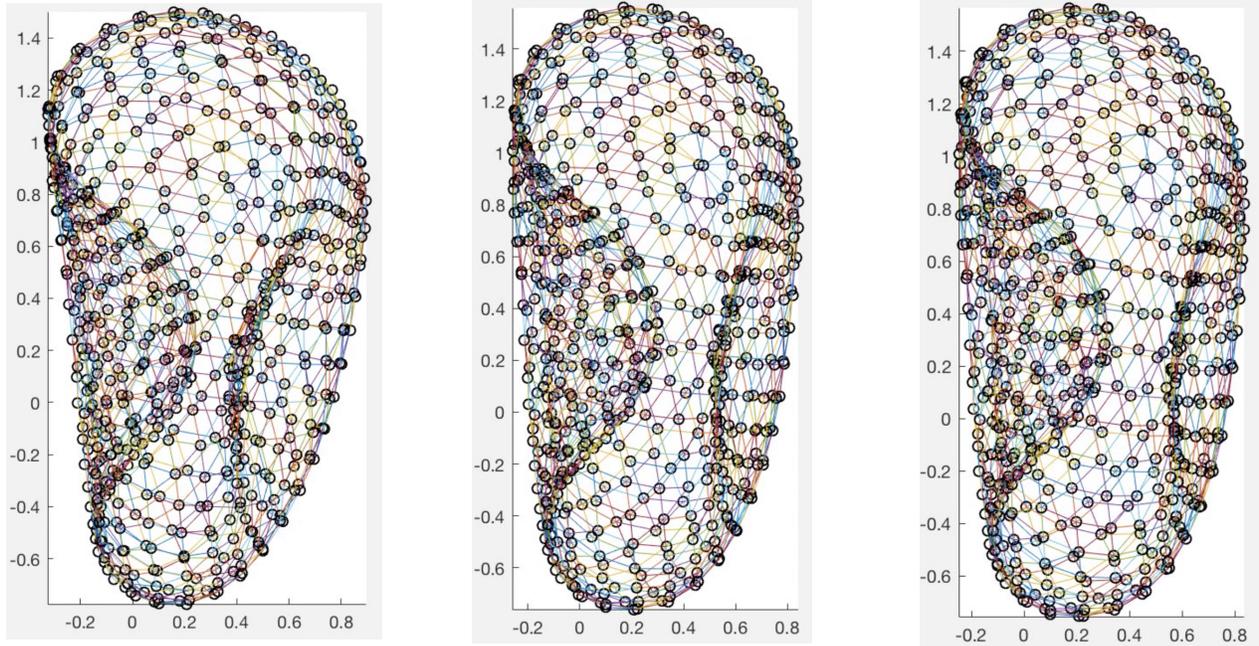
We use Euler method to solve equation 2:

$$\mathbf{X}_k^{(n+1)} = \mathbf{X}_k^{(n)} + \Delta t \cdot \frac{d\mathbf{X}_k^{(n)}}{dt},$$

where  $\Delta t$  is the time step, and  $\mathbf{X}_k^{(n)}$  is the coordinate vector of the  $k$ -th point at time  $t = n \cdot \Delta t$ . We apply equation 2 to calculate  $d\mathbf{X}_k^{(n)}/dt$ . The parameter  $\Delta t$  is chosen small enough to avoid numerical instability and to ensure that both volume and area constraints are followed. We use  $\Delta t = 10^{-5}$  in our model.

## 3 Results





Figures 3(a)-(i)

*These nine figures are viewed from the side.*

Figures 3(a)-(i) show results at time  $t = 0, t = 1.5, t = 4.5, t = 7.5, t = 11.5, t = 15, t = 18, t = 20.5,$  and  $t = 22$ , respectively. We can see that the shape is changing gradually from a perfect sphere to biconcave. It is important to note that the symmetry of the initial shape is broken in the process of finding a direction to bend inward. Also, our refinement method is effective in keeping the surface smooth at every time step. We can take a closer look at the final stage by looking at figures 4(a)-(c). From figure 4(a), we can see that the surface is perfectly round viewing from the top, which is exactly how red blood cell looks from the same point of view. Viewing from the side, as shown in figures 4(b)-(c), the upper and bottom surfaces have bent inward as expected.

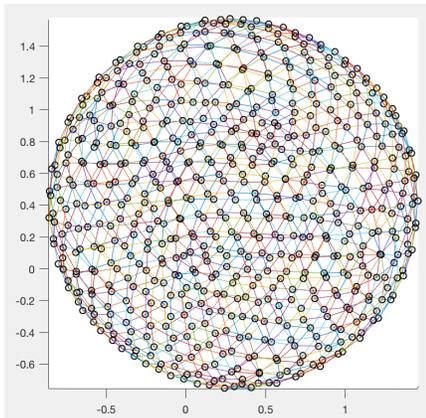


Figure 4(a)

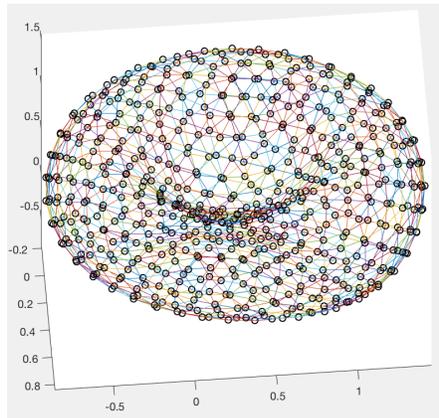


Figure 4(b)

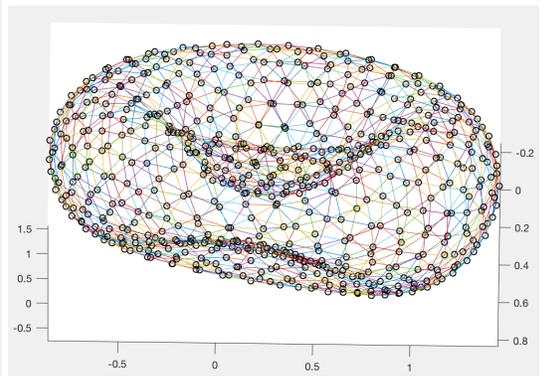


Figure 4(c)

*Figure 4(a) is viewed from the top. Figures 4(b)-(c) are viewed from the side.*

Also, the model performs well in following constraints in equations 1 and 2. We plot the total surface area  $A$  against time  $t$ , see figure 5(a). The plot shows that  $A$  has not changed much in the time range  $[0, 22]$ , so the constraint on area  $dA/dt = 0$  is followed. We also plot the total volume  $V$  against time  $t$ , with the  $V_0$  curve defined in 1, see figure 5(b). Although two curves

are plotted, they overlap each other so we can only see one curve. This shows that  $V$  is changing with  $V_0$  curve perfectly in the time range  $[0, 22]$ , so the constraint on volume  $dV/dt = dV_0/dt$  is followed. Figure 5(c) shows the distribution of side length ratios of triangles on the surface. Here, we take each triangle and calculate the ratio of its maximum side length to its minimum side length. The concentration of ratios around 1.0 shows that most triangles on the surface are approximately equilateral; thus, deformations of triangles are restricted.

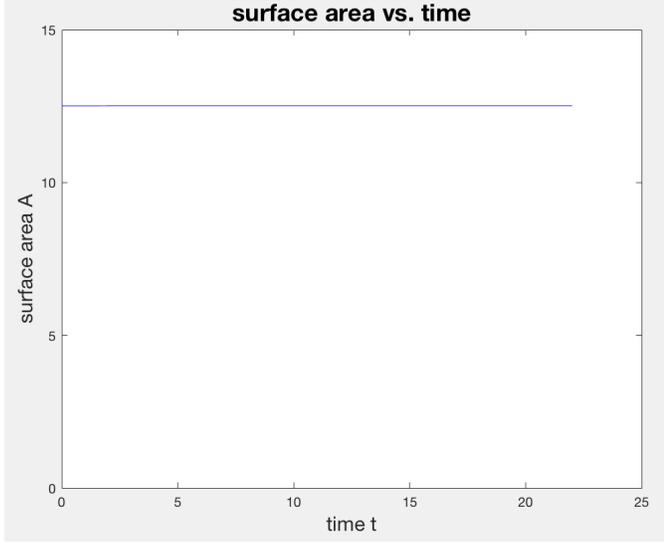


Figure 5(a)

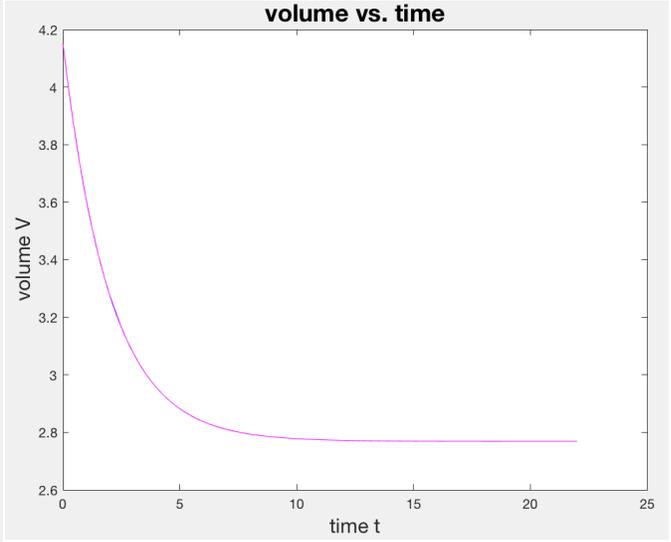


Figure 5(b)

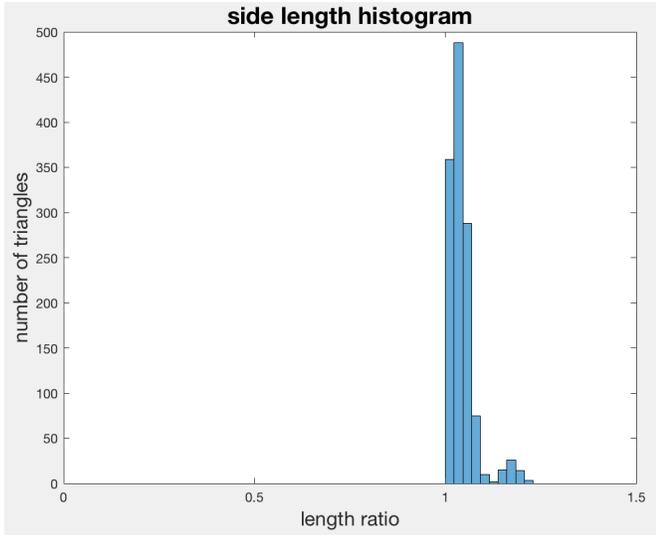


Figure 5(c)

Figure 5(a) shows the change of total surface area  $A$  over time  $t$ . Figure 5(b) shows the  $V_0$  curve (pink line) and the change of total volume  $V$  over time  $t$  (blue line). Figure 5(c) shows the histogram of number of sides against side length ratio.

## 4 Conclusion

Using our discrete model, we successfully generate a biconcave shape that matches our expectation. Although there have been previous studies on simulating the shape of red blood cell, our model

have advantages in simplicity and can be easily applied to other shapes to obtain final phases that minimize the surface energy. The refinement method used in this model also has practical values. By equipping with the refinement tool, a continuous surface can be represented by discrete points which will maintain the smoothness of the surface in any course of movement.

## 5 Acknowledgement

I would like to show my gratitude to my mentor Professor Charles S. Peskin for his great guidance and encouragement. It is his wisdom that shows me the light through difficulties. I would also like to present my special thanks to Dr. Pejman Sanaei and Mr. Jason Kaye for their patient assistance and critiques of the research project. I would also like to thank Professors Miranda Holmes-Cerfon and Aleksandar Donev for leading and supporting the undergraduate research program. Finally, I would like to thank NYU Math Department for funding this research.

## References

- [1] Reece, J. B., Urry, L. A., Cain, M. L. 1., Wasserman, S. A., Minorsky, P. V., Jackson, R., and Campbell, N. A. (2014). *Campbell biology*. Tenth edition. Boston: Pearson.
- [2] Charles S. Peskin. Matlab codes that generate a sphere.
- [3] Charles S. Peskin. Notes on defining bending energy on a discrete surface.
- [4] Canham, P.B. (1970). The minimum energy of bending as a possible explanation of the biconcave shape of the human red blood cell. *Journal of Theoretical Biology*, 26(1), 61-81. doi:10.1016/s0022-5193(70)80032-7.
- [5] Sullivan, J.M. (2006). Curvatures of Smooth and Discrete Surfaces. *Discrete Differential Geometry Oberwolfach Seminars*, 175-188. doi:10.1007/978-3-7643-8621-4\_9.
- [6] Joseph, F. Hoffman (2016). Biconcave shape of human red-blood-cell ghosts relies on density differences between the rim and dimple of the ghost's plasma membrane. *Proceedings of the National Academy of Sciences*, 113(51). doi:10.1073/pnas.1615452113.