SPEKTRA: Jurnal Fisika dan Aplikasinya
Volume 4, Issue 2, August 2019
Homepage: doi.org/10.21009/SPEKTRA

Check for updates

DOI: doi.org/10.21009/SPEKTRA.042.01

THE SPRING VARIATION IN TWO DIMENSIONAL MODELING OF RED BLOOD CELL DEFORMABILITY BASED ON GRANULAR

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Received: 28 October 2018
Revised: 30 May 2019
Accepted: 13 August 2019
Published: 31 August 2019

SPEKTRA: Jurnal Fisika dan Aplikasinya
p-ISSN: 2541-3384
e-ISSN: 2541-3392

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ABSTRACT

The red blood cell membrane has a complex structure and high deformability. Simulation of that complex red blood cell membrane can simpler use granular-based modeling. Red blood cell is modeled consisting of 50 granular particles connected by springs. An *i*-particle is connected with two of its first nearest particles which are *i+1*-particle and *i-1*-particle and with two of its second nearest particles which are *i+2*-particle and *i-2*-particle. Each particle has a spring force and forces from internal hydrostatic pressure. Spring force is a product of the spring constant and change of spring length of two particles. Meanwhile, forces of internal hydrostatic pressure is a product of particle diameter and the difference in the outside and inside pressure of red blood cell membrane. In this research, there is variation in spring length and spring constant that can model deformability of three shapes of red blood cell; those are biconcave, ellipse, and circle. This variation in spring length and spring constant for every cell shape in this modeling can also use for other initial cell shapes, which shows that initial cell shapes deform into shape according to variation used.

Keywords: deformability, granular, internal hydrostatic pressure, red blood cell, spring

INTRODUCTION

Under the reasonable condition, red blood cell has a biconcave discoid shape. This biconcave shape can turn into an ellipse and circle because of the shear flow without membrane distension [1]. The biconcave shape has surface-area-to-volume (S/V) ratio greater than ellipse and circle shape, which gives a large deformation ability that is a large reversible elastic transformation to another shape. The decrease in S/V value causes a decrease in red blood cell deformability.

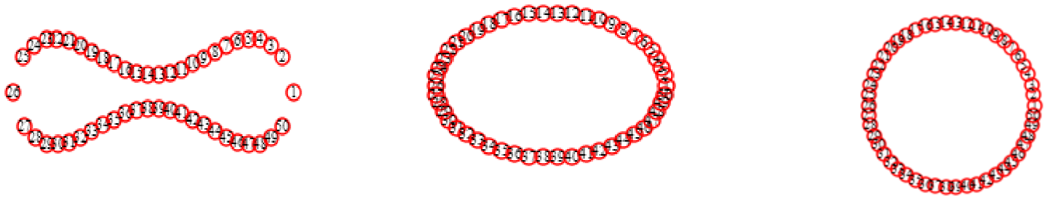
The deformability of red blood cell is defined as the ability of red blood cell to change its shape when an external force is given and returns to its initial shape when the external force removed. Red blood cell must resist large deformation when flowing in blood vessels which have smaller size than its diameter. Changes in the structure of red blood cell membrane affect its deformability. The changes of deformability are also related to the pathogenesis of various red blood cell abnormalities, such as elliptocytosis, spherocytosis, sickle-cell anemia, and hemolytic anemia [2,3]. Therefore, the measurement of red blood cell deformability is essential in understanding the diseases related to red blood cell.

That is the background to do this modeling of red blood cell deformability. The model that has been extensively used and simple to simulate elastic objects in a molecular scale is a spring granular model [4]. Previous modeling of red blood cell deformability based on granular which consisting of stretching and bending springs has not been able to show the deformability of red blood cell that undergoes changes in its shape and surface area and returns to its initial shape and surface area for various spring lengths and spring constants [5]. In this research, the red blood cell membrane is modeled consisting of granular particles connected by a spring and has an internal membrane pressure called internal hydrostatic pressure. When red blood cell changes its shape, the internal hydrostatic pressure also changes. So in order the shape return to the initial shape, the internal hydrostatic pressure must also return to its initial value. In this research also analyzed variation in spring length and constant that can model deformability of three shapes of red blood cell, those are biconcave, ellipse, and circle.

MODELING METHODOLOGY

Geometry of Model

In this research, modeled three shapes of red blood cell membrane those are biconcave, ellipse, and circle. The membrane of red blood cell for each shape modeled consisting of 50 granular particles connected by spring as in FIGURE 1.



(a) (b) (c)

FIGURE 1. Shapes of the red blood cell model. (a) Biconcave (b) Ellipse (c) Circle.

The initial position of each those granular particle for biconcave cell shape in Cartesian coordinate determined as follows.

$$y_i = y_0 \pm D\sqrt{1-\frac{4x_i^2}{D^2}}\left(a_0 + \frac{a_1 x_i^2}{D^2} + \frac{a_2 x_i^4}{D^4}\right), \qquad x_i \in \left[-\frac{D}{2}, \frac{D}{2}\right] \qquad (1)$$

x_i and y_i are position of i-particle on the x and y axis, D is diameter of cell, a_0 = 0.05179025, a_1 = 2.002558, and a_2 = -4.491048 [6].

The initial position of each granular particle for ellipse cell shape determined as follows.

$$x_i = x_0 + R_x \cos(\theta_i) \qquad (2)$$

$$y_i = y_0 + R_y \cos(\theta_i) \qquad (3)$$

$$\theta_i = (i-1)\frac{2\pi}{N} \qquad (4)$$

R_x and R_y are the horizontal and vertical radius, and N is a number of granular particles. Meanwhile, the initial position of each granular particle for circle cell shape determined as the ellipse cell shape with $R_x = R_y = R$ which is radius of the cell.

Simulation

In this model, each particle is connected with four other particles by a spring. An i-particle is connected with two of its first nearest particles which are $i+1$-particle and $i-1$-particle by a spring with spring constant k_s and with two of its second nearest particles which are $i+2$-particle and $i-2$-particle by a spring with a spring constant, k_b. The interactions between particles shown in FIGURE 2.

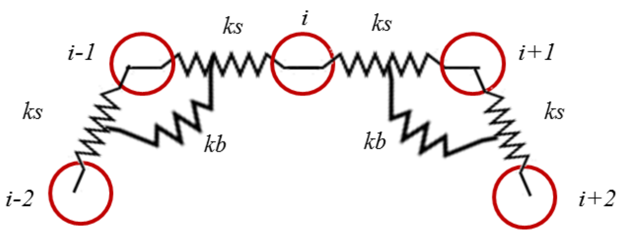


FIGURE 2. Interactions between particles in the red blood cell model.

The initial velocity of each particle is zero. Under the normal or initial condition, the pressure inside the red blood cell membrane is the same as the pressure outside membrane [7]. In this model, the pressure outside membrane is constant.

The Spring force of each particle with its first nearest particles defined as

$$\vec{F}_{s_{ij}} = -k_s(r_{ij} - l_{ij})\hat{r}_{ij}, \qquad (5)$$

with r_{ij} is the distance between two particles i and j and l_{ij} is normal length of the spring that connected two particles i and j. Meanwhile, the spring force of each particle with its second nearest particles defined as

$$\vec{F}_{\tau_{ij}} = \frac{1}{r_{ij}^2}(\vec{\tau}_{ij} \times \vec{r}_{ij}) \tag{6}$$

$$\vec{\tau}_{ij} = -k_b(\vec{\theta}_{ij} - \vec{\theta}_0) \tag{7}$$

with r_{ij} is the distance of two particles i and j, θ_{ij} is an angle between two particles i and j, and θ_0 is the normal angle of the spring that connected two particles i and j.

The red blood cell membrane also has pressure inside the membrane called internal hydrostatic pressure. When the value of internal hydrostatic pressure and pressure outside membrane is different, thus cell membrane will have the force of the internal hydrostatic pressure which defined as

$$F_{P_i} = (P_0 - P_I)D_i, \tag{8}$$

with P_0 is pressure outside the cell membrane, P_I is pressure inside the cell membrane, and D_i is a diameter of i-particle. The direction of F_P force is in line with the normal vector of the membrane surface.

The three forces for each particle are then summed as follows.

$$\vec{F}_{total_i} = \sum_{\substack{j=1 \\ j\neq i}}^{N} \vec{F}_{s_{ij}} + \sum_{\substack{j=1 \\ j\neq i}}^{N} \vec{F}_{\tau_{ij}} + \vec{F}_{P_i} \tag{9}$$

Each particle which connected by spring also has potential energy. The total potential energy of a shape of the cell membrane (U_{total}) is a summation of potential energy from each particle (U_i) determined as follows

$$U_{total} = \sum_{i=1}^{N} U_i \tag{10}$$

$$U_i = \sum_{\substack{j=1 \\ j\neq i}}^{N} \frac{1}{2} k\left(r_{ij} - l_{ij}\right)^2 \tag{11}$$

with k is spring constant both k_s and k_b. When the total potential energy of a shape to the minimum, indicates that this shape is an equilibrium state [8]. Therefore, the calculation of total potential energy can be used to determine the equilibrium shape of the deformed cell shape.

Value of acceleration, velocity, and position of the new particles are determined using Newton's II Law and Euler method as follows.

$$\vec{a}_i = \frac{1}{m_i} \sum_{\substack{j=1 \\ j\neq i}}^{N} \vec{F}_{s_{ij}} \tag{12}$$

$$\vec{v}_i(t + \Delta t) = \vec{v}_i(t) + \vec{a}_i(t)\Delta t \tag{13}$$

$$\vec{r}_i(t+\Delta t)=\vec{r}_i(t)+\vec{v}_i(t)\Delta t \tag{14}$$

m_i is mass of i-particle.

Value of angular acceleration, angular velocity, and the angle between particles of the new particles are also determined using Newton's II Law and Euler method as follows.

$$\vec{\alpha}_i=\frac{1}{I_i}\vec{\tau}_i \tag{15}$$

$$\vec{\omega}_i(t+\Delta t)=\vec{\omega}_i(t)+\vec{\alpha}_i(t)\Delta t \tag{16}$$

$$\vec{\theta}_i(t+\Delta t)=\vec{\theta}_i(t)+\vec{\omega}_i(t)\Delta t \tag{17}$$

I_i is the moment of inertia of i-particle.

The new membrane surface area (A') is also calculated. When red blood cell membrane changes its shape, its internal hydrostatic pressure (P_I) also changes. Thus, the product of internal pressure and membrane surface area must have a constant value in order red blood cell undergoing deformation can return to its initial shape, which is equilibrium shape. The new internal hydrostatic pressure defined as

$$P_I^{'}=\frac{P_I A}{A^{'}} \tag{18}$$

A is an initial membrane volume and A' is a new membrane volume when the shape changes. Thus, the difference in new internal and external pressure can be calculated. This simulation is carried out with a time interval (Δt) of 10^{-3}.

Variation of Spring Length and Spring Constant

Variation in spring length and spring constant carried out for biconcave cell shape determined in TABLE 1 below.

TABLE 1. Variation of spring length and constant for biconcave shape.

Variation	Spring Length	Spring Constant
1	l_1, $l_{(N/2)+1}=0.9l_0$, $l_{other}=l_0$	$k_s=5$, $k_b=3$
2	$l_i=1.03l_0$	$k_s=5$, $k_b=3$

Variation in spring length and spring constant carried out for ellipse cell shape determined in TABLE 2 below.

TABLE 2. Variation of spring length and constant for ellipse shape.

Variation	Spring Length	Spring Constant
1	l_1, $l_{(N/2)+1}=0.7l_0$, $l_{other}=l_0$	$k_s=5$, $k_b=3$
2	$l_i=0.1l_0\sin(\theta_i)$	$k_s=5$, $k_b=3$

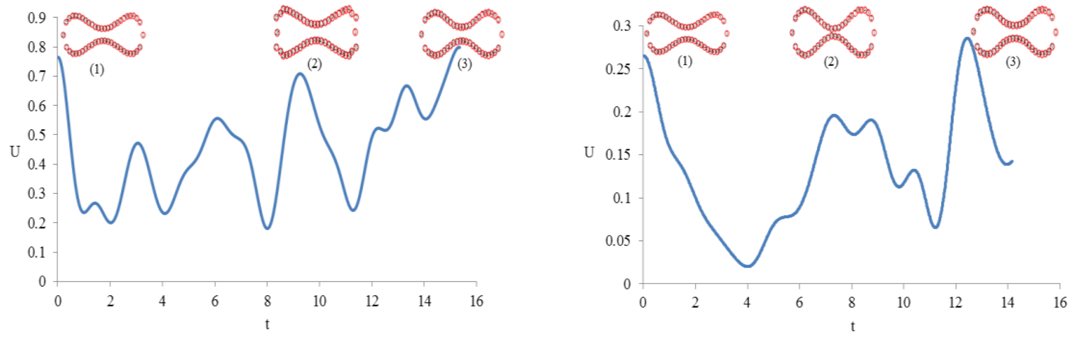
Meanwhile, variation in spring length and spring constant carried out for circle cell shape determined in TABLE 3 below.

TABLE 3. Variation of spring length and constant for the circle shape.

Variation	Spring Length	Spring Constant
1	l_1, $l_{(N+2)/4}$, $l_{(N/2)+1}$, $l_{(3(N+2)/8)-1}$ = 0.6l_0, l_{other} = l_0	k_s = 6, k_b = 3
2	$l_{i,even}$ = 0.2l_0, $l_{i,odd}$ = 0.5l_0	k_s = 6, k_b = 3

RESULTS AND DISCUSSIONS

The simulation results with spring length and spring constant values in TABLE 1 for the initial shape of the biconcave cell are shown in FIGURE 3 below.

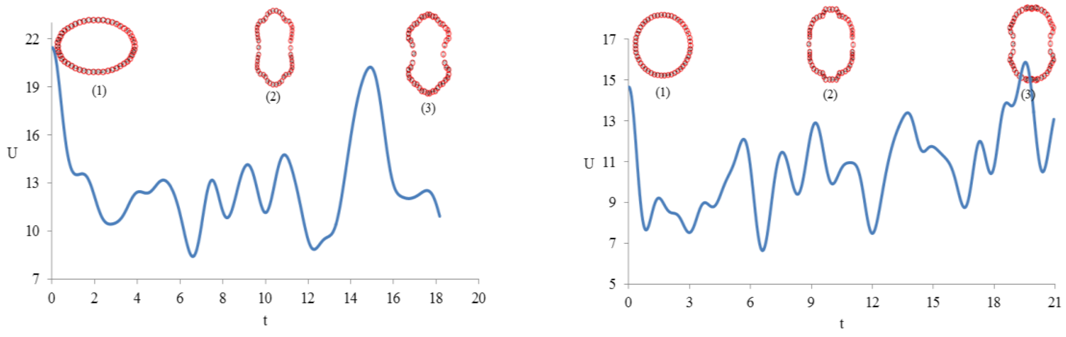


(a) (b)

FIGURE 3. Graph of potential energy vs time for deformation of biconcave cell. (a) First variation: (1) t = 0 (2) t = 10.221 (3) t = 15.254. (b) Second variation: (1) t = 0 (2) t = 7.564 (3) t = 14.033.

The pictures in those graphs show the biconcave cell that undergoes deformation and returns to its initial shape and surface area several times. The first variation in spring length and spring constant shows that biconcave cell changes largely when its spring length only slightly changes from its normal length. The second variation in spring length and spring constant shows expansion of the surface area because the spring length is greater than its normal length.

When the initial shape is an ellipse, and the first variation in spring length and constant of the biconcave cell are carried out, and when initial shape is a circle and the second variation in spring length and constant of biconcave cell are carried out, the simulation results are as follows.

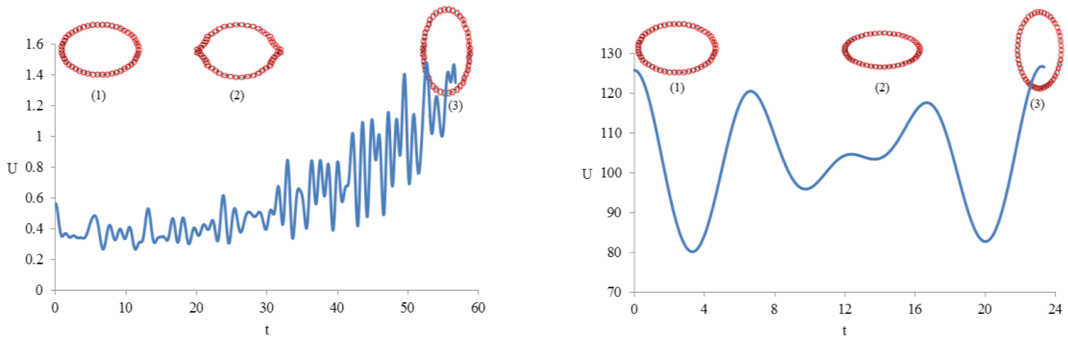


(a) (b)

FIGURE 4. (a) Deformation of ellipse cell becomes biconcave: (1) t = 0 (2) t = 10.35 (3) t = 18.064. (b) Deformation of circle cell becomes biconcave: (1) t = 0 (2) t = 10.847 (3) t = 20.836.

The pictures in those graphs show that for any initial shape when used a variation as in TABLE 1, the shape will adjust or deform to become biconcave. The surface area of the biconcave shape resulted is the same as the surface area of its initial shape. Thus, the variation of spring length and spring constant in TABLE 1 can model the deformability of biconcave cell shape.

The simulation results with spring length and spring constant values in TABLE 2 for the initial shape of the ellipse cell are shown in FIGURE 5 below.

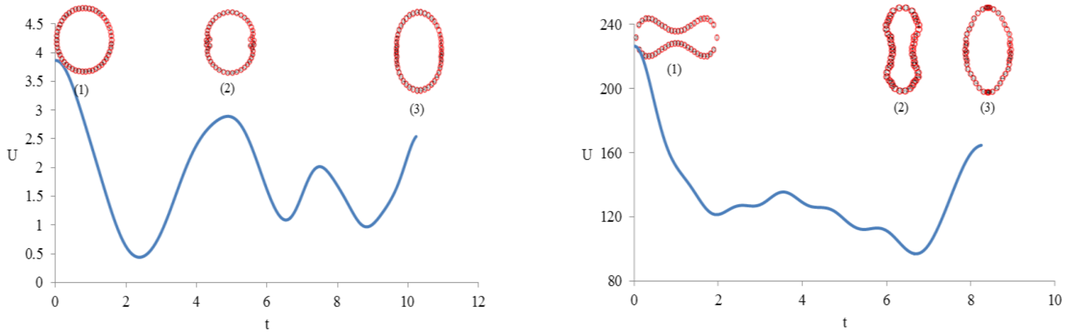


(a) (b)

FIGURE 5. Graph of potential energy vs time for deformation of ellipse cell. (a) First variation: (1) t = 0 (2) t = 25.155 (3) t = 56.639. (b) Second variation: (1) t = 0 (2) t = 14.161 (3) t = 23.24.

The pictures in those graphs show the ellipse cell that undergoes deformation and returns to its initial shape and surface area several times. In the second variation of spring length and spring constant, shows compression of the surface area because the spring length is smaller than its normal length. If compared to the biconcave shape, the time to return to the initial shape of ellipse shape is longer.

When the initial shape is a circle and the first variation in spring length and constant of ellipse cell are carried out and when the initial shape is biconcave and the second variation in spring length and constant of ellipse cell are carried out, the simulation results are as follows.

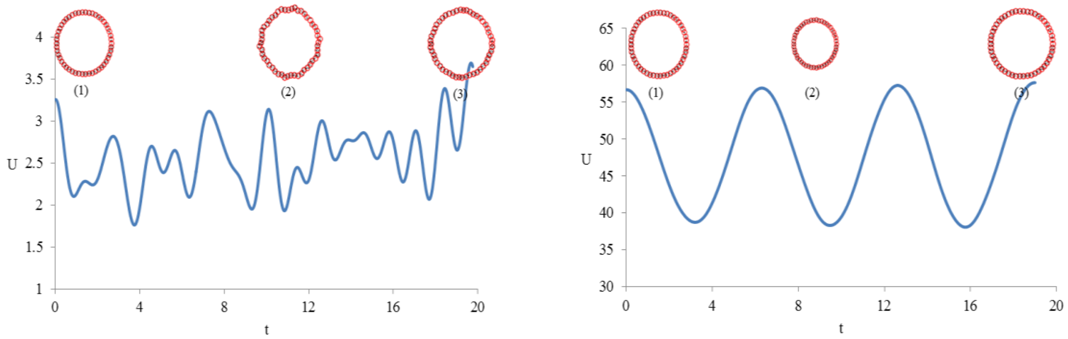


(a) (b)

FIGURE 6. (a) Deformation of circle cell becomes ellipse: (1) t = 0 (2) t = 5.735 (3) t = 10.134. (b) Deformation of biconcave cell becomes ellipse: (1) t = 0 (2) t = 6.775 (3) t = 8.157.

The pictures in those graphs show that for any initial shape when used a variation as in TABLE 2, the shape will adjust or deform to become elliptical. The surface area of the ellipse shape resulted is the same as the surface area of its initial shape. Thus, the variation of spring length and spring constant in TABLE 2 can model the deformability of ellipse cell shape.

Meanwhile, the simulation results with spring length and spring constant values in TABLE 3 for the initial shape of circle cell are shown in FIGURE 7 below.

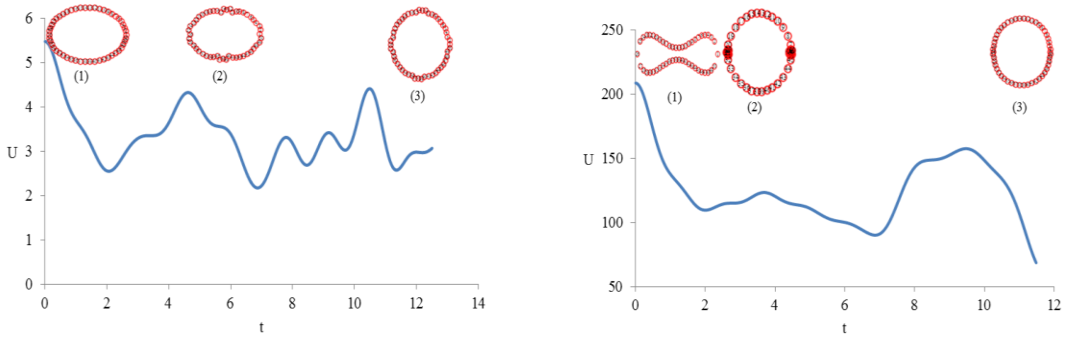


(a) (b)

FIGURE 7. Graph of potential energy vs time for deformation of circle cell. (a) First variation: (1) t = 0 (2) t = 11.034 (3) t = 19.659. (b) Second variation: (1) t = 0 (2) t = 9.64 (3) t = 18.932.

The pictures in those graphs show the circled cell that undergoes deformation and returns to its initial shape and surface area several times. In the second variation of spring length and spring constant, shows compression of the surface area because the spring length is smaller than its normal length. The circle shape only undergoes small changes compared to biconcave and ellipse shape.

When the initial shape is an ellipse and the first variation in spring length and constant of circle cell are carried out and when the initial shape is biconcave and the second variation in spring length and constant of circle cell are carried out, the simulation results are as follows.



(a) (b)

FIGURE 8. (a) Deformation of ellipse cell becomes circle: (1) t = 0 (2) t = 5.911 (3) t = 12.402. (b) Deformation of biconcave cell becomes circle: (1) t = 0 (2) t = 3.361 (3) t = 11.382.

The pictures in those graphs show that for any initial shape when used a variation as in TABLE 3, the shape will adjust or deform to become a circle. The surface area of circle shape resulted is the same as the surface area of its initial shape. Thus, the variation of spring length and spring constant in TABLE 3 can model the deformability of circle cell shape.

CONCLUSIONS

Modeling of red blood cell membrane using spring-granular model and the presence of internal hydrostatic pressure in the membrane in this research has been able to show the deformability of red blood cell that can undergo changes in shape and surface area that return to its initial shape and surface area.

In this research, variation in the values of spring length and spring constant has been obtained which can model the deformability of three shapes of the red blood cell. Variation of spring length and constant of biconcave shape are shown in TABLE 1. When the initial cell shape is not biconcave, it is ellipse and circle, using these variations the initial shape deformed to become biconcave. Variation of spring length and constant of ellipse shape are shown in TABLE 2. When the initial cell shape is not an ellipse, it is circular and biconcave, using these variations the initial shape deformed to become elliptical. Meanwhile, variation of spring length and constant in circle shape are shown in TABLE 3. When the initial cell shape doesn't circle, it is an ellipse and biconcave, using these variations the initial shape deformed to become a circle. Thus, for any initial shape when the variation of spring length and spring constant in this research used, the initial cell shape will deform into the shape according to the variables used.

The graphs of potential energy with time indicate that the final shapes have not yet shown the minimum potential energy which is the most equilibrium conditions. Therefore, fluid attenuation is needed so that the simulation stops at the most equilibrium shape. Future research from this modeling can also be done when the cell passes through smaller gaps, which represent blood vessels.

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