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Thermo-fluidic devices and materials inspired from mass and energy transport phenomena in biological system

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Abstract Mass and energy transport consists of one of the most significant physiological processes in nature, which guarantees many amazing biological phenomena and activities. Borrowing such idea, many state-of-the-art thermo-fluidic devices and materials such as artificial kidneys, carrier erythrocyte, blood substitutes and so on have been successfully invented. Besides, new emerging technologies are still being developed. This paper is dedicated to presenting a relatively complete review of the typical devices and materials in clinical use inspired by biological mass and energy transport mechanisms. Particularly, these artificial thermo-fluidic devices and materials will be categorized into organ transplantation, drug delivery, nutrient transport, micro operation, and power supply. Potential approaches for innovating conventional technologies were discussed, corresponding biological phenomena and physical mechanisms were interpreted, future promising mass-and-energy-transport-based bionic devices were suggested, and prospects along this direction were pointed out. It is expected that many artificial devices based on biological mass and energy transport principle will appear to better improve various fields related to human life in the near future.

Keywords bionics, mass transport, energy transport, artificial devices and materials, biology system, nature phenomena, medical device.

1 Introduction

The existing colorful biosphere came into being after millions of years of natural evolution. In this long and intense

struggle to survive, every species has obtained its numerous amazing abilities. Such natural phenomena provide many great inspirations for humans to solve immediate puzzling problems in science and technology.

In fact, it has been a long history of people learning from nature. A long, long time ago, Chinese ancestors had invented the saw by mimicking some grasses with notched leaves, and manufactured the kite after observing the soaring activities of birds (Fig. 1). However, these inventions, which were far ahead of modern science and technology, were still only simple imitations of biological phenomena on a superficial level, without any analysis and deduction on the scientific issues. The symbol for establishing bionics as an independent science can be dated back to the bionics congress held at Dayton, Ohio, on September 13–15, 1960 which was during the third technological revolution, and the rapid development of science and technology provided favorable conditions for bionics. Meanwhile, there is no doubt that bionics markedly promote the third technological revolution. It almost becomes a fact that every subject can get help from studying bionics. Therefore, strictly speaking, bionics is not only a subject, but also a methodology, a new thought model of human problem solving.

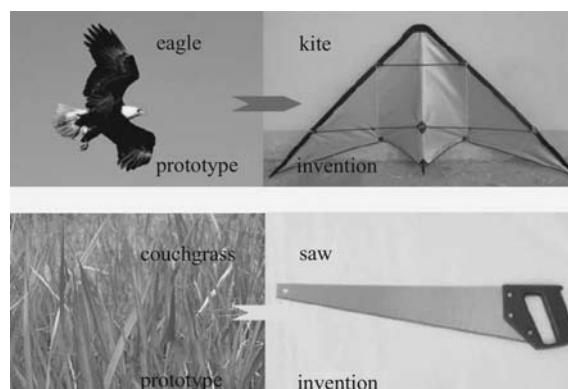


Fig. 1 Several living prototypes and relevant bionic products inspired from nature

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In general, the causes leading to various biological phenomena can be classified as mass and energy transport activities. Many behaviors originated from such processes in biological tissues, such as the electrogenesis of the electric eel, and the movement of the spider's legs driven by hydraulic pressure. On the system level, every organism is a unit which has to exchange substances with its environment to maintain a normal physiological activity and to offset the entropy increase caused by the activity *in vivo*. Clearly, organs, tissues, and cells are just such kind of systems. Therefore, investigating the phenomena and fundamentals of mass and energy transport in the organisms has considerable significance, which may benefit many fields with concerns of human life, such as disease treatment, sterilization and disinfection etc.

With a great many technological progress and marked development of bionics, many devices and materials are now successfully invented by borrowing ideas from biological mass and energy transport mechanisms. Among the many applications of artificial devices and materials, medicine is one of the largest realms. And it has led to tremendous progress in saving human life. This article is dedicated to present a relatively complete overview of thermo-fluidic devices and materials inspired from mass and energy transport phenomena in biological system. For clarity, these artificial devices and materials are categorized into five kinds: organ transplantation, drug delivery, nutrient transfer, micro operation, and power supply. Prospects in this area will be pointed out.

2 Bioinspired or stimulated medical devices and materials

2.1 Organ transplantation

Mild organ sickness can generally be treated very well by traditional medicine. However, when it comes to serious illness, replacing the original organs with substitutes which can function normally may be the best choice. These substitutes include donor organs and artificial devices. So far, it has already been very common to transplant a donor organ into the patients' body. But the shortage of donors and the rejection between patients and transplanted organs become a big constraint on this practice. With the development of biology, medicine, material and other relevant subjects, artificial devices have become a major focus in organ transplantation. Naturally, artificial devices are expected to solve the problem encountered by donor organs. However, due to the complexity of the organism, artificial devices also encounter great dif-

ficulties. There is still a long way to go before artificial devices could completely replace the donor organs and function as normal organs.

2.1.1 Total artificial heart

There are millions of people who suffer from cardiopathy with various degrees, which bring great agony to them and seriously imperil their health. Today, about 50000 patients need heart transplants in the US each year, and only 2192 of them were successfully treated in 2006¹⁾, while others did not have the chance due to shortage of donor organs. Furthermore, transplantations of human hearts do not seem to be the best way to avoid rejection between patients and the transplanted organ. Therefore, artificial hearts are needed to extend the life of patients and improve their quality of life.

Historically, mechanical circulatory support (MCS) was used before the first sample of heart transplantation. In 1953, Gibbon first used his design, the heart-lung machine, which can oxygenate and circulate the blood in an extracorporeal circuit, on patients who suffered from congenital heart disease. Though three out of the four patients died, this design was regarded as a milestone in the research of artificial heart [1].

In the past 50 years, many different types of artificial hearts have been reported, which can generally be classified into three kinds based on their functions: short term assistance system, long term assistance system, and total artificial heart (TAH). TAH is considered as the most attractive since it can replace the human heart perfectly, extend human life and improve the living conditions of those who suffer from serious heart disease and that should have had heart transplants.

In 1969, Cooley and Frazier first implanted a TAH, developed by Liotta, in the bridge-to-transplant operation. This TAH performed its function as a human heart till a donor was provided, and then a heart transplantation was conducted for the patient [2].

In 1982, Devries and his team first placed Jarvik-7 (Fig. 2(a)) for permanent use [3]. Though it supplied hemodynamically stable support for patients, there still raised many complications such as hemorrhage, stroke and sepsis which impaired its performance. A major progress is that during 5 implantations performed in 1985, the longest period at which Jarvik-7 sustained the patients is 620 days²⁾.

The CardioWest total artificial heart (Fig. 2(b))³⁾, which evolved from the Jarvik-7, is the first TAH approved by the Food and Drug Administration (FDA). This apparatus did not cause any device-related

¹⁾ American Heart Association. Organ donation. 2006, <http://www.americanheart.org/presenter.jhtml?identifier=4697>

²⁾ Henahan S. State-of-the-art in artificial hearts. 2001, <http://www.accessexcellence.org/WN/NM/ozpage1.html>

³⁾ Jack D, Copeland G. Jarvik-7 artificial heart. 1985, <http://www.smithsonianlegacies.si.edu/objectdescription.cfm?ID=172>

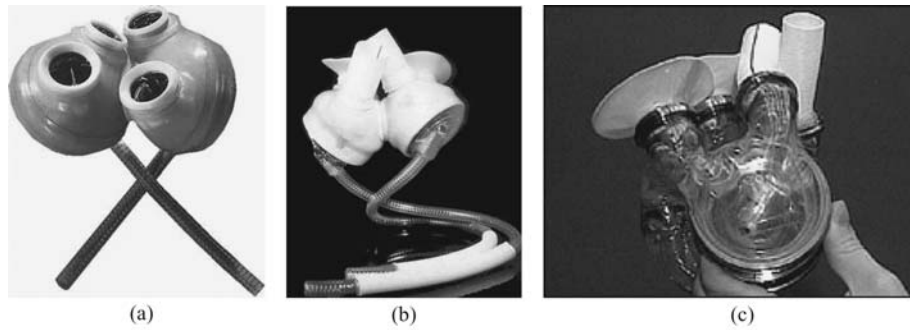


Fig. 2 Several typical artificial organs
(a) Jarvik-7³⁾; (b) CardioWest TAH⁴⁾; (c) AbioCor artificial heart⁵⁾

mediastinal infection. In those 36 patients who received implantation with CardioWest TAH as a bridge to transplantation, 29 survived to heart transplantation, and after then the longest survival time was found to be up to 7 years [4].

In 2001, the AbioCor artificial heart (Fig. 2(c)), as the first completely implanted device, was adopted to replace the damaged heart to sustain a patient's life¹⁾. A transcutaneous energy transmission technology (Fig. 3) continually provides electricity to the internal lithium batteries, which is used to drive the motor to maintain a stable blood flow, without any percutaneous lines [5]. This new technology significantly reduces infections and makes it possible for the patient to free himself from the limitation of an external battery pack. Some new materials were developed to solve the problems of clotting, calcification, toxicity, flexibility and durability [6]. With the use of these new technologies, AbioCor markedly improved the quality of patients' lives. Among the 7 critically ill patients who received implantation of AbioCor since 2001, 4 survived beyond 2 months, and 2 were discharged from the hospital, while the remaining 3 failed [7].

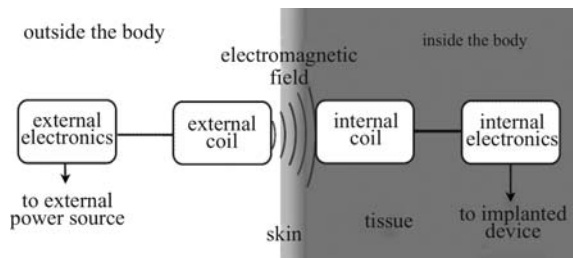


Fig. 3 Transcutaneous energy transmission system, modified from Ref. [8]

These TAH have significantly extended the patients' life and improved the quality of their lives. However, they are still far from being perfect. Future efforts can be focused

on the following problems: ① New biocompatible materials, which never bring forth any rejections and infections, are needed. ② Device-related complications should be restrained. ③ Hemodynamics should be studied and simulated accurately to provide hemodynamically stable blood flow. ④ New energy supply technologies should be developed to abate the limitation of an external battery pack.

2.1.2 Artificial kidney

Though kidneys account for no more than 0.5% of the body's weight, they can filter all the blood of an adult in 50 minutes. Without this function of kidneys, toxins and other small molecular wastes produced during metabolism will accumulate and endanger the health and life of the host. Nowadays, about 100 000 Americans are awaiting transplants of lifesaving organs, and the waiting list is increasing by 5 new names per hour [9]. Therefore, new methods should be developed to save patients' lives and improve their living conditions.

In 1913, Abel et al. first proposed the concept of "artificial kidney" [10]. In 1924, Haas first applied the dialysis to humans but failed due to technical difficulties and limited clinical success [11]. In 1960, Quinton et al. reported an external shunt for permanent vascular access and successfully applied intermittent hemodialysis for treating chronic renal failure [12].

Recently, major treatments include hemodialysis, kidney transplantation, bioartificial kidney, and recombinant genetic engineering. However, there are some limitations such as intermittent treatment, several serious complications and lack of metabolic, regulatory and endocrine function of renal tubules, which make hemodialysis incapable of substituting for the kidney [13]. The kidney transplantation is constrained by the rejection and lack of donors, and every day 17 people die while waiting

⁴⁾ U.S. Food and Drug Administration. FDA approves temporary artificial heart. 2004, <http://www.sciencedaily.com/releases/2004/10/041019085051.htm>

⁵⁾ Rowland R. Patient gets first totally implanted artificial heart. 2001, <http://archives.cnn.com/2001/HEALTH/conditions/07/03/artificial.heart/>

[9]. Although recombinant genetic engineering can produce many needed proteins, it is not enough to improve the patient's health completely. This is because the disease is not caused by the absence of few proteins but by the deviation from the normal interaction of cell components [14].

These technical limitations call for the development of a new permanently implanted device with total function, that is, bioartificial kidney. The bioartificial kidney is the intersection of many scientific disciplines, such as tissue engineering, immunology, transplantation biology, regenerative medicine, and so forth, and is considered as the most exciting field for treating renal failure. Recently, the most promising type of bioartificial kidney (Fig. 4) has been designed which consists of two parts—a bioartificial hemofilter and a bioartificial renal tubule assist device (RAD).

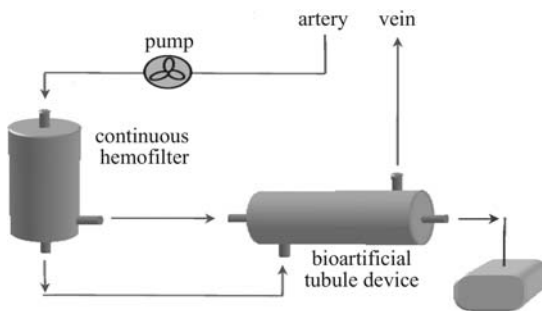


Fig. 4 Flow diagram of bioartificial kidney, modified from Ref. [13]

Clinically, common hemofilters should be replaced once a week. This is because a long period of operation may lead to some complications, such as systemic heparinization, bleeding, protein deposition. These replacements may bring serious inconvenience for patients. Therefore, an antithrombogenic continuous hemofilter should be developed to enhance performance of bioartificial kidneys. Saito et al. proposed a method for this purpose, using the inner surface of the hollow-fiber membrane pretreated with methacryloyloxyethyl phosphorylcholine (MPC) polymer which mimics the phospholipids of human cell membranes [13].

Humes et al. [15] developed a bioartificial RAD and tested it in vitro for a variety of differentiated tubular functions. They first made a tubular scaffold (Fig. 5) using high-flux hollow fiber hemofiltration cartridges with membrane surface areas of 97 cm² or 0.4 m², then seeded porcine renal proximal tubule cells, which were prepared with a synthetic extracellular matrix protein, into the intraluminal spaces of the hollow fibers. These cells grew in the tubular scaffold, and then produced confluent monolayers containing up to 1.5×10^9 cells (3.5×10^5 cells/cm²), thereby significantly improving recovery rates for perfused inulin to at least 95%. The hollow fiber could also protect these cells against

immune proteins for these large molecules with a molecular weight of over 150000 cannot penetrate through the hollow fiber [16]. And the test results indicated that the RAD achieved a marked improvement in transport, metabolic and endocrinological function of the kidney [15].

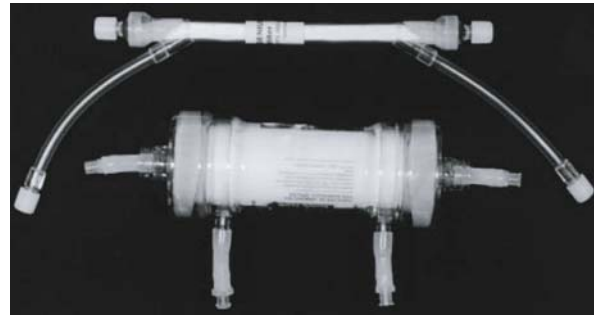


Fig. 5 Bioreactor hollow fiber cartridges used as scaffold of bioartificial RAD [15]

To develop a permanently implantable bioartificial kidney, future study may be focused on continuous hemofiltration and the full metabolic, regulatory and endocrine function of kidneys. For these purposes, a wearable roller pump is needed for the clinical application of a continuous treatment system. And new membranes with better antithrombogenic properties of the surface should be developed. Meanwhile, the metabolic function of renal tubule cells on the artificial membranes should be improved. Transfection of functional protein genes into renal tubule cells, which can increase the transport capacity and metabolic function of the bioartificial tubule device [13], should be investigated.

2.1.3 Salt gland: artificial kidney

Marine birds live in the sea where there is no fresh water supply for them, and the sea water is about 3 times the concentration of salt in birds' body fluid. The kidney of marine bird is not so well developed as those of mammals, so marine birds cannot rely on the kidneys to regulate the concentration of salt in their body fluid. To adapt to the salty environment, marine birds evolved and developed salt glands which can help them discharge the redundant salt in their bodies. This organ was also found in many other animals, especially those who live in the sea or desert, such as reptiles.

The avian gland, which constitutes a very small percentage, about 0.1 percent of the body weight, is an efficient organ, especially compared with mammal kidney which accounts for 1 percent of their body weight. Every marine bird has two crescent-shaped salt glands in shallow depression in the frontal bone on the top of the skull (Fig. 6) [17], and they are so similar in structure and so close in location that they can be considered as one

organ⁶⁾. The gland (Fig. 7) consists of a tubules network in the form of arborization, in which tubular glands radiate from a central canal penetrating through longitudinal lobes. In the blood supply to the gland there is a counter-current system, which is helpful in the transportation of salt, but that is not convincing enough to explain why the concentration of the secretion is much higher than that of the plasma [18].

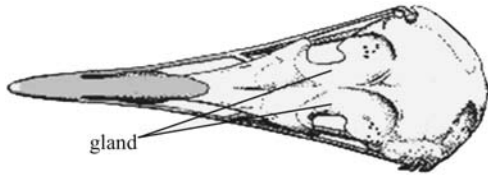


Fig. 6 Location of gland in herring gull, modified from Ref. [18]

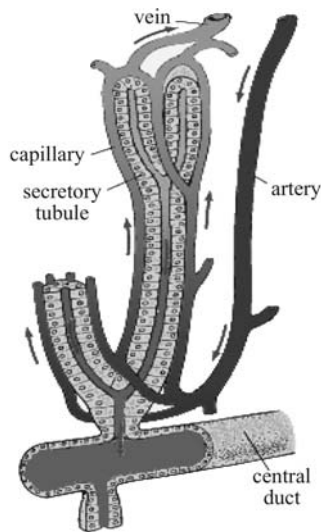


Fig. 7 Structure of the salt gland, modified from Ref. [19]

Figure 8 shows the secretion process of salt glands. The secretory cell is rich in $\text{Na}^+\text{-K}^+\text{-ATPase}$ and mitochondria [20]. With the energy provided in the form of ATP by mitochondria, each $\text{Na}^+\text{-K}^+\text{-ATPase}$ transport 3 Na^+ out of the cell and 2 K^+ into the cell once. Consequently, an inwardly directed sodium gradient is established. This driving force translocates the Cl^- through the Na^+ -coupled cotransport carrier in the basolateral membrane into the lumen of the secretory tubules. Then Cl^- flows out of the cell to the tubular gland via the apical membrane which has an increase in the Cl^- permeability, and the Cl^- flux generates an electric potential which is helpful to the Na^+ transportation [21].

The gland activity is an intermittent process but not a continuous one as the kidney operates, and starts once there is a salt load while completely stops when the salt

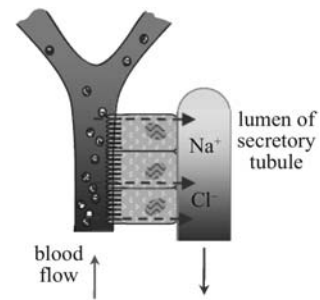


Fig. 8 Secreting process, modified from Ref. [19]

load is eliminated. The gland is innervated from the ganglion ethmoidale, which is supplied by a relatively large branch of the ophthalmic nerve and a smaller one from the facial nerve [18]. Not only does this parasympathetic nerve [22] control the gland activity, but several chemicals can also influence the secretion. Epinephrine and carbonic anhydrase inhibitors can inhibit the activity while acetylcholine and parasympathomimetic substance methacholine (mecholy) can stimulate the gland to secrete [18].

The secreted fluid is several times the concentration of salt in the urine, and is almost neutral, colorless, containing sodium and chloride in approximately equivalent amounts, and potassium of a relatively small amount, some bicarbonate, and very little urea. But there is less magnesium and sulfate which are the major components of solute in sea water. The gland responds to electrolytes as well as nonelectrolytes, such as sucrose. But the secretion stimulated by the latter is still with a high concentration of sodium chloride [18].

The high desalting efficiency of salt gland cell makes it a potential cell used in artificial kidney to substitute for the kidney cells in the devices. The function of salt gland cell may be simple, but this device is very effective in treating some special illnesses, such as hypernatremia. In fact, the artificial devices which utilize certain cells that can filter specific materials from the blood to treat relevant illnesses are not only organ substitutes, but also effectual therapeutic equipments. This kind of devices will be a new focus of medical research.

2.2 Drug delivery

Whether a disease can be healed or not depends heavily on the concentration of the drug delivered to the target site. Some drugs, especially enzymes, will be cleaned by the immune system, while some drugs which will do harm to the normal tissue should be prevented from penetrating to other tissues when delivered to the focal tissue. Therefore, effective delivery of drug to the target tissue without waste in the pathway is extremely important.

⁶⁾ Ritchison G. Urinary system, salt glands, and osmoregulation. 2003, http://people.eku.edu/ritchisong/bird_excretion.htm

2.2.1 Carrier erythrocyte

The forms of sugar-coat and capsule can inhibit drugs from being absorbed until it reaches the stomach. Though these forms only help the process of transporting drug through the mouth and esophagus, the idea of enclosing drug into certain capsules inspired scientists to develop new methods to efficiently deliver drug in human bodies.

The ideal material adopted as the capsule is autologous erythrocyte, which will not cause any infection and rejection. Erythrocyte is a kind of simple cell, without karyon, easy to handle and alter, and can regenerate quickly. With so amazing deformability, it can transport across capillary vessels of a smaller dimension. It can act as a drug reservoir and prolong the effective time of the drug.

In 1973, Ihler et al. first used the erythrocyte as the carrier to deliver enzyme in human body to heal certain diseases successfully [23]. This approach opened a new field of using erythrocyte as drug carrier in clinical practice. Figure 9 illustrates the procedure of enclosing drugs into erythrocytes. First, erythrocytes are obtained from the human body. Then, a hypotonic saline solution is added to make the pores in the cell surface open larger. Next, the drug runs across these pores into the interior of the cells. Finally, the added osmolarity causes the resealing of membrane pores, and meanwhile, the non-entrapped drug is washed out [24].

However, the approach of encapsulation is not limited to the one mentioned above. Many new methods have been developed which can be classified into two types: osmosis-based and non osmosis-based methods. The former is based on the fact that exposing erythrocytes in a hypotonic solution will lead to an enhancement in the permeability of the membrane and an enlargement of pores in the membrane. And this type includes hypotonic hemolysis, hypotonic dilution, hypotonic dialysis, hypotonic preswelling, osmotic pulse, and so forth [25–29]. The latter includes electroporation, chemical perturbation, protein recombinant, and drug-induced membrane internalization, etc. Electroporation is based on the fact that a strong external electrical field can induce pores in the membrane. Chemical perturbation is based on the fact

that certain chemicals can enhance the uptake of ions as well as small and large molecules. Protein recombinant is based on the fact that the amalgamation of certain recombinant with cell membrane can bring the drug associated with it into the cell. Drug-induced membrane internalization is based on the fact that some membrane-activated substance can induce membrane internalization in erythrocytes so as to bring drugs into cells [30–33]. Among all these approaches, hypotonic dialysis and hypotonic pre-swelling are the most widely used because of their high encapsulation rate, low demand for apparatus and simple operation.

As for those large molecules which are difficult to move through the erythrocyte membrane, it is impractical to make effort to enclose these drugs into the cells. But it does not mean that erythrocytes can not be used as their carriers. The method of connecting drug with the surface of cell membranes includes EPOR-mediated combination [34], CR₁-mediated combination [35], and the like. In 2003, Murciano et al. demonstrated that a fibrinolytic agent consisting of a tissue-type plasminogen activator (tPA) coupled with the surface of erythrocyte can enhance the selectivity of the nascent clots, therefore avoiding the danger of bleeding caused by the elimination of old clots when free tPA is used [36].

If drugs are loaded into the cells in vitro, it will be easy to control the parameter and handle the operation. But after the erythrocyte solution was injected into the human body, the action would be out of control. It is difficult to know and handle when the carriers will release the drug and its concentration. Therefore, these problems should be the focus in future study.

2.2.2 Nanoparticle enabled drug delivery system

The problem caused by the difficulties in the clinical use of drugs, such as toxicity and immunoreaction, leads to the appearance of drug targeting technologies. With the development of processing technology and biology, the nanoparticle was proposed to be the new carrier for drugs. And in the last 30 years, nanoparticle drug delivery system (NDDS) has been established to improve the delivery performance of drug carrier. NDDS can provide a

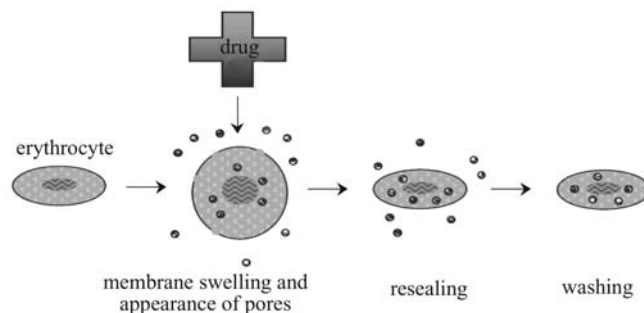


Fig. 9 Procedure of enclosing drugs into erythrocytes, modified from Ref. [24]

prolonged, controlled, or targeted action of the incorporated or encapsulated drugs [37]. Compared with the carrier erythrocyte, the action of NDDS is more targetable to the focal tissue and easier to control in general. Though some nanoparticles are not biocompatible, the modification of the surface can improve their physiological properties so as to solve this problem.

Based on the method it takes, NDDS can be classified into three types: passive targeting, active targeting, and physical targeting. In the process of passive targeting, the drug associated with the carrier is absorbed by macrophages and leucocytes, and then accumulated in liver, spleen, lung and so forth [38]. This type of NDDS includes synthetic polymer nanoparticles, natural polymers nanoparticles, solid lipid nanoparticles, and polymeric noise.

Active targeting is based on the specific interaction between drug carrier and selective tissue. As Fig. 10 indicates, in this process, the carrier is associated with certain ligand or antigen, and the drug is translocated into the cell when the ligand or antigen binds with the receptor or antibody respectively. The surface of the carrier is modified to avoid being recognized and phagocytosed by macrophages and leukocytes, so a high concentration in liver and spleen is prevented. This type of NDDS includes antibodies and transferrin [39,40]. Active targeting can enhance the selectivity of specific cells, and therefore increase the efficiency of drug delivery. However, some researchers did not think that active targeting is superior to passive targeting in all clinical use. For example, in some case of anticancer drug delivery, passive targeting can obtain a high selectivity by the enhanced permeability and retention (EPR) which can increase vascular permeability of solid tumor tissue and make it easier for macromolecular drugs to be transferred across the vessel to the tumor, while no tumor-specific antigens appearing in this transfer process [41,42]. The actual condition in vivo is more complex than that in vitro so that selective drug delivery using active targeting system is not easy to achieve. Several difficulties, such as the loss of antibody specificity due to the chemical conjugation with drugs and the nonspecific uptake of drug-antibody conjugates due to unfavorable physicochemical properties caused by the conjugated drugs, should be addressed [41].

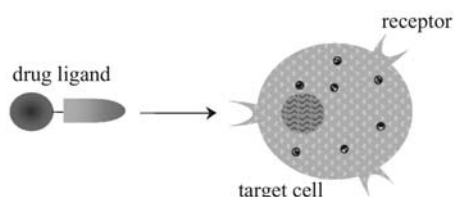


Fig. 10 Model of ligand and receptor, modified from Ref. [41]

Physical targeting is based on the physical characteristics of the carrier. This type of NDDS includes ferrite

containing liposome and thermo-responsive carriers [43,44]. The former can be driven by the external magnetic field; therefore the drug it carries is delivered to the pathological site. The latter is a kind of thermosensitive material whose penetrativity will be enhanced with the added heat in the phase transition temperature so as to release more drugs. Physical targeting improves the control on the process of drug delivery. And with the help of advanced imaging technology, the process can be monitored and controlled at any moment.

All these NDDS as mentioned above need active reactions of target cells. So the performance of the carrier depends on the characteristics of the pathological cells to a great extent. Here, a new type of carrier-virus can be proposed. In this method, certain viruses are inactivated to eliminate their infectivity and to decrease the immune reaction. When these inactivated viruses are attacking (Fig. 11) the pathological cells, the drug attached to them can run across the membrane into the interior of the cells. This method is active targeting delivery in its absolute sense, and it greatly diminishes the dependence of NDDS upon the target cells. The performance of delivery is improved, and the control on delivery parameter is enhanced. However, there are still some problems which should be addressed in the study of clinical use. First, the inactivated virus should be modified to decrease the immune reaction, which is extremely important for those patients whose immune system has been damaged. Second, some macromolecule protein drugs have such a large volume similar to virus that it is difficult to deliver them by virus.

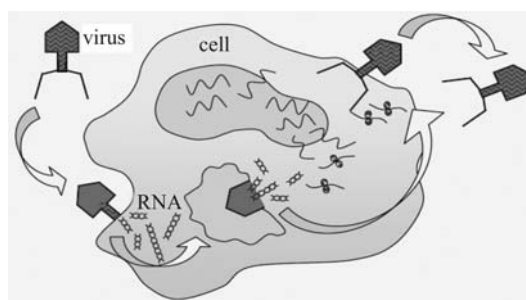


Fig. 11 Process of virus attacking cell, modified from Introduction to viruses (Hurlbert R E. 1999, <http://www.slic2.wsu.edu:82/hurlbert/micro101/pages/Chap11.html>)

2.3 Nutrient transport

Nutrient, especially oxygen, is very important for maintaining health. Human tissue will die within several minutes when it is short of oxygen. As is well known, blood and vessel constitute the main system to transfer nutrient and oxygen to the various tissues of human body. Clearly, enough blood with normal function is needed in whole body every second. Serious loss of blood should be

treated in time with transfusion to avoid death of the wounded. Patients who suffer from anemia always feel dizzy and sometimes will lose consciousness due to insufficient oxygen in their brain. Great progress has been made in the research on blood substitutes in recent years.

Artificial blood

Transfusion is utilized when patients suffer from some emergencies or lengthy surgeries. The demands for blood are huge. As indicated by the data of National Blood Data Resource Center of the US, about 12.54 million allogeneic blood unites were transfused in the year 2000, which is increased by 4%–5% from 1999 [45]. However, there are several disadvantages to limiting the utilization of human blood. First, the allogeneic blood collections tend to not meet the demand. There were 13.37 million unites collected and this is 6.2% of surplus decreased from the 7.4% of un-transfused unites in 1997 [45]. Second, the shelf life of human blood is short, and the methods to maintain the donor blood should be developed, improved and utilized. Third, the patient may suffer from potential hazards of being infected by HIV, HCV and other diseases, though the risk is decreasing year after year (Fig. 12). And finally, the ABO-incompatibility in transfusion sometimes leads to death.

To eliminate these limitations and to satisfy the vast demand of some emergencies, especially during natural disasters and war, people turn their attention to the blood substitute. An ideal blood substitute should ①absorb, transport and release oxygen, ②be compatible with any blood group, ③has no side effect, ④ will not be cleared by the immune system, ⑤ have long work time, ⑥ have long shelf life, ⑦ need no specially designed procedure to preserve them, ⑧ could be manufactured on a large scale via certain inexpensive ways. The present artificial blood can be classified into two types: hemoglobin-based oxygen

carriers (HBOCs) and perfluorocarbon emulsions (PFCs) [46].

(1) HBOCs

Hemoglobin solution is a natural blood substitute. In the 1970s, Rabiner et al. first tried to develop blood substitutes by concentrating cell-free solutions of human hemoglobin [47]. Though hemoglobin outside of the red blood cell still has the ability to transport oxygen, it will break into monomers and dimers soon and then be eliminated by the kidney. Chemical modification is used to establish specific chemical cross-lines between polypeptide chains in order to prevent the breakdown of hemoglobin [48].

HBOCs can be made from the donor blood which has not been used in the approved storage period and several animal blood, such as bovine blood. An apparent advantage which makes bovine blood as a cheaper resource is that bovine hemoglobin is immune-free for the human body when other proteins are stripped off. However, the most serious factor which impairs its acceptance is that it could bring about prion pathogen that may lead to bovine spongiform encephalopathy [48].

(2) PFCs

The concept of “blood substitute” is not new, and can date back to 1656 when Wren et al. transfused some wine into a dog as a substitute for blood [49]. In 1966, Clark and Gollan reported that mice can survive under certain PFC liquids for several hours [50]. Their work opens a new era of developing blood substitutes with practical value. But the particles in the emulsion Clark used are so large that it is difficult to remove from the human body and will cause chronic toxicosis. In 1976, Natio and Yokoyama developed a new artificial blood, Fluosol-DA. Its good performance is indicated by the summary of 186 cases in ten years. There was no anaphylactoid or

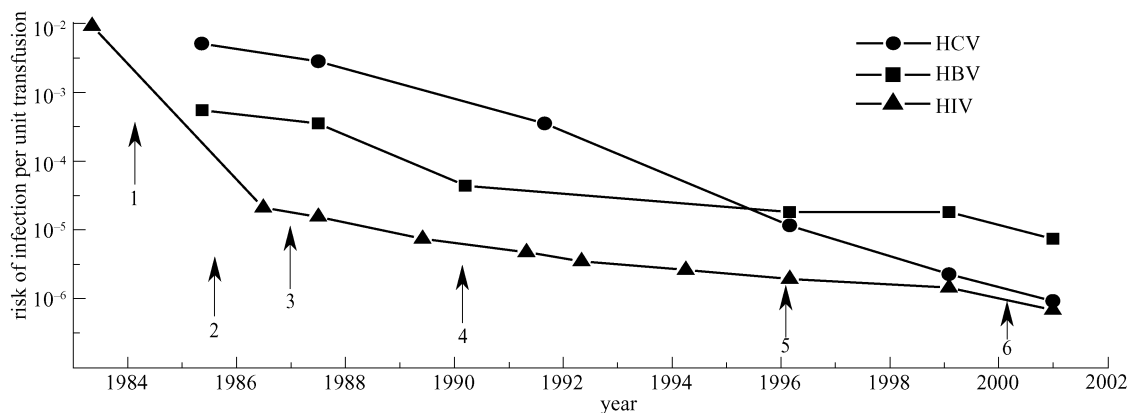


Fig. 12 Risks of transfusion-related transmission of HIV, HBV, and HCV in USA, redrawn from Ref. [45]

1—donor screening criteria changed; 2—screening for HIV-antibody; 3—surrogate screening for non-A non-B hepatitis; 4—screening for HCV-antibody; 5—testing for p24 antigen; 6—nucleic acid testing for HCV/HIV

other untoward reaction observed or reported when it was infused [51].

PFCs can be mass-produced with no dependence on human and animal blood. And it is the best choice of those patients who do not accept the transfusion of human blood for some religious reasons. But it still has some disadvantages such as having only a short period of working time and increasing the viscosity of blood [52].

Though these artificial bloods as mentioned above greatly improve patients' lives, they still cannot substitute for human blood completely. The major functions of human blood are transporting oxygen and nutrition to the tissue, protecting the body against certain virus and bacteria, stanching the wound, maintaining the acid-based equilibrium, and regulating body temperature. Recently, the function of artificial blood is limited to oxygen transportation alone, which can satisfy some demands of component transfusion but not total blood transfusion. Future study will focus on the development of some total-function artificial blood to fulfill the increasing demand.

2.4 Micro operation

Surgery is a common and effective approach to treat some illnesses. But it often takes a long time for the wound to heal, especially when it is large. The technology of minimally invasive surgery developed in recent years minimizes the wound and markedly relieves the patients. However, the agony of the wound always exists, and it will multiply while repeated surgeries are needed. Furthermore, when patients need surgery in several parts of body, pain will be the greatest concern. Considering these problems, micro operation *in vivo* is thus proposed. In this regard, micro robots have been placed into the patient's body, usually in the vessel, and they move freely with the flow of blood. When they arrive at the operation sites, auto-recognition program will lead them to move toward the pathological sites. This technology is particularly effective when it comes to the chronic vessel disease because the robots can work for a long time after being implanted one time.

Hydraulic drive of spider

There are a lot of animals, such as dragonfly larvae and leech, whose movement is driven, entirely or partially, by hydraulic force, and the most common one is the spider. Though most spiders are very small, only a length less than 1 cm, they can jump to a height more than ten times their body length. This phenomenon attracted the attention of many scientists who discovered gradually the physical and biological mechanism behind it.

Until 1909, scientists held the opinion that the locomotion in each joint of spider's leg is driven by antagonistic muscles. Petrunkevitch [53] discovered that there are no extensor muscles in the two most important flexor

extensor joints in the leg, the femoro-patellar and tibio-metatarsal joints. He also put forth an assumption that the function of extension has been taken over entirely by the elastic interarticular membrane.

Ellis [54] examined Petrunkevitch's assumption with some experiments, and discovered that interarticular membrane have little if any elasticity, therefore the theory based on the elasticity has been rendered unsustainable. He also reported that extension relates closely to changes in the volume of blood and in the internal fluid pressure in the spider's leg.

Parry and Brown [55] further studied the internal pressure of the leg and the torque at the hinge joints, and established an empirical relation between them. As to the distribution of resting pressure, they suggested that the pressure might be limited to the prosoma, the abdomen being at atmospheric pressure, and in the pedicel there might be some form of valve or sphincter which serves to regulate prosomal pressure. However, further investigation is needed. When a spider is stimulated, a transient pressure up to 45 cm Hg will occur in the prosoma, and a well developed aortic valve in the pedicel plays an important role in preventing the prosomal circulation from being stopped by the sudden rise of pressure. It is fatal when a spider suffers from some minor damages such as bleeding to the prosoma. However, a recovery mechanism has been developed that the withdrawal of blood and the relaxation of the prosomal muscles can lower the pressure immediately to save its life.

Parry and Brown [56] discovered that the sudden straightening of the fourth pair of legs almost entirely contributes to the jump of a spider (Fig. 13). This is because the extension torques occurs at the two joints which have no extensor muscles. The erection of leg spine when jumping indicates that hydraulic forces are involved in the jump.

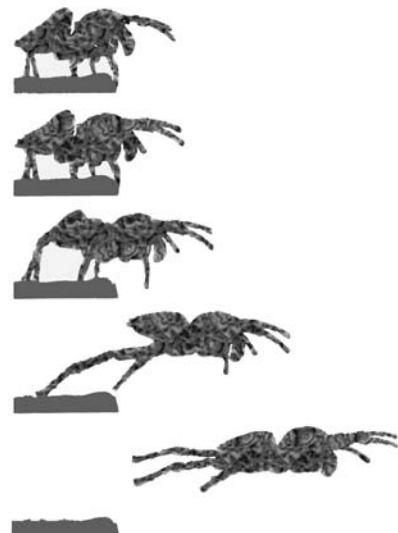


Fig. 13 Jump of salticid spider, modified from Ref. [56]

Stewart and Martin [57] studied the blood pressure and reported that heart rate and amplitude vary in response to various stimuli. The heart and the abdominal tension contribute together to the pressure in the heart. Resting pressure in any pair of legs is higher than that in the prosomal, and a maximum pressure of 63993.56 Pa was recorded in the prosoma when the spider is excited. A recovery mechanism was also reported that an immediate decrease in heart pressure occurs when blood withdraws, and muscular adjustments might lead to recovery.

The hydraulic mechanism gives an inspiration for the design of some new machine, such as brakes, jacks, cranes, bulldozers and so forth. These hydraulic machines can multiply a relatively small force to produce a considerable one with high pressure fluid. And they are used in many cases of modern industry because of their powerfulness and agility. However, there are some hazards in these machines since they operate with fluid under high pressure, and the leakage of fluid may cause injury. The recovery mechanism of spider when bleeding may give a final solution to this problem.

The development of MEMS technology makes it possible to manufacture a tiny robot utilizing hydraulic mechanism. In this design, a structure similar to a spider's leg is driven by the pressure variation of working fluid. Bubbles produced by certain methods, such as heating, chemical reaction, and electrolysis, can increase the pressure of work fluid, and the release or dissolution of the bubbles can decrease the pressure. This robot can be used to clean out the thrombus in blood vessels or for other purposes in the near future.

2.5 Power supply

The power supply is always an important issue in the devices *in vivo*. The power supply of some devices which need a high power or need to work for a very long time is the key factor that influences their successful running. Many batteries were thus developed to solve this problem and succeeded in some aspects. The traditional models include one-time cell, rechargeable cell, and even atomic energy cell. However, these batteries have their inherited shortage. One-time cell which has a short working time can only supply a small power. The rechargeable cell which needs to be charged time and again is not very convenient. The atomic energy cell, however, has potential danger. Therefore, it is urgent that a safe, durable, biocompatible, and high-power cell should be developed.

Crampfish: electrogenesis

In the long period of evolution, many kinds of creatures, such as electric eel, electric catfish, torpedo fish, and so forth, obtained the ability of discharging electricity to capture its preys and avoid being captured by its predators. Electric eel is the most typical species of crampfish. With a length of about 2 m, an electric eel can generate electric shocks of up to 600 V and 1 A.

The electric organs, which occupy 4/5 of an electric eel's body, consist of about 4000 electrocytes. Each electrocyte generates a very small electricity of only 150 mV [58]. However, stacked in sequence, they can emit shocks strong enough to paralyze some large animals, such as horse and cattle, when they discharge at the same time.

The electrocytes are a kind of highly specialized cells, which can produce and discharge electricity in accordance with the neural and chemical stimulations. This cell, with a flat and disk-like shape, contains two sinuous profiles; the posterior is innervated while the anterior is non-innervated [59]. Figure 14 shows the process of discharging. At rest, the ion channels at the membrane are closed, and there is a balance between the amount of Na^+ driven by the $\text{Na}^+\text{-K}^+$ pump into the cells and that driven by concentration and electrical gradient, therefore keeping the membranes at a resting potential of 60 mV [58]. Whereas an intact cell shows that no voltage for the potential in posterior is offset by that in the anterior. When the electric eel is discharging, a signal is sent via the nervous system to the organs, and then acetylcholine reacts with the corresponding receptor on ion channels. As a result, ion channels open and Na^+ flows into the cells. Consequently, the cells depolarize, and the potential in the posterior is enhanced by that in the anterior because they are syntropic, therefore the cells show voltage.

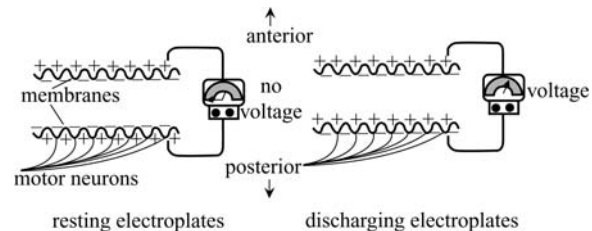


Fig. 14 Discharging process, modified from Ref. [60]

The papillae at the anterior profile are more pronounced than that at the posterior (Fig. 15). Most of the organelles are located close to the cell membrane and at the extremity of the papillae, around nuclei, while the other regions of the cell are homogenous. Nerves adjacent to the posterior face via the connective tissue, and at the cell surface there are some synapse [59].

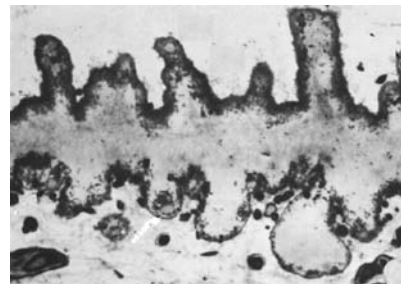


Fig. 15 Structure of electrocyte, examined by light microscope [59]

The anterior and posterior membranes are differentiated from the cytoplasmic membrane of the cell. The former is non-innervated, and serves the function of active transport. It is rich in adenosine triphosphatase (ATPase), an enzyme which is ouabain sensitive, $\text{Na}^+\text{-K}^+$ activated. While the latter is innervated and the nerve receives terminal, they respond to both electrical and chemical stimulation. It is rich in acetylcholinesterase (AcChE) [61].

The surface area of anterior face is increased significantly and the transportation of ions is enhanced. This is because the tubular invaginations of the electrocyte membrane are longer, more numerous and closely packed (Fig. 16) [59]. Both membranes present $\text{Na}^+\text{-K}^+\text{-ATPase}$, but less in the anterior and much more in the posterior. Therefore, a small flux of ions occur in the posterior while a more intense transportation of Na^+ and K^+ across the anterior face is observed [62].

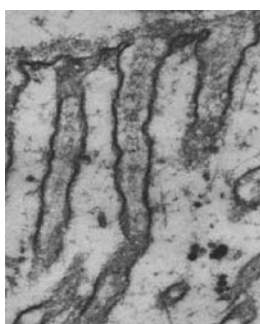


Fig. 16 Tubular invaginations [59]

The ATPase activity in electrocytes is similar to that in red cells in that more than 90% of them needs the presence of Na^+ , K^+ and Mg^{2+} , and is inhibited by ouabain. It also can be inhibited, partly or completely, by sodium lauryl sulphate, oligomycin, a number of reducing and oxidizing agents, and several sulphhydryl reagents [63]. Electrostatic forces may be an important factor in the interaction of the AcChE with the membrane and the process is concerned with Ca^{2+} [64].

Additionally, the strong electric currents not only serve as a powerful weapon, but also electrolyze water into oxygen to sustain the breathing, especially in some environments lacking air. When the water in an electric eel's body is decomposed, oxygen is dissolved in the blood directly and hydrogen enters the intestines and then it discharges via the mouth.

The invention of voltaic cell was inspired by the electrogenesis mechanism of electric eels. The voltaic cell is made by separating zinc plates and copper plates with paper plates in the solution. The small voltage of each electroplaques is multiplied by stacking many ones up.

Considering the principle of electrogenesis and the biological environment, the electrogenesis phenomenon can be used in the power supply of devices in vivo, and a micro power generator can be designed from this inspiration. In

the design, a scaffold can be manufactured in the type of hollow tubule with many pores in the wall, and electrocytes or other cells with similar function are enclosed in the tubules. When this device is put in the blood, small molecules can transfer through the pores in the tubule to supply enough nutrients to the electrocytes, and large molecules such as immune proteins and other materials which cannot pass through the pores are kept out of the tubules to avoid immune reaction. The electricity generated in this process can be used to supply the device in vivo or to function as a pacemaker directly.

3 Discussion

The issue of mass and energy transport in organisms can be generally classified into two aspects: microcosmic transmission through various membranes including similar structures, and macrocosmic transport in various conduits. These two aspects are greatly different in theoretical model, experimental measurement and so forth, but they are often combined closely in certain physiological process.

Membrane plays a pivotal role in the vital process. On the organism level, where membrane means skin and wall of various conduits, the research focuses on the issue of mass and energy transport through pores and intercellular space. On the cellular level, where membrane serves to separate the internal and external environment of cell and provides the channel of mass and energy transport between the inside and the outside of cell, the research focuses on the function and mechanism of channel protein. On the organelle level, where membrane not only provides channel for mass and energy transport but also offers important sites for biochemical reaction. The research on this issue can help to solve some problems of biochemical reaction in artificial organ to improve their excretive function. Nowadays, the major issue of mass and energy transport through membrane is to enhance the efficiency and improve the selective penetration. Many theoretical models of mass and energy transport through membrane have been established to explain the various mechanism and structure of the membrane, while many mysteries still remain undiscovered. It is convincing that new progress in the mass and energy transport through membrane can strongly promote the development of medicine, chemical engineering, energy engineering, and other related subjects.

The research on macrocosmic transport is comparatively complete. The major issue is to increase the efficiency and decrease the energy consumption of transport, and to achieve the real flow situation in vivo. The fundamental involves fluid dynamics, especially on the non-Newtonian fluid, elasticity dynamics, and so forth. The macrocosmic transport in vivo is always related

to the binding and releasing of materials with carriers. To effectively control the binding and releasing of certain materials and transport of carriers to specific sites is a very significant issue.

High performance, low consumption and cost are always the goals of research on mass and energy transport. But that is not enough when it involves the clinical application for the complex condition in human body. Moreover, the biocompatibility and durability of materials is also a major demand. The final goal is to achieve the total substitute of certain organ. Investigations along this direction are worthwhile.

4 Conclusions

In the past few decades, great progress was made in the research on biological mass and energy transport. Some artificial medical devices and materials were put into use, greatly expanding the extent of human activity, improving the living conditions of patients, prolonging patients' life span. However, these devices and materials are still subjected to certain disadvantages which make them incomparable with the ingenious biological organs and tissues. In order to increase their efficiency and make them total substitutes for biological structures, advancement on many other subjects besides mass and energy transport, such as material science and processing technology, is needed. A great many biological phenomena are waiting to be investigated and imitated. Learning from nature is a long and arduous but interesting course. The development in other subjects will greatly promote the advancement of bionics. There are many reasons to convince people that many artificial devices based on biological mass and energy transport will appear to better improve various fields related to human life in the near future.

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