Design for Detecting Red Blood Cell Deformation at Different Flow Velocities in Blood Vessel

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Abstract. Molecular communication (MC) holds considerable promise as the next generation of design for drug delivery that allows for targeted therapy with minimal toxicity. Most current studies on flow-based MC driven drug delivery application consider a Newtonian fluid and laminar flow. However, blood is a complex biological fluid composed of deformable cells especially red blood cells, proteins, platelets, and plasma. For blood flow in capillaries, arterioles and venules, the particulate nature of the blood needs to be considered in the delivery process. The ability to change shape is essential for the proper functioning of red blood cells in microvessels. The different shapes of red blood cells have a great impact on the performance characteristics of whole blood (blood and plasma). Changes in the properties and shape of RBC substances are often associated with different blood diseases and diseases, such as sickle cell anemia, diabetes, and malaria. Based on the state of the red blood cells in the microtubules at different flow rates, this paper proposes a design for detecting the ability of the cells to deform. Based on the difference in the concentration of the nanoparticles at the receiving end at different flow rates, the ability of the red blood cells to deform is determined, and the blood state is determined. Further, the related blood diseases can be initially predicted.

Keywords: Flow-based molecular communications · Blood vessel · Red blood cell deformation

1 Introduction

With the development of nanoparticle manufacturing technology, research related to the use of molecular communication to monitor human health has continued to develop [1]. Early detection of changes in health can significantly improve treatment outcomes, improve quality of life, and increase life expectancy [2]. Plasma and red blood cells (RBC) are the two main components of human blood [3]. A healthy RBC has a biconcave shape when it is not subject to any external force, with a diameter of about 8.0 μm and a thickness of about 2.0 μm [4].

Y. Chen et al. (Eds.): BICT 2020, LNICST 329, pp. 226–238, 2020.
https://doi.org/10.1007/978-3-030-57115-3_20

At present, there are many methods for measuring the deformability of red blood cells, which can be basically divided into two categories [5]: the first one uses the red blood cell suspension to indirectly estimate and compare the average deformability of the red blood cell population [6]. The second type is the use of a single red blood cell to determine its deformability and mechanical characteristics of the cell membrane.

In this article, we propose a molecular communication system designed to quickly detect the deformability of red blood cells in blood vessels. The system is based on nanoparticles released in the bloodstream and then measures the concentration of the nanoparticles at the receiving end. Measurement statistics of the absorption process can infer the deformation of the cells without resorting to slower and invasive blood tests, as well as in-vitro tests with large errors. The system can be implemented by means of a device capable of releasing the molecules in the container and monitoring the downstream absorption of these molecules [7]. Based on the statistics of the received signals, the health status can be distinguished from the pathological status.

The structure of this paper is as follows: In the second part, introduce the mathematical model established by the system. In the third part, introduced the design of the system, which is implemented on a reference architecture capable of performing deformation detection. Simulation results are presented in Sect. 4, and conclude in Sect. 5.

2 Methods

2.1 Blood Environment

The detection environment is in the blood. In previous studies [8], molecular transfer in blood vessels was generally considered as molecular diffusion, and blood was considered as Newtonian fluid. However, under certain conditions (small blood vessels and low shear rates), the Carson velocity distribution model can be used to simulate blood flow, which takes into account the effect of blood cells suspended in Newtonian fluid, that is, the plasma composition. The blood is assumed to be axially symmetric, laminar, stable, and non-Newtonian incompressible mucus (blood) in the shape of a bell-shaped bellow that flows along the axis (z) along a circular artery with a mildly narrow bell shape [9]. Therefore, the plasma composition is Laminar flow is simulated, where the velocity of the central layer of the fluid is the highest and the velocity of the outer layer is minimized. This is due to the friction with the blood vessel wall, which is related to the opposite resistance to adjacent layers [7].

Under the assumption, the longitudinal shape of the container can be thought of as a set of concentric cylinders. The space between concentric cylinders is a layer [10]. The laminar flow consists of fluid particles moving in a straight line along the longitudinal direction of each layer. The velocity distribution of this laminar flow is shown as a parabola. Poiseuille equation modelling:

$$\rho\frac{\partial v}{\partial t} + \rho(v.\nabla)u = -\nabla p + \nabla \cdot \tau\nabla \cdot v = 0 \tag{1}$$

v and p represent blood flow velocity and pressure, ρ is blood density, and τ is super stress tensor. The system shuts down with appropriate initial and boundary conditions. Among them, according to Bernoulli's equation:

$$P + \frac{1}{2}\rho v^2 + \rho gh = constant \tag{2}$$

The parameters in the formula: P is pressure, ρ is density, v is flow velocity, h is height, and g is gravity acceleration. The product of the average longitudinal velocity v over the same cross-sectional area is constant and equal to the volume flow rate Q through the pipe. The average flow rate across a cross-sectional area is the same when the distance from the center of the blood vessel is equal, and it is proportional to the flow through the blood vessel [7]:

$$\bar{v} = \frac{Q}{A} \tag{3}$$

Area A is the cross-sectional area of the hypothetical blood flow $A = \pi R^2$.

As simulated by the Poiseuille equation, this condition corresponds to a decrease in flow velocity, and the flow velocity at a distance r from the center of the blood vessel is

$$v(r) = \frac{1}{4\eta}\frac{\Delta P}{L}\left(R^2 - r^2\right) \tag{4}$$

2.2 Red Blood Cells (RBCs)

To match the characteristics of red blood cells in practice, the red blood cells in the blood are modelled using the stress-free shape of an elastic spring network. The stress-free shape corresponds to a spherical shape with a reduced volume of 0.96. Recent simulation studies [6,11] have shown that a stress-free shape close to a spherical shape best reproduces the experimental results [1].

When the shear modulus is constant, the flow rate when the final shape of the red blood cells reaches the steady state is proportional to the initial flow rate and the cell relaxation time [12]. (Here the flow rate is characterized by shear rate):

$$\dot{\gamma}^* = \bar{\dot{\gamma}}\frac{\eta_o D_r}{\mu_r} = \bar{\dot{\gamma}}\tau_\mu \tag{5}$$

Where

$$\bar{\dot{\gamma}} = \bar{v}/D \tag{6}$$

is the effective shear rate,

The effective diameter of RBC is Dr, γ is the dynamic viscosity of the suspension, and μ_r is the shear modulus of the membrane, where the RBC Relaxation time is

$$\tau_\mu = \eta_o D_r / \mu_r \tag{7}$$

In order to further analyse the relationship between the deformation of red blood cells and the change of flow, in the model, the size of red blood cells and the diameter of blood vessels are fixed [3]. At low flow, due to the deposition in the channel, it may occupy the center position. As shown in the figure, the red blood cells do not rub against the tube wall. The blood viscosity γ is set to 5 (close to the human body) and the blood flowing through the red blood cells is laminar [10].

2.3 Nanoparticles

Nanoparticles (NPs) are modelled as rigid particles with a volume similar to that of platelets, which are drained through blood in the blood vessels [13]. The flow direction is a longitudinal straight flow along the laminar flow. Collision with red blood cells and tube walls is their driving force [14]. Regardless of the presence of red blood cells in the blood, the nanoparticles perform as follows. The additive noise term corresponding to the Fokker-Planck equation. The Langevin equation rewrites the Eq. (19) [11]:

$$\frac{\partial c(x,t)}{\partial t} = -vp\gamma \frac{\partial c(x,t)}{\partial x} + D\frac{\partial^2 c(x,t)}{\partial x^2} \tag{8}$$

$c(x,t)$ is the molecular concentration of the emission source and time t at point x. $\partial c(x,t)$ is the sum of the second derivative of n-dimensional space of $c(x,t)$. D is the diffusion coefficient of the medium. The nanoparticle concentration distribution conforms to the following formula [15]:

$$c(x,t) = \frac{C}{\sqrt{4\pi Dt}} e^{-\frac{(x-vpt)^2}{4Dt}} \tag{9}$$

Nanoparticles are modeled as rigid particles with a volume similar to that of platelets, which are drained through blood in the blood vessels. The flow direction is a longitudinal straight flow along the laminar flow [9]. Collision with red blood cells and tube walls is their driving force. Regardless of the presence of red blood cells in the blood, nanoparticle propagation conforms to the diffusion theorem:

In the presence of red blood cells, the collision between nanoparticles and red blood cells affects the particle receiving concentration. According to the dissipation kinetics, the deformation of red blood cells is not considered, and the nanoparticle concentration receiving conforms to:

$$\mathbf{V}_p = \left(\frac{\mathbf{F}_{\text{det}}}{\beta_t} + \mathbf{V}_f\right)\left(1 - e^{-\frac{B_t}{m}t}\right) \tag{10}$$

Among them, V_p and V_f are the particle velocity vector and the fluid velocity vector, respectively; $Fdet$ is the total determined force (including Brown force, adhesion, etc.) acting on the NP.

$$\beta_t = 3\pi\mu d \tag{11}$$

The coefficient of friction depends on several physical parameters, such as the viscosity of the fluid, the size and shape of the NP. The coefficient of friction of spherical particles can be easily derived from Stokes's law:

$$\mathbf{V}_p = \frac{\mathbf{F}_{\text{det}}}{\beta_t} + \mathbf{V}_f \tag{12}$$

Equation (13) actually describes that the deterministic force acting on the particles is balanced by the resistance of the fluid. This is reasonable because the mass of NP is so small that the effect of inertia is ignored.

By tracking the position of NP in the direction of fluid flow, diffusion can be calculated by MSD [16]

$$<\xi(dtt)> = \frac{I}{N_c}\sum_{i=1}^{N_c}\frac{1}{N}\sum_{\alpha=1}^{N}\left[x_i^{\alpha}(t+dtt) - x_i^{\alpha}(t) - V_i^{\alpha}dtt\right]^2 = 2D_x dtt \tag{13}$$

Among them, i is the particle velocity at time step i, and D_x is the diffusion in the direction of fluid flow, which is represented by x. Because the displacement contains an axial displacement term, the observed MSD is a quadratic function of t.

When the flow rate increases from small, each fixed flow state corresponds to a different distribution probability of the cell state. When the ratio of cell size to blood vessel size is fixed, single-dimensional analysis, the red blood cells will eventually stabilize in the tumbled state, slipper/tank state, and parachute state. The different forms of red blood cells have different degrees of resistance to nanoparticles, as shown in the Fig. 1.

Think of this obstacle as modulation in the signal transmission process. Red blood cells in different states are modulation signals, nanoparticles are carrier waves, and the concentration reaching the receiving end is the required information. In the tumbling state, the cells (assuming in the center of the blood vessel) move in a periodic manner, and the concentration of the nanoparticles does not change basically.

As shown in Fig. 1, at the tank-treading state, after the cells are in a steady state, some of the nanoparticles released from the center are blocked by blood cells. When the blood flow stabilizes, it is difficult to receive the blocked nanoparticles again, resulting in a decrease in the concentration of nanoparticles at the receiving end. Parachute shaped, umbrella-shaped red blood cells have a stable shape, the released nanoparticles are blocked more, and the concentration of nanoparticles at the receiving end decreases. The concentration of nanoparticles at the receiving end will reflect the cell morphology in a stable state of the cell, and the specific design is as follows.

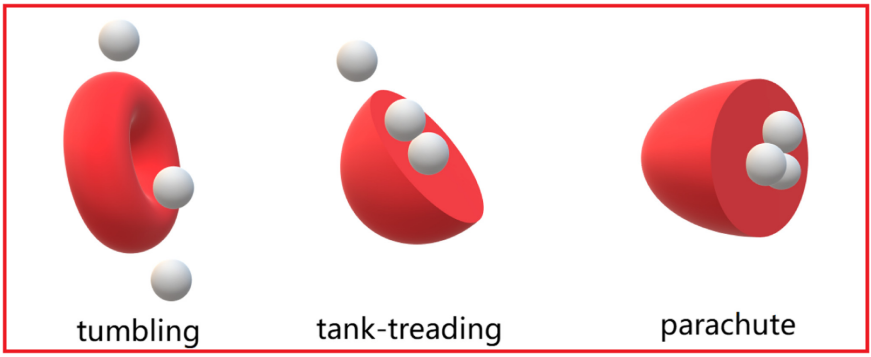

Fig. 1. Nanoparticles and three states of red blood cell

3 System Design

At the nanometer level, Brownian force becomes the dominant force that drives the nanoparticles to the vicinity of the vessel wall surface, while the resistance on the nanoparticles is relatively small. In the design, the resistance to the nanoparticles depends mainly on the state of the red blood cells.

At different flow states, a certain concentration of nanoparticles is released in the microtubules and received downstream. The receiving end receives and records the concentration of the nanoparticles. By comparing the concentration difference between the transmitting and receiving ends, the degree of red blood cell deformation is predicted, and the blood state is determined. Determine if there is a blood disease.

The simulation shows that when the flow rate is relatively low and the red blood cells are located at the center [3], the blood flow is subject to asymmetrical shear stress and begins to rotate. In this case, the fluid stress is not enough to transform the RBC shape into a parachute or slipper shape. In other words, at lower flow rates, if the cells are normal, the particle receiving concentration will not be affected by changes in cell shape. Further, if there is a large change in concentration at this time, it means that the cell is in an abnormal shape (such as a teardrop), or the normal function of the cell is lost (red blood cell death leads to increased blood viscosity).

Considering the result of reference [14], when the position of the red blood cells is completely concentrated in the center, the probability of the appearance of the cell shape as slipper/tank state will be reduced. Therefore, in the detection scheme, the probability of the appearance of cells of the second shape is incorporated into the third. The cell deformation ability was compared only by comparing the change in particle receiving concentration between the two cases of high and low flow rates.

At the same time, the concentration change at the receiving end can be directly compared to determine the cell deformability. In extreme cases, such as during cell sclerosis, the concentration at the receiving end will not change

significantly regardless of the intravascular flow rate (after the cell reaches steady state), and when the cell morphology is easily changed, the receiving end concentration is also independent of blood flow, Does not meet the above rules, showing random traits.

Considering that the cell may undergo multiple shape changes during the process, the distance between the transmitting and receiving ends should not be too large, and can be set to about ten times the diameter of the blood vessel.

4 Numerical Simulation

Considering that the cell may undergo multiple shape changes during the process, the distance between the transmitting and receiving ends should not be too large, and can be set to about ten times the diameter of the blood vessel. To eliminate the effect of tube flow on the distribution of NPs, the diffusion coefficient was set to average $IMSD{<}\xi(dtt){>} = 4.38 \times 10^{-10}\mathrm{cm}^2$, the diffusion coefficient is $D_x = \frac{<\xi(dtt)>}{2dtt} = 2.19 \times 10^{-8}\mathrm{cm}^2/\mathrm{s}$.

The simulation data of each parameter in each simulation case is recorded in Table 1.

Table 1. Simulation parameters

Parameters	Value	Description
μ	1 mPas	Plasma viscosity
v	[0.1,0.9,2.2] mm/s	Blood flow velocity
d	1 nm	Molecule radius
D_r	0.15 m	RBC radius
R	3 mm	Blood vessel radius
L	1.5 mm	Blood vessel length
r	4810 N/μ_{m}	Membrane shear modulus

Based on the determination of existing experimental results, the simulated shape of red blood cells is estimated. With the shear rate as the only variable, set the RBC size (within about 6.5–9 μm), the elasticity of the RBC $\mu \in [2, 10]N/\mu m$, the bending stiffness of the membrane, and the solute and membrane viscosity as fixed The probability curve of the RBC observation state is plotted as shown in the Fig. 2.

For RBCs with fixed size in blood vessels, we use the shear rate as the main parameter to control the shape of the RBC. Therefore, without loss of generality, we can assume that the change in the shear rate in the Fig. 2 also represents the feature of $_r$. The corresponding changes in the shear modulus of the cells are visualized with the probability of the appearance of the cell shape.

It can be seen from the Fig. 2 that when the shear rate is 0–0.1 mPas, the possibility of tumbling state is greater. When the shear rate is 0.1–0.3 mPas, the

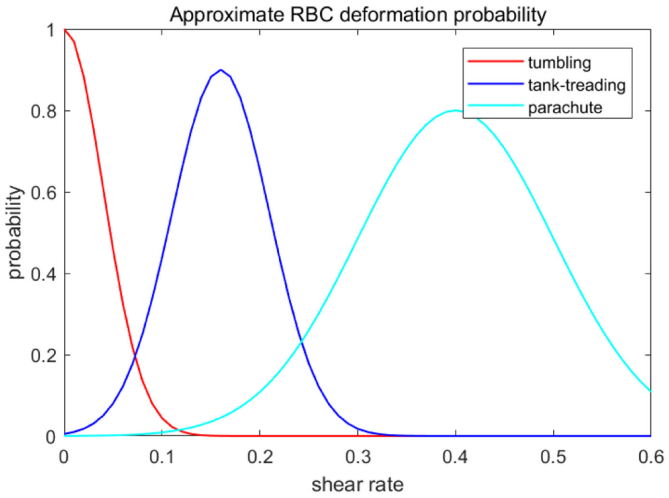

Fig. 2. The relationship between x and t^{opt}

possibility of tank-treading state is the main part. After 0.3 mPas, parachute state is most likely to appear. However, there is a clear boundary between different states, and the state of red blood cells corresponding to different sizes of shear rates is also clearly indicated.

Among them, the width of the shear modulus distribution in the state is directly related. Therefore, a narrower distribution of the shear modulus results in a cross distribution from one state to another. In the Fig. 2 above, the deformation behavior of red blood cells takes into account the distribution of young and old cells in the blood. It is assumed that the shear modulus has a Gaussian distribution as Fig. 3. This is represented by the Gaussian distribution of the new RBC as a linear shift towards a larger shear modulus.

In the previous inference, we know that the speed of the nanoparticles is related to the blood flow velocity, and if the time is long enough, the small changes in blood viscosity caused by the red blood cell deformation are ignored, and the speed of the nanoparticle receiving end is not affected by the red blood cell deformation. The effect, as time changes, shown as the concentration's change of nanoparticles in blood vessels.

The curves in the Fig. 4 are the changes of nanoparticle velocity with time at low, medium and high flow rates. It is clear from this that the nanoparticle velocity at high and low flow rates will eventually float near the blood flow rate. The cross-sectional area of blood flow is constant, and the flow is proportional to the average blood speed.

The size of the nanoparticle concentration at the receiving end reflects the degree of cell deformation. According to the above formula, nanoparticles in non-Newtonian fluid are released, transferred, and received. When the particle deformation is not considered to block the particles, the final particle concentration

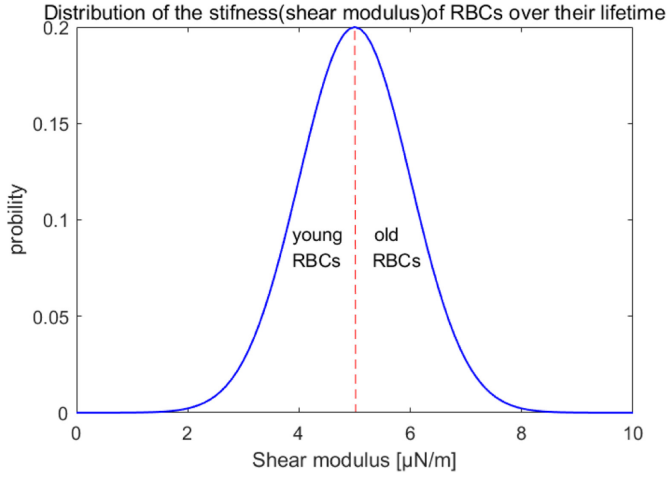

Fig. 3. Nanoparticle velocity at different blood flow rates

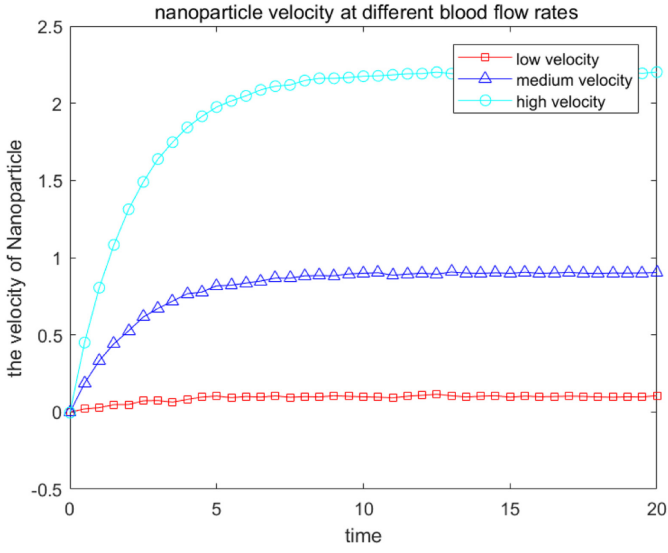

Fig. 4. Nanoparticle velocity at different blood flow rates

tends to 0 at low, medium, and high flow rates. However, considering the steady state of red blood cells under shear stress, the transmission of the particles at the center of the emission is directly prevented, after reaching the steady state, the difference between the concentration at the receiving end and the concentration at the transmitting end appears to be different.

The change of blood flow velocity along the longitudinal axis of the blood vessel is shown in the Fig. 6. The closer to the center of the longitudinal axis of

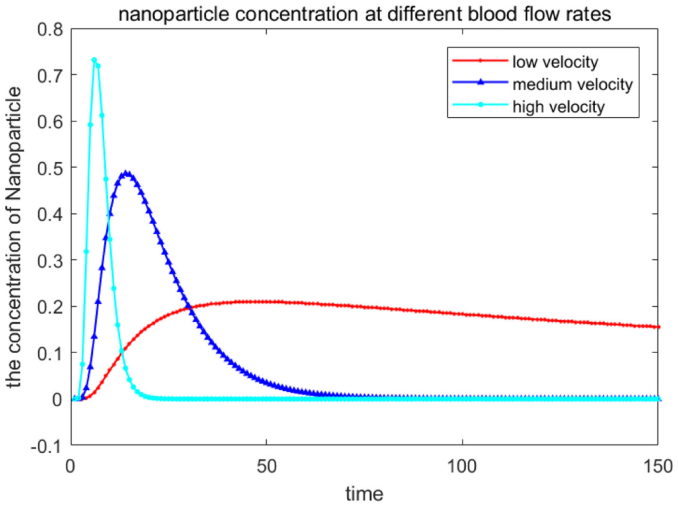

Fig. 5. Nanoparticle concentration at different blood flow rates

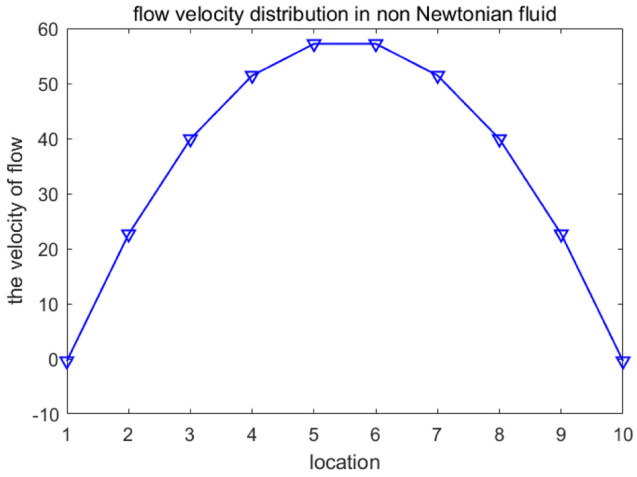

Fig. 6. Flow velocity distribution in non Newtonian fluid

the blood vessel, the greater the flow velocity. According to the model setting, the flow rate is characterized as the shear rate in the non-Newtonian fluid, and the curve of the blood flow rate as a function of the shear rate is shown in the Fig. 6. In the model assumption, the two are basically proportional.

Figure 7 shows that the average speed of a position is basically proportional to the shear rate at that point. That is, there is a one-to-one correspondence between the shape and flow rate of the same cell (with constant shear modulus) as represented by the shear rate. Under the determined correspondence

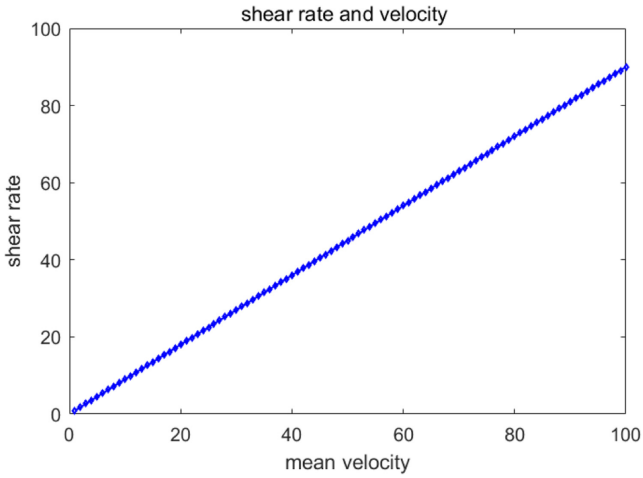

Fig. 7. Shear rate and velocity

relationship, abnormal cells and abnormally deformed red blood cells will be clearly displayed by changes in nanoparticle concentration.

5 Conclusion

In this article, we propose a solution to detect the ability of red blood cells to deform using the effects of red blood cell deformation on molecular transmission in blood vessels. Combined with the existing experimental data and the analysis of specific simulation activities, the feasibility of detecting the deformation ability of a single red blood cell was demonstrated. In more detail, given the molecules released in the blood vessels, simulation results show that, compared with normal conditions, abnormal cells affect the number of nanoparticles that the receiving end can receive.

It can also be seen from the results that the distribution of nanoparticles in blood vessels does not depend on the blood flow velocity after reaching steady state, so this design is applicable in vascular models with different flow rates. The detection of cell deformation can also be detected by its light scattering characteristics. The transmitting end emits light of a certain wavelength, and the receiving end absorbs and compares with the transmitting end to predict the cell shape.

Finally, the results of this paper can be further expanded to conduct more detections. For example, the aggregation effect of multiple red blood cells at a low flow rate corresponds to the deformation effect at a high flow rate, further enhancing the versatility of design applications.

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