CHAPTER 3 METHEODOLOGY

This study aims to identify the characteristic of early-stage nanorobots that could perform as artificial platelets under the influence of non-Newtonian blood flow in human bloodstream. The current nanorobot technology development cannot achieve yet but could potentially be available in the future. The mathematical models are used for simulating nanorobots and circulatory system. The designed characteristics and the probable technologies of nanorobots are described in section 3.1. Moreover, the PSO algorithm is also explained in section 3.1 as a nanorobot control mechanism. The detail of circulatory system model and non-Newtonian blood flow models are included in section 3.2.

3.1 Nanorobot Characteristics and Control Mechanism

3.1.1 Nanorobot Characteristics Design

The idea of using nanorobots operating as artificial platelets is advertent. Artificial platelet or clottocyte is designed by Freitas in [10] with spherical shape. It can carry a fiber mesh and release the mesh to attach the wound to prevent blood cells exiting the blood vessel. This idea seems to work effectively. Nevertheless, according to the current nanotechnology, this may seem too advanced. Another remarkable idea is from Boonrong and Kaewkamnerdpong [11] who proposed the simpler version of nanorobots to portray the early-stage nanorobots to find and repair the wound. In this simpler version, each nanorobot cannot carry a fiber mesh but assemble itself with others to form a mass to close the wound as a platelet does. This study adopts the idea of early-stage nanorobots; each nanorobot has only essential characteristics including;

- moving in three dimensions within a maximum velocity,
- operating inside human body with biocompatibility,
- programmability for self-operation,
- sensing and generating signals within limited range,
- interacting with other nanorobots within limited perception range, and
- connecting to others to assemble.

The nanorobots simulate activated platelets, which are 2 μm in diameter and spheroid in shape. It is assumed that nanorobots could sense chemical signal such as vWF released from the wound. When the nanorobots find the wound site and attach to the wound, they could generate attraction signal to stimulate other nanorobots within the proximity. In addition, they would connect to the others by the attraction force when they got close to each other enough.

For required abilities of nanorobots, they need to be constructed by using many nanoparts for instance nanomotor, nanosensor and nanoantenna. Nanorobots are designed for moving in the blood vessel, so that the actuators are needed. Nanoflagella [10] is one of the nanoactuators that are inspired by flagella motion of bacteria. Nanorobots can swim in the medium using the wave motion of nanoflagella. Another bacteria-based nanomotor is the Serratia marcescens-actuator which moves by spinning around the environment [9]. Moreover in the mechanical nanotechnology field, the electromagnetic motor which drives by magnetic force. The electromagnetic motor was fabricated by Texus engineers which claim to be the world's smallest and fastest nanomotor [21]. These nanoactuator examples could be used as actuators of nanorobots.

Regarding the ability to sense the chemical signal and communicate with others for coordinating and collaborating within the swarm, the signal generator and sensor are needed. The communication among nanorobots can help them sharing the information to make better decision depending on the control algorithm. The bio-signal sensor is needed to sense the bio-signal and vWF which is released from the wound site. An example of natural sensor could be found when the bacteria looks for the food source by sensing nutrient levels [12]. If they detected the higher nutrient level, they would leave the current food source and move to the new one. Nanorobots could also use the similar idea by sensing the interesting signal then follow the direction of the signal to find the wound and generate signal to attract other neighboring nanorobots. Another idea is the use of the fabricated target-responsive encapsulation (TRE) sensor with single-stranded DNA probes as a biomolecule-responsive cab to detect the α-thrombin, which is a coagulation protein [37].

The programmability is required for integrating the control mechanism to the swarm of nanorobots. Sharma and Mittal [17] mentioned to the silicon based MOS technology as the programmable device for nano-particles which is only 45 nm in length. Another example is DNA. In biology, transcription and translation are processes to translate information of DNA into proteins. In transcription process, DNA information can be duplicated into messenger RNA or mRNA. In translation process, mRNA can be decoded into amino acids which are connected into a protein chain. Hence, DNA is a blueprint which stores the information of living organism. Thus, the DNA can be applied to programmable part for nanorobots.

The nanorobots are designed to stop the bleeding by assembling together at the injured site. In the biological systems, the covalent bond could make atoms stick together and could be used for connecting nanorobots. Another example is DNA sticky ends [38]. An enzyme is used to cut DNA at one specific sequence for making the sticky end. DNA sticky ends could be linked together by DNA ligase when both ends are complementary. These ideas could be applied for connecting nanorobots together.

Due to the complexity of the natural system, these are the assumptions of nanorobots when its process inside the simulation,

- The nanorobots could move freely in all directions around the environment within the limited maximum velocity. It is also compatible with other particles and environment.
- The nanorobots could sense and measure the concentration of the chemical signal, vWF, which is released from the wound, and the attraction signal, which is released from the activated nanorobots. Moreover, nanorobots have abilities to generate and release the attraction signal when it adhered to the wound in the same way as the wound.
- The nanorobots could adhere to the collagen around the injured area and other nanorobots to cover the wound. After the bleeding is stopped, they could be dislodged from the wound as a clot, become deactivated and moved along the blood vessel to repair other wounds.
- When the nanorobots stay close enough to the activated nanorobots, they will be attracted to the activated nanorobots as atoms with covalent bond.

3.1.2 Nanorobot Control Mechanism

In this study, nanorobots perform as artificial platelets moving along the blood vessel, finding the wound, and adhering to others at the injured site to stop the bleeding. The purpose is to examine the feasibility of using Canonical Particle Swarm Optimization as nanorobot control algorithm in nanorobots when they become available in the future. Canonical Particle Swarm Optimization (PSO) is inspired by the cooperation of swarm of social animals such as ants, termites; each of which may not be equipped with complex abilities, but they can operate in collaboration to accomplish the complicated task like building a termite mound. Because such early stage nanorobots have only simple characteristics, which are similar to those in social animals [39, 40], PSO is chosen and employed to control the locomotion of nanorobots. Figure 3.1 shows the searching wound procedure of each nanorobot using PSO control algorithm.

```
For each nanorobot Initialize the position and velocity of nanorobots
Do
    For each nanorobot
        Calculate fitness value
        Update new personal best position
    End
    For each nanorobot
        Find the best fitness from the neighborhood
        Update new local best position
        Calculate new nanorobot velocity
        Update new nanorobot position
    End
While stopping criteria is not attained
```

Figure 3.1 The algorithm of nanorobots for finding the wound.

3.1.2.1 The Initialization of Nanorobots

The process starts with initializing the position and velocity of nanorobots by randomizing values with uniform distribution. The position of particles are represented by $x_i(t)$, which are the coordinate of nanorobots inside the blood vessel in three dimensions $[x,y,z]$. The initial velocity is randomized between $-VMax$ and $+VMax$, where $VMax$ is the maximum velocity of nanorobots. It should be noted that due to the simplicity of nanorobots in their early stage, nanorobots may not know the exact location of themselves inside the vessel. The personal best position that is used in the algorithm is regarded as the step size from the previously best position in their knowledge. Therefore, the personal best position is initialized as zero.

3.1.2.2 The Fitness Calculation

The fitness value is used to evaluate how well the current position is. If the fitness value of current position is higher than the fitness value of personal best position, the personal best position would be replaced. In this simulation, the fitness could be calculated by a summation of the concentration of vWF which is released from the wound and the intensity of attraction signal from the activated nanorobot. The attraction signal generator of nanorobots cannot yet be specified from the literature. Nevertheless, it is anticipated that it would be similar to natural particles inside human body. The attraction signal released by nanorobots is assumed to be corresponding to vWF. The

concentration of vWF and the intensity of attraction signal could be calculated from Ficks' second law,

$$\frac{\partial C_A(x,t)}{\partial t} = D_A \frac{\partial^2 C_A(x,t)}{\partial x^2} \tag{3.1}$$

where C_A is the concentration of the solute A, x is the distance from the activated nanorobot at the measurement position, t is time, and D_A is the diffusion coefficient of solute A [15]. The diffusion coefficient is set similar to natural platelets that is $4.5\text{x}10^{-12}$ m^2/s [41, 42].

3.1.2.3 The Position and Velocity of Nanorobots

The best position is divided into 2 types: the personal best position and local best position. Usually, the personal best position is selected from its historical position that has highest fitness value and the local best position is the best position selected in the same way from its neighbors. Still, the early-stage nanorobots did not know the coordinate of its current position in the vessel so they could only keep track of distance from their previous best position to their current position. Hence, in this study the personal best position would be calculated from the accumulation of their movement from the previous best position. For the local best position, due to the limitation of nanorobot abilities, they could only interact with neighbors within limited perception range. Moreover, the interaction ability did not allow nanorobots to exchange data between each other. Thus, the local best position for early-stage nanorobots needs to be calculated differently depending on the current nanorobot condition. When the neighbor is found, the neighbor is randomly selected and the local best position is calculated from the average position of all selected neighbors. If there is an optimal nanorobot, which is the nanorobot that found the wound, in the neighborhood, the local best position is the optimal nanorobot position. In the case when neither neighbors nor optimal nanorobots are found, the local best position is the current position.

Both personal best position and local best position are used for calculating the new velocity for nanorobots to find the path to the wound. The velocity is the function of the previous velocity and position, the personal best position and the local best position, which can be described by the equation (3.2),

$$v(t+1) = \chi\left(v(t) + c_1 r_1\left(x_{pbest} - x(t)\right) + c_2 r_2\left(x_{lbest} - x(t)\right)\right) \tag{3.2}$$

where $v(t+1)$ is the new velocity, $v(t)$ is the current velocity , $x(t)$ is the current position, x_{pbest} is the personal best position, x_{lbest} is the local best position, c_1 and c_2 are acceleration constants, r_1 and r_2 are random number between ± 1, and χ is constriction coefficient, which is used to control the exploration and exploitation in PSO; the higher constriction coefficient leads to higher exploration. The constriction coefficient can be computed from

$$\chi = \frac{2}{\left|2 - \varphi - \sqrt{\varphi^2 - 4\varphi}\right|} \tag{3.3}$$

$$\varphi = c_1 + c_2 > 4 \tag{3.4}$$

According to the study of Clerc and Kennedy, the suggestive value of φ for balancing between exploration and exploitation trade-off to converge to the optimal solution is 4.1 [43]. Hence, χ is equal to 0.729. Other important PSO parameters include acceleration constants c_1 and c_2. These two parameters are used for weighting the influence of its information and the received information from social interaction to the new velocity. These parameters can be used to regulate the exploration and exploitation search as well. With a higher c_1, which implies the higher confident in personal experience, will

promote the exploration search. On the other hand, a higher c_2 will lead to the increase chance for exploitation because neighbors will tend to move toward to the same local best position. After computing new velocity, the position will be updated. The new position of a nanorobot is computed from the new velocity using equation (3.5),

$$x(t+1) = x(t) + v(t+1) \quad (3.5)$$

3.1.3 Nanorobot System

In the simulation, each nanorobot has three main considerate characteristics including the perception range, the maximum velocity and the nanorobot response speed. The perception range or *PRange* determines the limited range of nanorobot perception to both other nanorobots and environment including the attraction signal. The lower the *PRange* value is, the narrower the nanorobot can perceive. The maximum velocity or *VMax* determines the maximum velocity that nanomotor could drive nanorobot in three dimensions. The higher *VMax* allows nanorobots to move against the blood flow. The nanorobot response speed or *NRTime* determines how fast the nanorobots can acknowledge to the change in the environment and respond accordingly. The smaller *NRTime* indicates that the nanorobots can response faster. At the beginning, each nanorobot is initialized as described in 3.1.2.1. The states of nanorobots are divided into 3 states:

- State0: when neither attraction signal nor any neighbor is found within its perception range.
- State1: when neighbors are found within its perception range but there is no attraction signal.
- State2: when attraction signal is found.

The attraction signal is generated from the wound or the optimal nanorobots that are at the wound.

At initialization, all nanorobots are set at state 0. Then, the fitness value will be computed from the current position as described in 3.1.2.2. This fitness value is used to evaluate the quality of the current position. The personal best position would be replaced if the new position provides the higher fitness value. After the personal best position is considered, the nanorobots start to check for the neighbors in order to update the local best position. If no neighbor is found, the current position is set as the new local best position. In the case when neighbors are found, the nanorobot would randomly select the position of neighbors. Then, the new local best position is set as the average of the selected position and the state of the nanorobot is set at state 1. If an optimal nanorobot is found, the local best position is the optimal nanorobot position and the state of nanorobot is set at state 2. After each nanorobot gets both the new personal best position and the new local best position, the new velocity is recalculated. Then, the new velocity is used to update the current nanorobot position. After that, all the processes except for the initialization would be operated over again until the stopping criteria is met.

For nanorobot adhesion, each nanorobot has 6 connectors. The connection could occur in either horizontal or vertical directions. Each connector can connect to both exposed collagen and the connectors of other nanorobots. The vWF is used as the binding material between the connector and the exposed collagen. When a nanorobot gets near the exposed collagen at the wound, the nanorobot will adhere to the exposed collagen. Then, it generates the attraction signal to influence nearby nanorobots to come to the

wound. If the distance between a nanorobot and an optimal nanorobot is less than 0.2 μm, it is assumed to adhere to one another due to the attraction force between them.
Normally, the nanorobot velocity and position are computed as described above. However, the collision between the moves might occur. A nanorobot could collide with other particles or collide with vessel wall. The possibility of collision between the nanorobot and others particles is defined in term of the probability *p*, which is dependent on the hematocrit. The hematocrit represents the percentage of red blood cells in the total blood volume. In this study, the hematocrit is 40% which is the average hematocrit for adult [35]. In the simulation, when nanorobots collide with other particles, the velocity is altered by reducing the amplitude in half and randomly changing the direction. In the case where nanorobots collide with the vessel wall, the nanorobots will move in the opposite direction with the remaining velocity.

The performance of the control mechanism could be investigated through two indicators: the wound coverage rate and the number of iterations. The wound coverage rate indicates the accuracy in the self-assembly task, while the number of iterations indicates the speed to complete the self-assembly task.

The wound coverage rate represents the density of optimal nanorobots at the wound. It refers to the capability of the swarm of nanorobots to close the wound. In the simulation, the wound coverage rate is computed by using Monte Carlo method. Normally, the wound coverage should be computed directly from the total wound area that is covered by optimal nanorobots. However, it is too difficult to accurately compute the covered area because the nanorobots are rigid sphere so there are many gaps among connected nanorobots. The first optimal nanorobot can adhere anywhere inside the wound and, then, other nanorobots could either adhere around the first optimal nanorobot or adhere at the different site of the wound. After self-assembly, there might be some cases where the remaining empty area might not fit the nanorobot size so the nanorobot cannot adhere. Hence, there are random sizes of empty space. This makes it hard to compute the covered area. Using the Monte Carlo approach, a number of testing points inside the wound area are randomly generated and tested whether there are any optimal nanorobots covering the testing points. Then, the wound coverage rate is calculated by the ratio of the number of testing points that is covered by optimal nanorobots to the total number of randomly selected testing points in the wound area. Thus, the wound coverage rate will be the real number from 0 to 1.

The number of iterations is the total number of iterations that nanorobots used in order to achieve the required wound coverage rate. This refers to the speed of nanorobots to achieve the goal. This number will be the discrete number from 0 to the predefined number of maximum iterations that is used as a condition for stopping criteria.

These indicators are used to determine the stopping criteria. In this study, the criteria for termination are set as follows:

- when the wound coverage rate are equal to or greater than 0.8, and
- when the number of iterations has reached the maximum iteration or 10,000 iterations.

3.2 Circulatory System Model

This study aims to investigate the performance of PSO algorithm for controlling the early-stage nanorobots to repair the damaged site in non-Newtonian blood flow inside a rigid blood vessel model. The assumption and details of simulated nanorobots are described in section 3.1. This section explains the circulatory system model and equations and parameters for non-Newtonian blood flow.

In this study, the vessel is represented as a cylindrical tube. Two ends of the tube are connected as a torus. The flow inside vessel is assumed to be the fully developed flow so the velocity profile will be unchanged [45]. In addition, it is assumed to be in no-silp condition that refers to the zero velocity at the wall. Moreover, the flow inside the vessel is laminar flow which the motion in the flow is smooth streamlines. It is reasonable to assume as this because the fluid will be turbulent flow when its Reynolds number is more than 300 [15]. In human vessel, blood has the Reynolds number less than 300 except in aorta. Hence, the flow inside arteriole is laminar flow. Because of the fully developed laminar flow, each particle moves freely in the constant streamline along the blood vessel without radial direction movement. In addition, it moves with constant velocity as it is the steady and fully developed flow.

Normally, the flow of blood is mainly driven by the pressure generated by the heartbeat, which causes the periodic flow. The total velocity is calculated from the summation of the periodic flow and the steady flow as expressed in equation (3.6).

$$V = V_z + V_\phi \tag{3.6}$$

where V_z is the steady velocity and $V_\phi$is the periodic velocity. These two velocities could be directly summed as they are the forces that happen in the same axis. The oscillatory velocity can be expressed as [15],

$$V_\phi = \frac{A_1}{i\rho\omega}\left(\frac{J_0(\lambda r)}{J_0(\lambda R)} - 1\right)e^{i\omega t} \tag{3.7}$$

where A_1 is the amplitude of the oscillating component, ρ is the blood density, J_0 is the Bessel function zero order of the first kind, $\omega = 2\pi f_p$, f_p is the pulse frequency, and

$$\lambda = \sqrt{\frac{i^3\omega}{\nu}} \tag{3.8}$$

where ν is the kinematic viscosity.

The blood flow in a small vessel exhibits rather like non-Newtonian fluid than Newtonian fluid in a large vessel [12]. The difference between these two fluids is the relationship between the shear stress and the shear rate. In the Newtonian fluid, the shear stress is linearly proportional to the shear rate and the graph passes though the origin. On the other hand, the non-Newtonian fluid, the shear stress is nonlinearly proportional to the shear rate [44]. Figure 3.2 showed graph between shear rate and shear stress of Newtonian and non-Newtonian fluid.

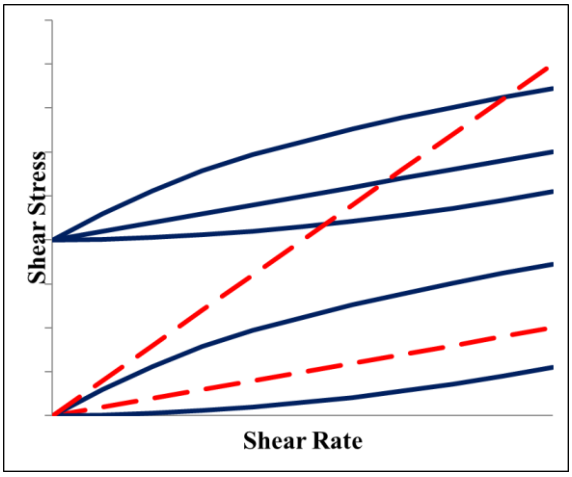

Figure 3.2 The shear stress versus shear rate of Newtonian fluid (red long dashes) and non-Newtonian fluid (blue line).

The non-Newtonian fluid can be divided into three types as follows [44]:

- shear-thinning or pseudoplastic behavior, which is the fluid that its viscosity decreases when the shear rate increases,
- shear-thickening or dilatant behavior, which is the fluid that its viscosity increases when shear rate increases.
- viscoplastic/viscoelastic behavior with or without shear-thinning behavior. This fluid could behaves likes both viscous fluid and plastic or elastic solid.

Blood is normally assumed to be viscoelastic fluid according to the elastic behavior of red blood cells, which are the main particles in blood [46, 47]. However, in this study all particles inside blood vessel including nanorobots are assumed to be rigid body for simplicity. Thus, it is reasonable to simulate the blood flow as viscoplastic fluid to be corresponding to the rigid characteristic of particles.

The viscoplastic fluid shows the combination behavior between Newtonian and non-newtonian or even between different types of non-Newtonian. The main character of the viscoplastic fluid is the yield stress. The yield stress is the constant value depending on the material. The yield stress affects directly to the fluid to flow. In other words, the fluid will flow only when the shear stress exceeds the yield stress. The graph of shear rate and shear stress of viscoplastic fluid is illustrated as the blue line in Figure 3.3. In the literature, the visco-plastic fluid can be described by three models including [44]

- Bingham plastic fluid model: the fluid that can be represented by this model has linear flow curve when shear stress exceeds the yield stress,
- Herchel-Bulkley fluid model (H-B model): the model represents a yield-pseudoplastic fluid, which exhibits shear-thinning behavior when the shear stress exceeds the yield stress, and
- Casson model will be used for other fluid that has steady shear stress or shear rate.

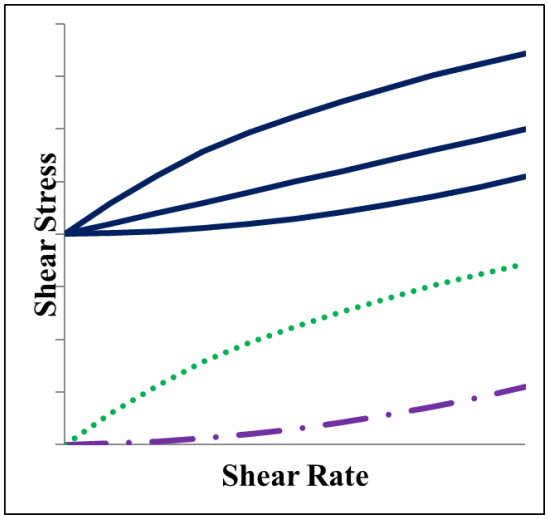

Figure 3.3 The shear stress versus shear rate of non-Newtonian fluid: shear-thinning fluid (green dot), shear-thickening (purple dash dot) and viscopalstic and viscoelastic fluid (blue line).

As the average diameter of an arteriole is 30 μm, Iida [48] reported that when the blood flows in the arterioles of diameter less than 0.1 mm, the velocity profiles could be generally described by both Casson and Herchel-Bulkley (H-B) fluid models and that the velocity profiles of blood flow in the arterioles with diameters less than 0.065 mm could only be described by H-B fluid model. Hence, the H-B model is the appropriate model. The H-B model in term of shear rate can be represented by [44]

$$\gamma = \begin{cases} -\dfrac{dV}{dr}, & r > R_p \\ 0, & 0 \le r \le R_p \end{cases} \tag{3.9}$$

where γ is the shear rate, V is the blood velocity, r is the vertical position in the vessel, and R_p is plug core radius, which can be computed by,

$$R_p = R\left(\frac{\tau_y}{\tau_w}\right) \tag{3.10}$$

where R is vessel radius, τ_y is the yield stress, and τ_w is the shear stress at wall. The shear stress, τ, can be expressed as

$$\tau = \tau_y + m\gamma^n \tag{3.11}$$

where m is the consistency index, and n is the power law index, $n < 0$. In addition, the shear stress can be represented as a function of pressure gradient, which is

$$\tau = \frac{r}{2}\left(-\frac{dP}{dx}\right) \tag{3.12}$$

where $-\frac{dP}{dx}$ is the pressure gradient.

The shear stress at wall can be computed by substituting $r = R$ in equation (3.12),

$$\tau_w = \frac{R}{2}\left(-\frac{dP}{dx}\right) \tag{3.13}$$

The viscosity can be expressed as

$$\nu = \frac{d\tau}{d\gamma} \tag{3.14}$$

where ν is the viscosity. The velocity can be computed from equation (3.9) and equation (3.11)-(3.13) following by taking integration with respect to r to obtain

$$V_z = \frac{nR}{n+1}\left(\frac{\tau_w}{m}\right)^{\frac{1}{n}}\left[\left(1-\frac{\tau_y}{\tau_w}\right)^{\frac{n+1}{n}} - \left(\frac{r}{R}-\frac{\tau_y}{\tau_w}\right)^{\frac{n+1}{n}}\right] \tag{3.15}$$

where $r \leq R_p$ or in the plug core region, the velocity will be constant and equal to V_z at R_p. Hence, the plug core velocity is computed by substituting $r = R_p$ and using equation (3.10) in equation (3.15),

$$V_p = \frac{nR}{n+1}\left(\frac{\tau_w}{m}\right)^{\frac{1}{n}}\left(1-\frac{\tau_y}{\tau_w}\right)^{\frac{n+1}{n}} \tag{3.16}$$

The comparison between velocity profile of Newtonian and non-Newtonian fluid is illustrated in Figure 3.4. The velocity profile of non-Newtonian fluid is flatter at the center of the flow due to the constant velocity at plug core region. In the plug core region, the blood velocity is the greatest. With high blood velocity, nanorobots might go forward too fast and overstep the wound. In non-Newtonian blood, the high velocity region is larger than Newtonian blood. It is anticipated that nanorobots in non-Newtonian blood may have higher possibility to overstep the wound and need to move against the blood flow back to the wound. The performance of PSO-based nanorobots is demonstrated in Chapter 4.

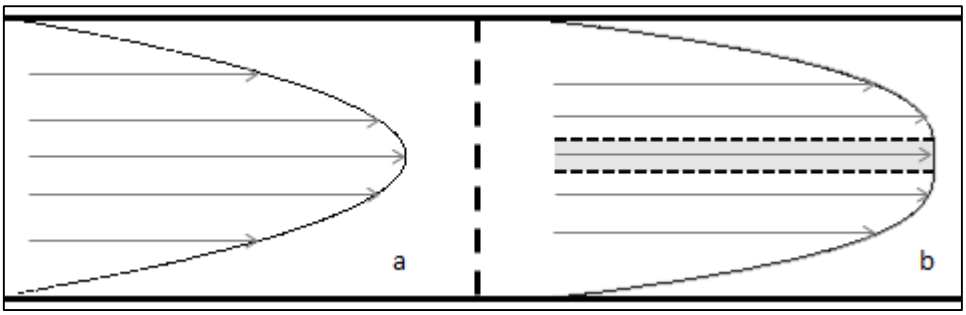

Figure 3.4 The velocity profile of (a) Newtonian and (b) non-Newtonian fluid.