CHAPTER 2 THEORETICAL ISSUE/RELATED WORK

In this chapter, the nanorobot application and nanocomponent literatures are reviewed in section 2.1. The examples of nanorobot application literatures show the commonly identified characteristics and abilities of nanorobots. The research of nanocomponent point out the current development of nanotechnology and allow us to envision the possibility of identified characteristics as well as supporting technologies for future nanorobots. Section 2.2 describes the swarm intelligence (SI) techniques inspired by the behavior of decentralized and self-organized systems in nature. The review of various SI techniques could lead us to choose the suitable algorithm for controlling swarm of nanorobots inside bloodstream environment. Next, the behavior of platelets and their characteristics are explained in section 2.3. The hemostasis processes are also described in this section in order to elaborate on how the platelets perform and their roles in the wound healing process. Finally, section 2.4 introduces about the circulatory system and shows the differences characteristics of blood inside a large vessel and a small vessel. Moreover, the fluid models which could be used for describing the blood flow are described.

2.1 Nanorobots

2.1.1 Nanocomponents

The advance of nanotechnology has inspired medical researchers about the new possible medical treatments by using nanorobots for repairing the damage site [5, 17, 18], and delivering drug to the target areas [7, 18]. Nanorobotics is the research field of nano-scale robots that could perform the defined task. The advantage of its size allows the treatment to go to the more specific area without harming normal healthy cells. There are many researchers currently concentrating on the development of the nanocomponents from many technologies including DNA-based technology [77, 8], bacteria-based technology [9] and mechanical technology [5, 18]. This section shows some examples of the current nanotechnology and considers the possibility of using these nanocomponents as parts of nanorobots. Due to the current stage of nanotechnology, most of nanocomponents are in the theoretical aspect. However, some nanocomponents are practically built.

2.1.1.1 Bio-based Nanotechnology

The development of medical nanoparticles aims to find the material which can be used for constructing nanorobots that can perform the assigned task and can work inside human body without affecting other organs and processes. Three examples of materials that were normally mentioned in the literature of nanotechnology: DNA-based, protein-based and bacteria-based nanotechnology.

DNA-based nanotechnology is widely researched. The concept is based on the well-known technique, DNA binding. The DNA consists of four chemical building blocks which are adenine (A), cytosine (C), guanine (G) and thymine (T). The nucleotide (A) always pairs with (T) and (C) always pairs with (G). This is the main key for constructing 2D or even 3D nanostructures from DNA. Constructing nanostructure can be produced in many ways including Crossover Junctions, Holliday Junctions, n-Point stars, 3D DNA nanostructure and DNA origami [20]. All procedures can construct 2D and 3D DNA object except for the crossover junctions that can only construct 2D array.

Each procedure has different strong points. The main advantage of n-Point stars is the end of the structure can be generated as both sticky end and blunt end. The sticky ends can be the candidate of fabricating the assembled device. For encapsulating device, the 3D DNA nanostructure could be the selected method because it can form a stable binding. For small size or free form component, DNA Origami is the good choice.
DNA origami is the bottom-up method that uses the single stranded DNA (ssDNA) to construct a 2D or even 3D object as illustrated in Figure 2.1 [8, 19, 20]. The constructible property of DNA enables the possibility of building various structures of nanocomponents. This technique can be used for constructing future nanorobots.

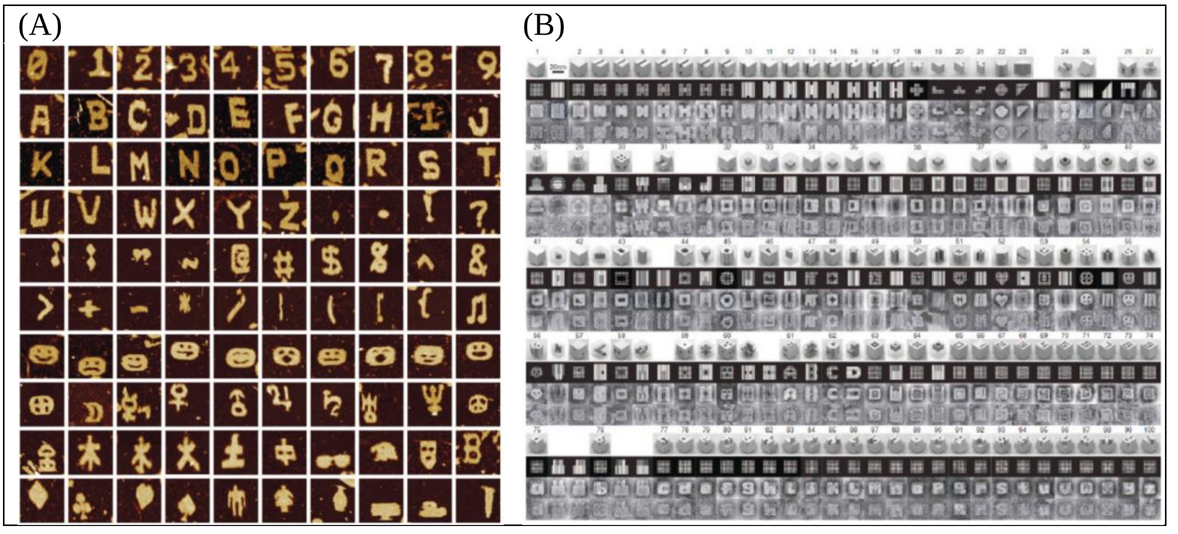

Figure 2.1 The images of DNA origami objects which (A) the 2D shapes of DNA origami taken by an atomic force microscopy (AFM) [19] and (B) the 3D shapes of DNA origami taken by a transmission electron microscopy (TEM) [20]

The DNA origami method has been used in many applications. The drug delivery is one of the interesting issues. The Temperature-Controlled Encapsulation of self-assembled DNA Nanocage [7] is one of the real nanoparts which can encapsulate and release an active enzyme called horseradish peroxidase (HRP) at the defined temperature. The Cage is the six corner structure with 10 nm in inner diameter. The aperture of the lattice is 5.5 nm, which is small enough to hold the HRP. The processes of the nanocage are represented in Figure 2.2. However, it still cannot be used inside human body because the free DNA strands will be destroyed by natural human body process.

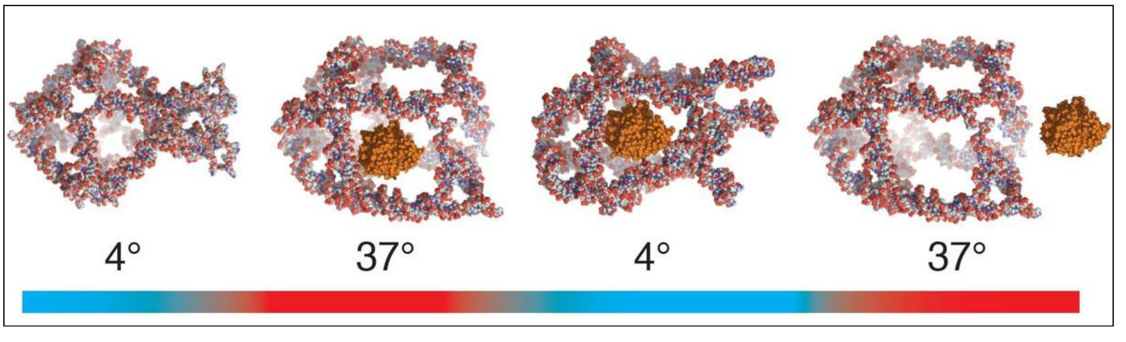

Figure 2.2 The open and close process of nanocage [7]

Besides DNA, protein is another interesting material that is commonly used in pharmaceutical and nutraceutical. Protein is the synthetic polymer that has low toxicity and biodegradability. There are many types of proteins that can be used as nanoparticle material [6]. The selected material is considered based on the purpose such as the designed structure size and functionality. The albumin is a protein used in the maintenance of osmotic pressure, binding and transport of nutrients to the cells. The advantages of albumin are biodegradable and easy to prepare. However, it is soluble in circulating system, which could not be used for nanorobots in this study. The gelatin is a major component of skin, bones and connective tissues. It is inexpensive and can be sterilized and non-pyrogenic. This protein is also low antigenicity. Elastin is the elastic polymer, which can reform its after stretching. This protein can aggregate under selected condition of concentration and temperature. This property promotes the elastin to be one of the interesting materials for the assembled parts. Other proteins that could be the proper choices for the assembled part are gliadin and legumin because these two proteins can self-assemble after aggregating or crossing link with glutaraldehyde. Zein, the hydrophobic protein that is commonly used for films and coating, could probably be a good substance for covering the wound.

Furthermore, due to the advantages of bacteria on the excellent swimming ability, micro-size and the ability to obtain energy from environment [9], bacteria based nanodevice is another interesting technology. Park et al. [9] proposed two types of bacteria microactuators: Serratia marcescens-actuated microrobot and Salmonella typhimurium-actuated microrobot. These two microrobots are practically built. The Serratia marcescens bacteria are adhered to the negative polymeric photoresist SU-8 microcubes coating with bovine serum albumin (BSA). It is cube-like in shape and its thickness is approximately 30 μm. It moves by spinning around the environment. The Salmonella typhimurium actuator is fabricated by patterning bacteria on the surface of polystyrene microbeads (PA) using BSA. It is 5 μm spherical.

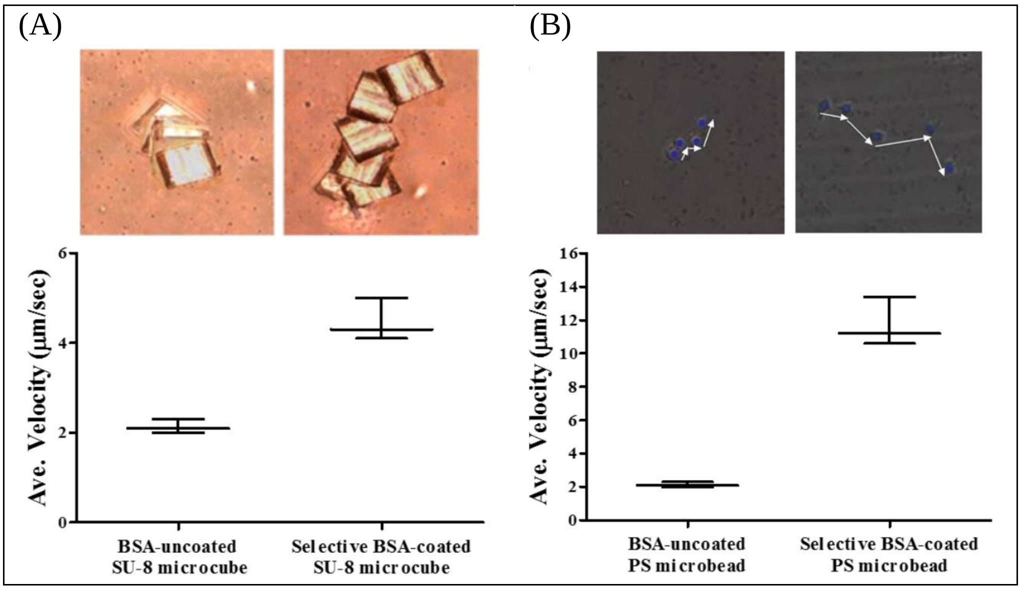

Figure 2.3 The graph of average velocities of bacteria microactuator (A) Serratia marcescens-actuated microrobot and (B) Salmonella typhimurium-actuated microrobot [19]

In Figure 2.3 , the result shows that both bacteria-based actuators move faster than the original actuators; Serratia marcescens-actuated SU-8 microrobot and Salmonella typhimurium PA are two times and five times faster on average velocity than the normal SU-8 and PA respectively. The idea of using bacteria as the driving device like these two microrobots could be applied to our nanorobots.

2.1.1.2 Mechanical Nanotechnology

Most of the nanotechnology researches are in the biological field of study. However, researchers in mechanical and electrical fields also proposed some bottom-up designs of nanocomponents as well. An example is an ultrahigh-speed rotator. This is the new nanoscale motor fabricated by Texus engineers. It is claimed as the world's smallest, fastest and longest-running nanomotor [21]. This nanomotor could spin approximately 18,000 rpm and continuously spin for 15 hours while other comparable nanomotor could spin more slowly around 14 - 500 RPMs and only rotated for a few seconds. Moreover, several nanomotors can synchronously work with controllable angle and speed.

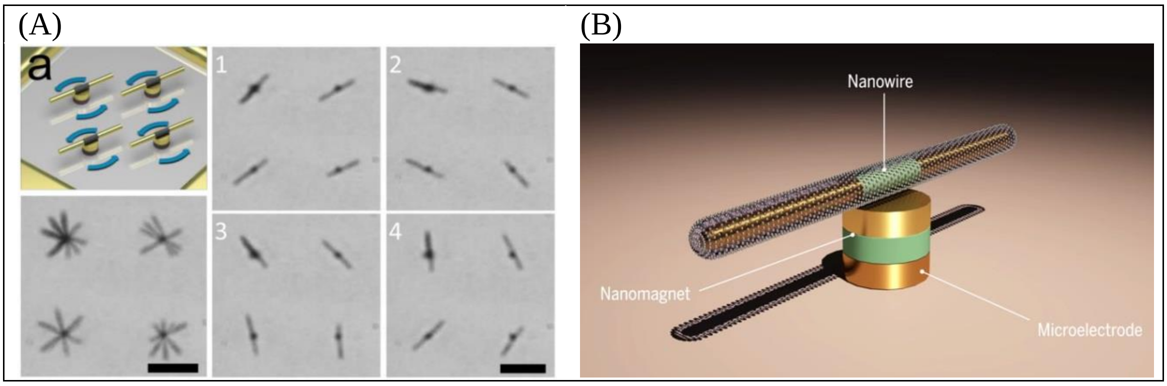

Figure 2.4 (A) Schematic diagrams and snapshot images of nanomotor array which synchronously rotate clockwise. The scale bars are 10 μm and (B) the component of a nanomotor [21]

The nanomotor consists of three nanocomponents as showed in Figure 2.4. The nanowire is acting as rotors. The nanomagnet is the bearings. The microeletrode is used as the stators. The nanowire is the multisegment of Au/Ni/Au. It is 20-400 nm in diameter and 6-10 μm in length. The nanomagnet is 500 nm – 2 μm in diameters and consists of tri-layer thin-film stacks. The top Au layer is used for adjusting the magnetic attraction between the nanowire and magnetic field. The middle layer is the magnetic field. The lowest layer is Cr layer that is used for adhering to the substrate. The manipulation technique is the electric tweezer which can transport nanoentities to the precise location within 150 nm.

This nanomotor could apply to a drug delivery application. The nanomotor could allow a nanodevice to travel inside human body and release the drug at the target site. The rotation-controlled biomolecule releasing nanodevice is one example of the drug delivery machine that spins to release the biomolecule adhered on nanowire at the cancer cells as illustrated in Figure 2.5 [21].

However, due to the current size of this nanomotor and its capabilities, it might not be a good candidate for nanorobots in our purpose. Nevertheless, this nanomotor shows the fascinated step in developing technology for nanoscale devices.

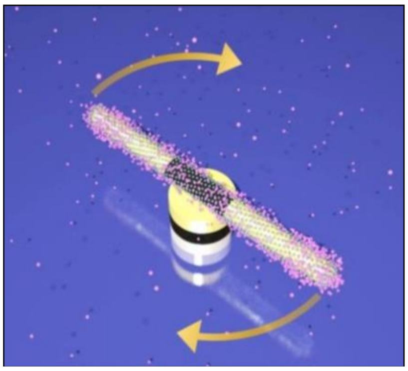

Figure 2.5 The rotation-controlled biomolecule releasing nanodevice [21]

2.1.2 Nanorobot Applications

In order to prepare for upcoming technology, the characteristic, capability, programmability and feasibility of nanorobots become the concentrating issues. The nanorobots are widely researched in many fields. In dentistry [4], nanorobots can be used for preventing dental disease, restoring the damaged teeth or nerve and assisting in the curative procedure. In pharmacy, the idea of using nanorobots to deliver drug is interesting. Sending the drug directly to the damage site is more effective. Another idea is for cancer detection and treatment by sending nanorobots into the body to find the cancer cells and eliminate them. This can decrease the side effects to other normal cells compared to chemotherapy. In surgery, nanorobots will be useful for the case that the surgical area is hard to access such as in the brain or heart. Medical doctors can send nanorobots to the site for monitoring or even healing the conditions. For some cases, they could help medical doctors to operate without opened-wound, for example by sending them into the blood vessel for cutting some tumors. In diagnosis, testing and monitoring, nanorobots can be put into our bodies for recording and reporting the information such as temperature, blood pressure and etc so that doctors can make diagnosis from that information. For heart disease patients, nanorobots can be used to monitor the heart pulse and produce alert signals when detecting the abnormal state. In gene therapy, nanorobots possibly have an ability to reattach the DNA chain that could be used for eliminating virus or cancer cells. In this section, the capabilities and characteristics of nanorobots in each application are reviewed in order to identify the common characteristics for nanorobots in our model.

2.1.2.1 Nanorobot for Brain Aneurysm

The brain is the most complex organ that has the main role in controlling all systems in our body. When the problems occur to the brain, it affects all other systems tremendously. Thus, the problem should be diagnosed and treated immediately and precisely. In order to achieve that, medical doctors need to glean a lot of information from many sources such as a computed tomography (CT) scan, magnetic resonance imaging (MRI) and positron emission tomography (PET).Medication can be used to reduce the symptoms, but in some cases, e.g. brain tumor or strokes, the surgery is needed. However, performing a brain surgery would affect the brain tissue. It would be better to cure without opening wound.

Cavalcanti et al. proposed a new idea in 2009 [3] about exploring the brain by sending nanorobots into the blood vessel inside the brain instead of surgery. Due to their small sizes, nanorobots will not damage the brain tissue. Nanorobots are sent into the blood vessel to find the position of the aneurysm and send the information back to the operating doctor. The illustration of this nanorobot is showed in Figure 2.6. This information could be used for guiding or supporting other results.

In [3], the characteristics of nanorobots include chemical sensor, actuator, power supply and data transmission. For chemical sensor, CMOS-based sensor could be used. It could be built by using carbon nanotubes. This sensor could be used for sensing the NOS protein which exists only in the brain. Nanorobots could use this for knowing their own position. CMOS-based actuator could be used as the locomotion system for nanorobots. For the power source [3], the resonant electric property from nanocircuits could be used. It can provide 1.7 mA at 3.3 V. Nanorobots could send the signal to the doctor outside the body using RF communication. It could take around 1mW to send the signal. The blood vessel is the environment for this simulation, which consists of red blood cells, white blood cells, platelets and nanorobots [3]. Nanorobots are a cylindrical shape 2 µm in length and 0.5 µm in diameter. In the study, 1012 nanorobots are used in the entire 5-liter blood volume of a typical adult, which are 0.2 g total mass. Their velocity is around 1 mm/s. They can sense the NOS protein which indicates that there is aneurysm.

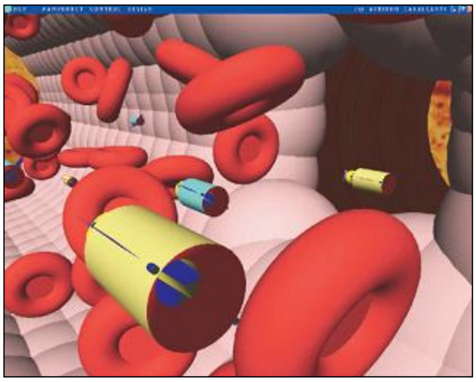

Figure 2.6 Nanorobot model for Brain aneurysm [3]

2.1.2.2 Nanorobot for Repairing a Damaged Nerve

The dymyelination is the disease of the nervous system. The damaged nerve cannot send or receive the brain signal as illustrated in Figure 2.7. Patients can lose their movement or cognition depending on which nerve is affected.

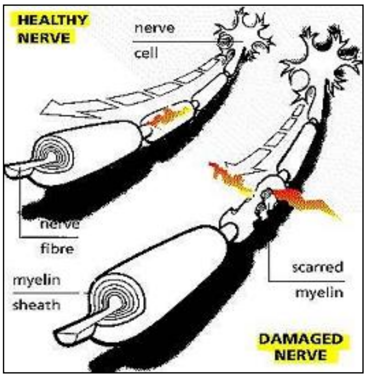

Figure 2.7 The damaged nerve [4]

Al-Arif et al. [4] showed the idea of using nanorobots to find and repair the nerve. In [4], nanorobots will be placed on the nerve. They will sense the electrical signals to choose the way. After they find the damaged nerve, nanorobots will repair it by sheathing synthetic myelin on it. In [4], the characteristic of nanorobots are concerned about 5 things including actuator, directional control, speed control, weight control and energy supply. The actuator could be CMOS based on biological patterns. One nanorobot could have 4 sensors in the front as showed in Figure 2.8. The direction could be computed from the voltages at each sensor. The speed could be controlled by the back wheels. It can speed up when there is no disturbance. It will decrease the speed, if there is disturbance. The weight control [4] could use the concept of attractive force between two current carrying conductors. The energy comes from ambient energy. The temperature displacement could generate the voltage differentials.

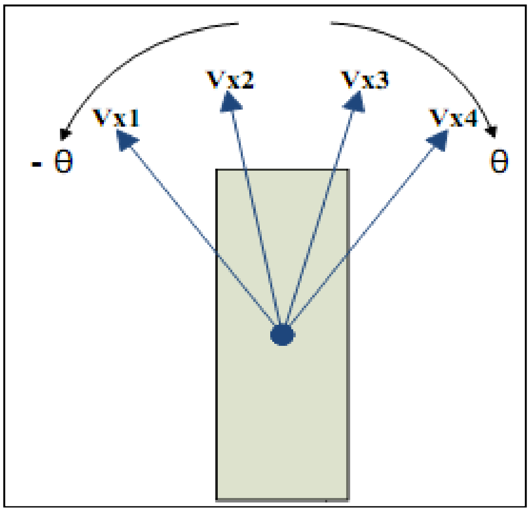

Figure 2.8 Nanorobot model for damaged nerve [4]

2.1.2.3 Nanoparticles for Cancer Therapy

Cancer is a very well-known disease for that it is the major cause of death with no effective treatment [6]. There are many methods of treatment such as chemotherapy, surgery, radiation. Normally, more than one way are used for the most effective result. Each of the treatments has side effects. Surgery can damage the surrounding tissue, and it has opportunity to infect. The examples of the side effects from chemotherapy are blood disorders, hair loss, nausea and vomiting. Lohcharoenkal et al. [6] proposed the protein-based nanocarrier for cancer therapy. The size of it is defined around 130 nm. It is ideally sent into bloodstream then penetrates through various barriers to reach the target tumor. After that the tumor cells will be selected and killed by the nanorobots without affecting the normal cells. The albumin is used because it is a natural transporter and can also be used in several clinical trials, which is in progress [22].

2.1.2.4 Nanorobot in Dentistry

Nanorobots are widely interesting for researchers in many medical fields including dentistry. The nanorobot is designed for many functions including oral analgesia, desensitizing tooth, manipulating the tissue to re-align and straighten irregular set of teeth, and improving durability of teeth. The example of dental nanorobot is displayed in Figure 2.9. The expectations of nanorobots to patients are the elimination of diseases and painless recovery.

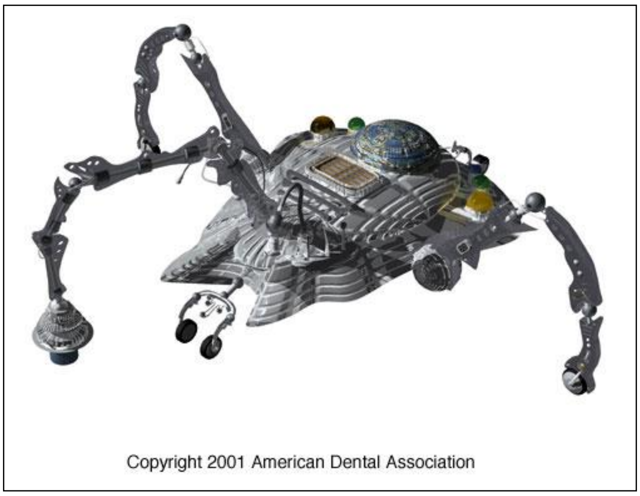

Figure 2.9 The remote-controlled dental nanorobot [23]

Nanorobot is designed to be 0.5-3 μm in diameter [5]. Glucose and oxygen are the energy sources. The characteristics of nanorobots include camera for determining the direction, swimming tail as a moving part, computational part for controlling nanorobots, communication which could be obtained by acoustic signal. The nanorobot knows its current position from the acoustic signaling navigational network installed in the body. The nanoparts could be constructed from many materials such as carbon, sulphur, hydrogen, oxygen and fluoride. Nanorobots will be excreted via the human excretory channels after finishing the assigned task.

The dental nanorobot is also designed for many applications such as inducing local anaesthesia, treating dentine hypersensitivity and treating the oral cancer [18]. The anesthetic dental nanorobot is designed for blocking the nerve from transmitting pain sensation signal. Nanorobots could be controlled by the operating dentist. First, nanorobots would be sent to the nerve. When the dentists desire to start the dental process, they will activate nanorobots and deactivate nanorobots after the process is complete. The advantages of using nanorobots for dentistry are better control over target area, lesser complication as it can maintain the anesthetized period. Moreover, it could improve the patient experience as it is the needleless process. For hypersensitive area, nanorobots could identify and seal the dentinal tube with desensitizing agents. This way provides the immediate and long-lasting relief to the patient.

Another designed application of dental nanorobots is for treating the oral cancer. Nanorobots would destroy the cancer cells by penetrating the cells and increasing the intracellular pressure or temperature with focal lasers, microwaves or ultrasonic waves.
This nanorobot is designed to be a multi-purpose nanorobot. It is spherical in shape with multi-armed for rapid movement. The pre-program is installed for controlling the nanorobot. The nanorobots have two-way communication with operating dentist using acoustic signals or electromagnetic waves. It can also interact with other nanorobots using light signals and chemical nanosensors. The diamondoid circular saturated hydrocarbons could be used as material of nano components. The advantages of saturated hydrocarbons are chemically and thermally stable, self-assemble and light in weight. The energy of nanorobots could come from two sources: internal source including radioactive particles, solar cells, and external source such as body heat as well as blood glucose.

2.1.2.5 Nanorobot for Blood Vessel Repair

The wound in the blood vessel can be everywhere. Platelets have responsibility for closing and healing the wound. For some patient who has a platelet disease, the number of platelets might not be enough. Freitas [10] proposed the design of an artificial mechanical platelet, which is called clottocytes [10]. The clottocytes are designed to repair the wound by releasing the carried fiber mesh over the injury site. These clottocytes could increase the hemostasis to 100-1000 times faster than natural hemostasis. Inspired by the clottocytes [10], Boonrong and Kaewkamnerdpong [11] proposed the idea for controlling nanorobots to repair the blood vessel. The study aims to simplify the characteristics of nanorobots. This early stage nanorobot design increases the possibility of constructing nanorobot in near future. The idea is to send nanorobots to travel along the bloodstream. When the wound is found by sensing the von Willebrand factor (vWF), nanorobots will assemble with others as a nanorobot plug to close the wound. Thus, the nanorobots must be able to move in the blood vessel, communicate with other nanorobots, assemble together, operate inside human body with biocompatibility and can be programmed for doing the defined task. In term of nanorobot control mechanism, particle swarm optimization technique (PSO) is chosen because it has few parameters and requires less memory [11].

From the review of nanorobot applications in section 2.1.2, the commonly identified characteristics for nanorobots are:

- movable in the defined environment,
- built from biocompatible material and getting along well with other systems,
- pre-programmable for controlling their operation,
- communicable with both other nanorobots, and
- capable of carrying some substance or treatment.

These characteristics are the possible list of characteristics that could be applied to nanorobots in this study. Due to their designed function for blood vessel repair, the nanorobot characteristics could be:

- movable in the bloodstream,
- compatible with other particles inside blood system,
- pre-programmable for controlling nanorobot behaviors,
- self-controllable without centralizing operation,
- capable of interacting with other nanorobots, and
- capable of carrying some substance or treatment.

The identified characteristics of nanorobots in this study are adequate when compared to the common characteristics. Moreover, from the current nanotechnology in both biological and mechanical approaches described in section 2.1.1, the possibility of building the real nanorobots could be enabled in the near future. Instead of carries the fiber mesh to release at the wound site, Boonrong and Kaewkamnerdpong [11] introduced the simpler version of nanorobots that uses itself to self-assemble into a mass to cover the wound. In [10], the capability to carry things requires the cage that could hold them with the nanorobots. This might increase the size of nanorobots and increase the complexity of nanorobots in order to release the fiber to the wound site in such highly dynamic environment. Thus, the early stage nanorobot seems more interesting in term of simplicity.

2.2 Swarm Intelligence

Nanorobots in this study are the early-stage nanorobots which have a few simple characteristics. In order to accomplish the complex tasks, they need to cooperate with others. The algorithm that could control the swarm of simple particles that can communicate in limited range with others is swarm intelligence (SI). This algorithm is a meta-heuristic technique which imitates the behaviors of insects in term of decentralized, self-organized and self-adaptive systems. Each insect did not have many abilities but they can accomplish a complex task. Moreover, it could robustly handle the changes in the environment. The systems achieve the goal even when some particles fail. In swarm intelligence, there are three main algorithms including ant colony optimization (ACO), artificial bee colony algorithm (ABC) and particle swarm optimization (PSO). In this section, each algorithm is explained and analyzed toward the use as the nanorobot control algorithm.

2.2.1 Ant Colony Optimization

Ant Colony Optimization (ACO) inspired by the behavior of ants for finding the shortest path from the nest to food sources. At the beginning, each of them randomly chooses the direction to the food sources. When it finds the food, it will carry some food back to the nest. Naturally, ants will leave pheromone, which is chemical substance, on the floor along their path, called the pheromone trail. This pheromone can evaporate over time. Thus, if the pheromone are all evaporated, it means that the first ant taking too long to go to the food source and come back. The shorter path will have higher pheromone intensity. The next ant at the nest can be decide whether to follow the pheromone trail of the previous ant or to randomly go to another path. The ants most likely follow the path with highest pheromone intensity, which implies the shortest path. When more ants travel on that path, the pheromone intensity will be increased. The farther path, which has lower pheromone intensity, will be finally abandoned. This ant behavior is presented in the Figure 2.10.

The ACO algorithm mimics the behavior of the natural ants. Each path in the algorithm represents the feasible solution and the food sources represent the optimum solutions. The pheromone concentration represents the quality of the solutions. The solution that has highest pheromone concentration so far is returned as the best solution to the problem. This algorithm allows both exploration and exploitation. The exploration is processed by the pheromone evaporation and a random search of new path. The exploitation process is done by determining path with probability based on the pheromone concentration.

ACO can be applied for solving travelling salesman problem, routing problem [24], redundancy allocation problem [25], scheduling problem [26] and other combinatorial problems. However, for nanorobots moving in the blood vessel, the search space is the continuous search space. Moreover, this algorithm requires leaving some signal or information in the environment to give the confident to that path, which is quite hard to apply this to the dynamic environment as in blood system.

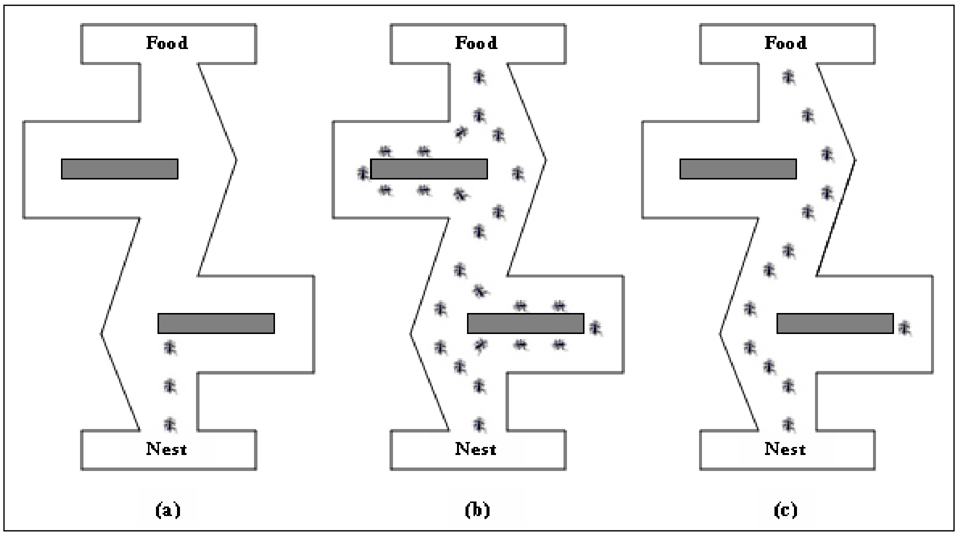

Figure 2.10 The self-adaptive behavior of ants, (a) the ants randomly go to seek for food sources; (b) ants follow a path between nest and food source; ants choose, with equal probability, whether to shortest or longest path; (c) the majority of ants have chosen the shortest path [27]

2.2.2 Artificial Bee Colony Algorithm

Artificial bee colony algorithm (ABC) is inspired by the behavior of bees finding food sources. In the algorithm, there are 3 kinds of bees: employed bees, onlooker bees and scout bees. Around the half of the colony are employed bees. Another half are the onlooker bees. Each employed bee will exploit around the area of their own best food source in order to find the better food source. After exploiting, they will come back and share their information with the onlooker bees that wait at the hive. Then, each onlooker bee chooses the interesting food source based on the quality of the food source and exploit more around the selected food source as employed bees do. After the quality of the food source did not improve for some predefined amount of times, the employed bees will be allocated as scout bees. The scout bees are responsible for exploring the new food source by randomly finding a new food source.

The ABC algorithm mimics this behavior of bees. Each bee represents a feasible solution. The food sources are the optimum solutions. The pseudocode of ABC algorithm is shown in Figure 2.11. Different types of bees provide the exploration and exploitation process. The exploration comes from the behavior of scout bees. The exploitation is from the behavior of the employed bees recruiting onlooker bees to perform fine searches in their areas. This algorithm can be used for solving the problems with large search space and many local optima. Moreover, it is also suitable for continuous search space as our search space inside blood vessel. However, this algorithm requires the mechanism of information sharing between different kinds of bees at the hive, which is similar to the centralization system. This may be hard to apply with a swarm of nanorobots that operates in dynamic environment like bloodstream.

```
Do
    For each Employed bee
        Produce new food source
          Do
                Exploit around the food source to find the better one
          while the better solution is not found
                and the number of unimproved solution is not exceed
          Share the position and quality of the food source to onlooker bees
          Determine the source to be abandoned and allocate employed bee
                as scout bee
    End
    For each Onlooker bee
        Select the food source from employed bees
          Do
                Exploit around the food source to find the better one
          while the better solution is not found
                and the number of unimproved solution is not exceed
    End
    For each Scout bee
        Random the new food source
          Allocate back to be employed bee
    End
    Memorize the best food source found so far
While stopping criteria is not attained
```

Figure 2.11 The pseudocode of ABC algorithm.

2.2.3 Particle Swarm Optimization

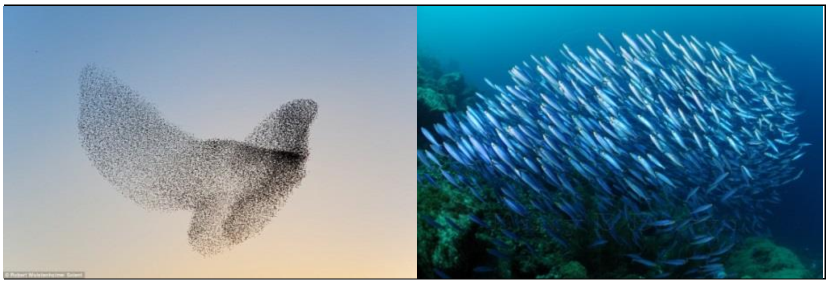

Figure 2.12 The nature flocking of birds and fish schooling.

Particle swarm optimization (PSO) is inspired by the behavior of bird in the flock as shown in Figure 2.12. In order to find the food sources, a group of birds randomly searches around the area. The birds do not know where the food is, but each of them can sense it. This information is shared within the flock. Thus, each bird decides to change direction and velocity based on both its own information and the swarm's information in order to find the best way to the food source.

From this concept, Eberhart and Kennedy proposed the Particle Swarm Optimization algorithm [28]. The main idea of this algorithm is that each particle can do the simple task and share the information to others directly in order to coordinately perform the more complicated tasks. Each particle consists of the current position, the current velocity, the personal best position (pbest) and the local/global best position (lbest/gbest). The personal best position represents the best solution so far of individual particle. The local/global best position is the best solution so far of the neighborhood. If the social best position is collected from the population, this will be called the global best position. If the social best position is collected from neighbors or only a group of swarms, this social best position will be called the local best position. The topology of the sharing information of the particles could be selected based on the suitability to the environment or search space. Figure 2.13 shows some example topologies that could be used. In some problems, the interaction between particles might be limited by the environment or even the ability of particle itself, the fully connected may not suitable. Some problems might require the combination of many types of topologies; for example, in the case where particles need to communicate within the small group but with centralization, the isolated and star topology could be used together.

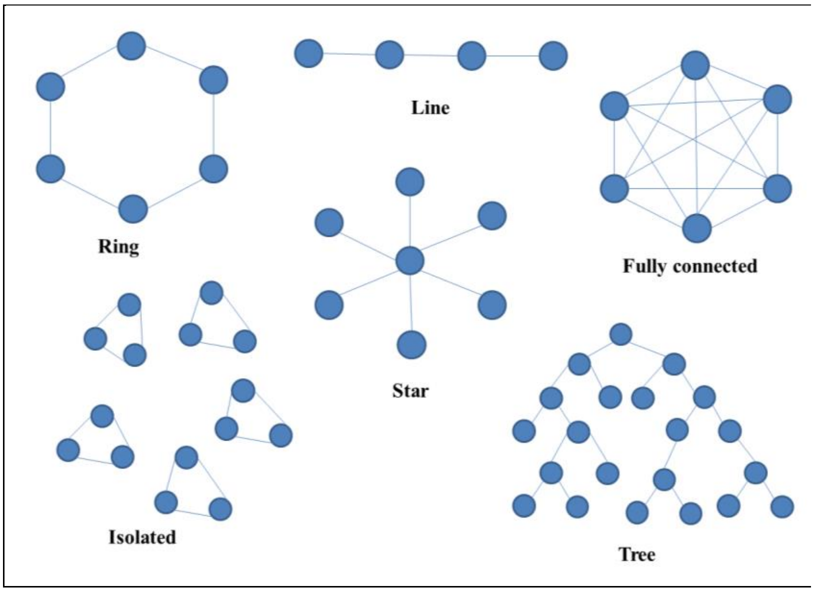

Figure 2.13 Some common neighborhood topologies.

The position and velocity will be updated on every iteration. The new position is the summation of the current position and the new velocity. The new velocity is computed from the current velocity, personal best position, local/global best position and some random parameters. The new velocity can be computed from equation (2.1),

$$v(t+1) = \chi\left(v(t) + c_1 r_1 \left(x_{pbest} - x(t)\right) + c_2 r_2 \left(x_{lbest} - x(t)\right)\right) \quad (2.1)$$

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 lead to higher exploration. The constriction coefficient can be computed from

$$\chi = \frac{2}{\left|2 - \varphi - \sqrt{\varphi^2 - 4\varphi}\right|} \quad (2.2)$$

$$\varphi = c_1 + c_2 > 4 \quad (2.3)$$

where c_1 and c_2 are the acceleration constants. These two parameters are used for weighting between the personal best position and local best position. These can be used to regulate the exploration and exploitation search as well. The higher c_1, which implies the higher confident in personal experience, will promote the exploration search. On the other hand, the higher c_2 will lead to the increase chance for exploitation because neighbors will tend to move toward the same local best position. The value that can indicate the quality of the solution is called the fitness value, which is calculated from the fitness function. The fitness function must be constructed based on the interesting values of each problem that can indicate the performance of the solution. The new best solution will be chosen from the solution that has best fitness value.

The PSO algorithm starts from initializing the position and velocity for each particle. Then, the fitness value of the current position of particles must be calculated. Then, the fitness value is compared with the fitness value of the personal best position. The higher fitness value will be stored as the new personal best position. For the first round, the current position will be the personal best position. After that, each particle shares and collects the best individual position from other particles according to the neighborhood topology. By comparing the fitness values of collected position to the fitness value of current local/global best position, the local/global best position is updated with the position that achieve the highest fitness value. After that, each particle recalculates the velocity and position. Redo all the process until it meets the stopping criteria. The stopping criteria could be when the number of iterations has been reached or when the expected fitness value is achieved. The pseudocode of PSO algorithm is shown in Figure 2.14.

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

Figure 2.14 The pseudocode of PSO algorithm.

The PSO algorithm can find the solution in continuous search space as in the bloodstream. In addition, it is good in both exploration and exploitation. The exploration process is from the stochastic parameters. The processes of updating the personal best position and local/global best position exhibit the exploitation process over the optimum solution. Moreover, this algorithm supports the decentralization mechanism from direct information sharing between particles. For these reasons, PSO seems suitable with the behavior of the natural platelets that can work individually with some cooperation. Due to the limitation of nanorobot size, the algorithm should require less memory as PSO has only few parameters. In addition, Boonrong and Kaewkamnerdpong [11] has demonstrated the use of PSO as a nanorobot control algorithm for blood vessel repair with Newtonian blood model and reported their result with good performance.

2.3 Platelet and Hemostasis Process

The platelets or thrombocytes are one of blood elements, which is 4.9% of formed element of blood [16]. Platelets are not the whole cells but small fragments originating from cytoplasts of megakaryocytes, which are the largest cell in bone-marrow. The cytoplast has many small pseudopods, which will slip off and become platelets with 2-4μm in diameter and 10 days lifespan in average. When platelets are in their inactivated states, they are discoid in shape but spheroid when activated [16]. Platelets can be activated after prolonged exposure to high shear stress or when the shear stress rapidly increases such as when vasoconstriction happens at damaged vessel [29]. Platelets also become activated after attaching to the exposed collagen at the wound [29].

Platelets are the main players in hemostasis, which is the process of stopping the bleeding in the vessel. In small blood vessel such as capillaries and arterioles, the hemostasis alone could stop the bleeding because the pressure inside the small vessels is not much higher than the pressure outside. On the contrary, the bleeding from medium to large vessel needs additional process because the pressure inside large vessels is much higher than the external pressure. In this case, pressing on the wound will increase the external pressure which could temporary pause the blood flow from injured area; after that, the surgery is needed.

2.3.1 Thrombocytopenia

Normally, there are 150,000 – 450,000 platelet cells per 1 ml of blood [30]. Patients who have platelet counts less than 150,000, will be diagnosed as Thrombocytopenia. In this condition, the bleeding can hardly be stopped. The risk for major bleeding could occur after platelet count is less than 10,000 [31]. More platelets or other methods to help closing the wound site and reducing blood loss are required. The signs and symptoms of thrombocytopenia that could easily see include,

- Contusion and bruise: patients might see the large areas of bleeding under the skin that could turn purple, yellow or green over time. It looks similar to the bruises that normally get from being hit, but it happen because the tiny blood vessels suddenly break.
- Bleeding: patient could get nose or gums bleeding easily.
- Prolonged bleeding: patient will bleed for longer time when injured. In women, the period may happen in longer period of time.
- Petechia: patients might see the pinpoint spot under the skin as shown in Figure 2.15

Figure 2.15 The petechia on the patient's back and arms [32]

There is no specific test for thrombocytopenia because the situation could be different from many causes including familial thrombocytopenia, hypersplenism, or systemic lupus, drug-induced thrombocytopenias and HIV infection [33]. The hypersplenism can enlarge the spleen because platelets are trapped inside the spleen. Thus, platelets will not circulate through the body. Sometimes, the immune system disorder could decrease the platelet count because it attacks the platelets. The platelet count could also decrease because bone marrow does not create enough platelets. This might happen with blood cancer patients such as leukemia.

The treatment can be varying with the causes. Normally, the medicine could be taken. This way, platelets will slowly increase. In the emergency situation, platelet transfusion is needed so the platelet count increases immediately. However, for obtaining enough platelets, the large amount of blood is needed. Moreover, the obtained platelets might be rejected by the immune system.

2.3.2 Hemostasis Process

Hemostasis has three steps: vascular spasm, primary hemostasis and secondary hemostasis. The vascular spasm occurs immediately after the blood vessel is cut or torn. In this step, the vasoconstrictive paracrines was released from the endothelium [34]. This causes the damaged vessel constriction which decreases the blood loss.

Then, the primary hemostasis as illustrated in Figure 2.16 instantaneously takes place. The primary hemostasis is also called the temporary hemostasis [34] because this process only creates the temporary seal from the platelet plug. Right after the vessel is injured, beside the vasoconstrictive paracrines, the collagens in the underlying connective tissue are exposed. The passing platelets will stick to these exposed collagens by two assistant factors including fibronectin, which is secreted by endothelial cells as well as platelets, and von Willebrand factor (vWF), which is used as glue [36]. This process is called "platelet adhesion". After bonding, platelets become activated. The activated platelets become more spherical in order to increase the surface area. The outer coat of platelets becomes stickier so that activated platelets could aggregate together and become a platelet plug. This process is called "platelet aggregation". The activated platelets release the platelet factors that contribute the platelet aggregation [34, 35];

- adenosine diphosphate (ADP) and platelet-activating factor (PAF) activate other surrounding platelets;
- PAF initiates the conversion of platelet membrane phospholipids to be thromboxane A_2;
- cytokines, serotonin and thromboxane A_2 reinforce the vasoconstriction.

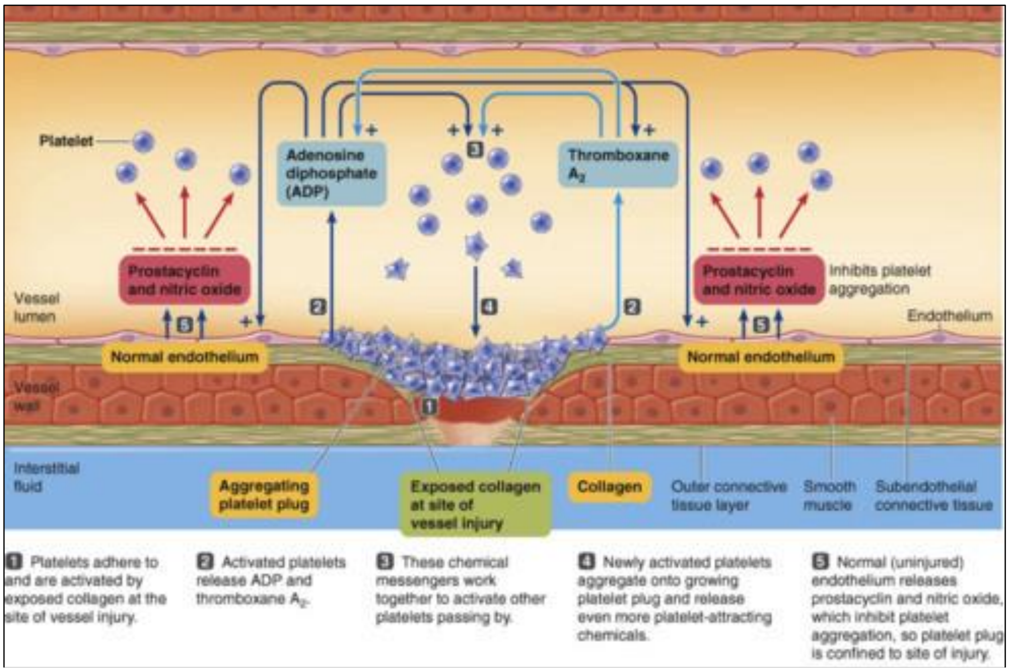

Figure 2.16 The primary hemostasis. Platelets adhere at the injured site by sticking to the exposed collagen. The activated platelets release many factors in order to form a platelet plug. The normal endothelium concurrently releases prostacyclin and nitric oxide to prevent the activated platelets from aggregating at the undamaged site [35].

The platelet plugs from the primary hemostasis are loose and temporary. Then, the secondary hemostasis takes place in order to strengthen and stabilize the platelet plugs by combining the fiber mesh with other blood cells such as the erythrocytes [35]. The strengthened platelet plug is called a “clot”. The secondary hemostasis is the complex process that requires a series of enzymatic reactions to form a fibrin protein fiber mesh [34]. This process could be called “Coagulation cascade”. This process has three major steps [36]: formation of thromboplastin, formation of thrombin and formation of fibrin. The thromboplastin is produced through intrinsic pathway and extrinsic pathways. The intrinsic pathway is from the interaction of platelets with the coagulation factors XII, XI, IX and VIII. In extrinsic pathways, the thromboplastin is released from the injured tissue. The thromboplastin activates the factor VII. Then, the thromboplastin, factor VII, V and X convert prothrombin to the activated thrombin. After that, the thrombin converts fibrinogen to fibrin. Finally, the fibrin clots are formed and stabilized by the factor XIII. As a result of this process, the wound is sealed by the stabilized platelet clot. The clot will stick to the damaged site until the vessel tissue is repaired. Eventually, the clot is slowly dissolved by the enzyme plasmin. The summary of coagulation factors are explained in Table 2.1.

Most of blood vessel injuries occur in the small blood vessel where the primary hemostasis alone could stop bleeding. However, if the large vessel injures, the primary hemostasis alone could not stop bleeding. The reason is the high pressure inside the vessel will spurt blood out. It requires the external pressure to compress the injured vessel. In some cases, the surgery is needed. In this study, nanorobots are designed based on the behavior of platelet in hemostasis. Thus, the environment for this study will be in small vessel. As described in section 2.3.2, the second hemostasis is too complex to simulate for the early stage version of nanorobots. Thus, this study designed the nanorobots to act as the platelets in the primary hemostasis.

Table 2.1 The coagulation factors [36]

Factor	Name	Synonym(s)
I	Fibrinogen	
II	Prothrombin	
III	Tissue thromboplastin	Tissue factor
IV	Lionized calcium	
V	Labile factor	Proaccelerin accelerator globulin (AcG)
VI	Stable factor	Proconvertin, serum prothrombin conversion accelerator (SPCA)
VII	(Not assigned)	
VIII:C	Antihemophilic factor (AHF)	Antihemophilic globulin (AHG), Antihemophilic factor A, subunit VIII:C
VIII:vWF	von Willebrand factor (vWF)	Subunit VIII:vWF
IX	Plasma thromboplastin component (PTC)	Antihemophilic factor B (AHB), Christmas factor
X	Stuart-Prower factor	Stuart factor
XI	Plasma thromboplastin antecedent (PTA)	Antihemophilic factor C
XII	Hageman factor	Glass factor, contact factor
XIII	Fibrin-stabilizing factor (FSF)	Fibrinase
Others	Prekallikrein (PK)	Fletcher factor
	High-molaecular-weight kininogen (HMWK)	HMW kininogen, Fitzgerald factor
	Fibronectin	
	Antithrombin III	
	Protein C	
	Protein S	