コンピュータシミュレーション

本研究グループでは以下のステップを経て，基板上に配置された poly(dA)・poly(dT)DNA 水溶液をコンピューター上で再現する．

1.Gaussian あるいは Amber (Nucgen) を用いて 10 塩基対 poly(dA)·poly(dT)DNA 断片の位置座標を pdb（プロテインデータバンク）形式で作成後，5' 末端および 3' 末端を水素終端処理する．

2.リン酸基へのカウンターカチオンとして Na^+ を付加し，poly(dA)·poly(dT)DNA を電気的に中性化する．

3.基板と poly(dA)·poly(dT) DNA を含む直方体領域を H_2O 分子で満たす．

4.基板を含む各原子に量子化学計算によって得られる Mulliken 電荷を与える．

次にシミュレーションの流れであるが，現実的な状態（平衡状態）へ少しでも早く近づけるため，プリプロセスとして系の緩和を行った後で MD（分子動力学）計算を実行する．すなわち，

1.DNA の基本形状が崩れないように DNA 構成原子を拘束したまま水分子とカウンターイオンのエネルギーを最小化することで系を緩和．

2.DNA，水分子，カウンターイオンの全エネルギーを最小化し，系全体を緩和．

3.DNA の基本形状が崩れないように Shake 法により水素原子を含む結合を拘束し，温度を 0K から 300K に上昇させながら計算を実行する．

4.1-3 を経て 300K にて計算ができるようになった状態を平衡状態 0ps とし，再び Shake 法により水素原子を含む結合を拘束し，全体の系を NTP アンサンブル（原子数・温度・圧力一定）にて MD 計算を行う．ただし，遠距離力であるクーロン力の算出には Particle Mesh Ewald 法を用いる．

著者らは分子動力学シミュレーションにおいて，著名な市販ソフトである Amber の力場を完全に含み，生体高分子の大変形や高温条件にも対応した力場ポテンシャルを提案し，並列化 MD シミュレーションにおいて，その有用性を確認している．すなわち，Amber Force Field（力場）ポテンシャルは次式で表される．

$$E_{\text{total}} = \sum_{\text{bonds}} K_r (r - r_{eq})^2 + \sum_{\text{angles}} K_\theta (\theta - \theta_{eq})^2 + \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}} \right]$$

これは，原子間の結合，角度，ねじれ（二面角），ファンデルワールス力（クーロン力を含む）の項から成り，2nd Generation Force Field として広く知られている．しかしながら，右辺第 1 項および第 2 項では，$r \approx r_{eq}$ あるいは $\theta \approx \theta_{eq}$ でなければ，ポテンシ

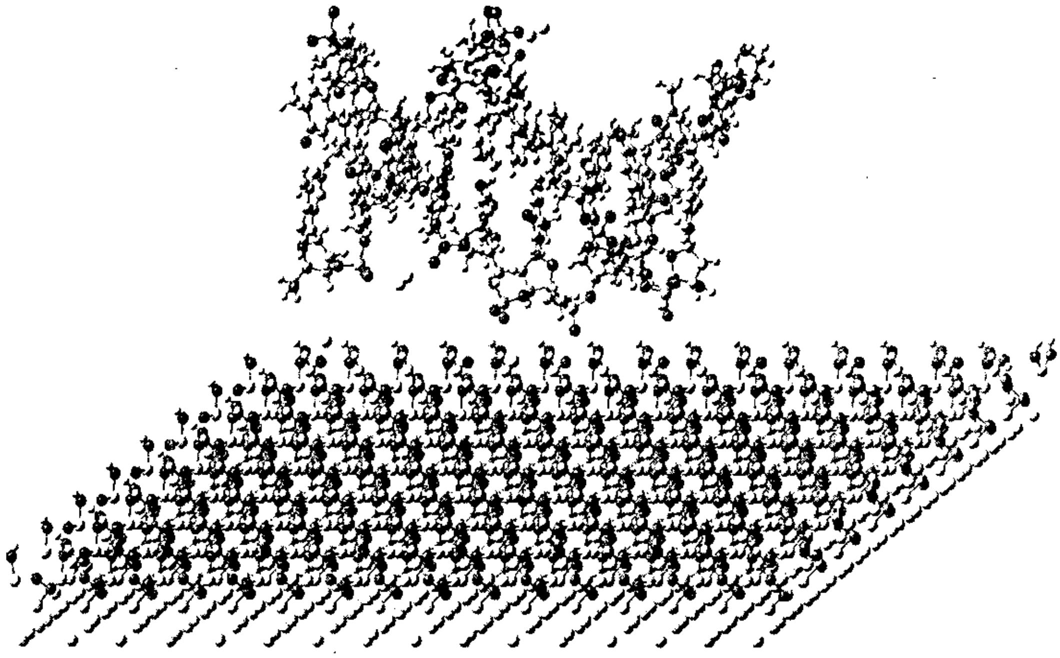
ャルが急激に発散することが明白で，これは，計算結果であるはずの分子構造が，pdb にあるX線回折等による構造解析結果，すなわち r_{eq} および θ_{eq} と大きく違わないような系でのみ有用である．現在まで著者らは，DNA 等の生体高分子に関する MD シミュレーションコードの基幹部分を完成させ，とくに，DNA の複製過程やたんぱく質の機能発現には，その二次構造が非常に重要で，生体高分子の大変形も考慮しなければならず，前述のポテンシャルでは取り扱いが困難であることを示した．そこで，著者らは，結合項を次のようなモースポテンシャルに変換した独自のコードを作成した．

$$E_{\text{total}} = \sum_{(\text{morse})\text{bonds}} D_e\left[1-e^{-a(r-r_{eq})}\right]^2 + \sum_{\text{angles}} K_\theta\left(\theta-\theta_{eq}\right)^2 + \sum_{\text{dihedrals}} \frac{V_n}{2}\left[1+\cos(n\phi-\gamma)\right] + \sum_{i<j}\left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\varepsilon R_{ij}}\right]$$

右辺第一項は，$r \approx r_{eq}$ を仮定して線形近似すれば，AMBER コードにおける右辺第一項と一致するため，我々のモデルは従来のモデルを完全に含有し，しかも，大変形ダイナミクスの取り扱いが可能となるように拡張されたことになる．物質毎のパラメータも簡単な理論解析により，既存のデータベースを利用して決定することができる．

ここでは，水素終端した SiO_2 基板に固着する 10 塩基対 poly(dA)·poly(dT)DNA の流動ダイナミクスシミュレーションを行った．t=900ps までの結果を図３示す．明瞭な可視化の為，H_2O 分子を無視している．時間が経過するにつれ，DNA の形状は変化し，5' 末端と 3' 末端が基板に付着していく様子が再現されている．

ただし，より厳密に言えば，経験則に基づく力場ポテンシャルを用いている限り，分子の励起状態や振動など，量子力学的現象が支配的であるような物理・生命現象には不向きであることがわかる．θ 方向への大変形問題も未解決であり，生体高分子の立体構造をある程度維持するために導入される拘束手法の開発も急務である．また，Mulliken 電荷の設定による量子力学効果の取り込みが可能になっているが，pH や電荷の時空間変化が，生命機能発現・維持において本質的であるから，さらなる力場ポテンシャルの高精度化と的確な量子力学的効果との融合化が急務となっている．



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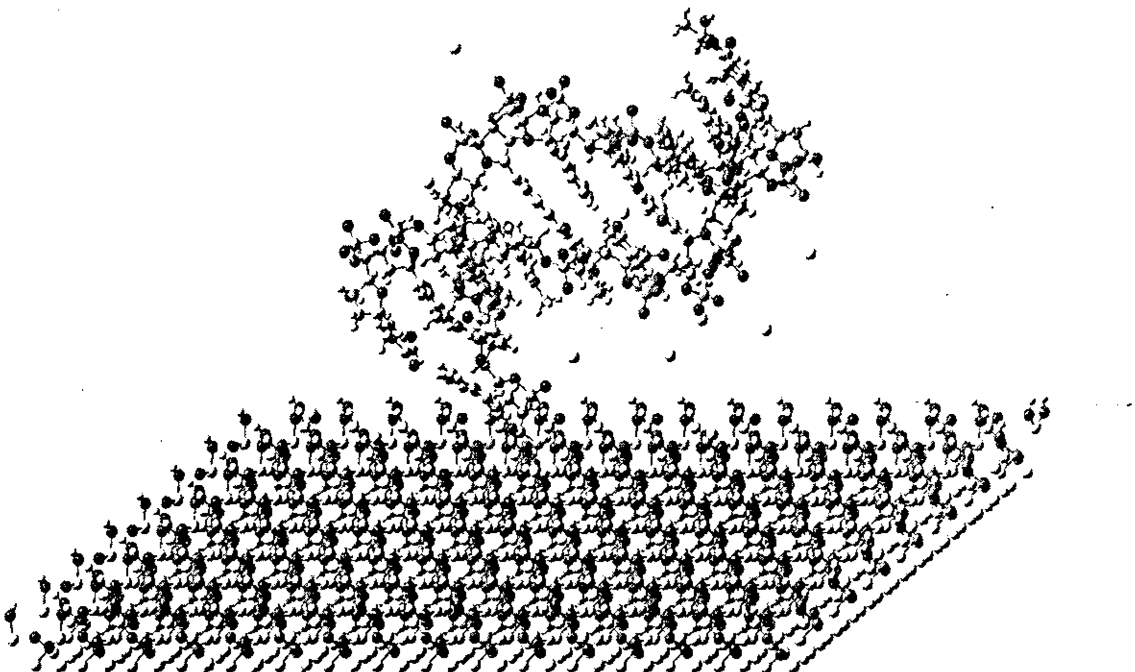

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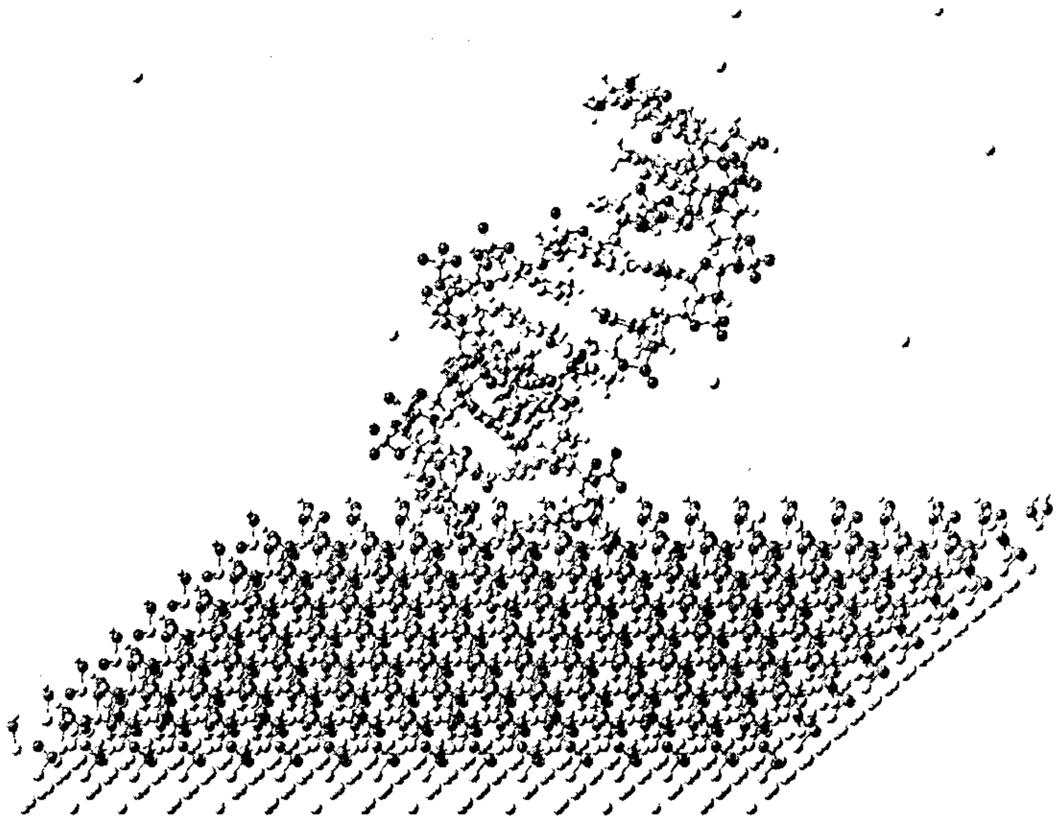

t=900ps

図3　SiO_2基板に固着する poly(dA)・poly(dT) DNA の流動ダイナミクスシミュレーション

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別紙5

研究成果の刊行に関する一覧表

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Recent Progress in Artificial Organ Research at Tohoku University

*Tomoyuki Yambe, †Makoto Yoshizawa, ‡Akira Tanaka, ‡Ken-ichi Abe, ‡Satoyuki Kawano, ‡Hidetoshi Matsuki, §Shigenao Maruyama, #Shintato Amae, #Naoshi Wada, #Takamichi Kamiyama, §Toshiyuki Takagi, §Run Luo, §Junko Hayashi, *Yuri A. Kovalev, *Dan X.D.Sha, *Shunsuke Nanka, *Yoshifumi Saijo, *Yoshiyuki Mibiki, *Mune-ichi Shibata, and *Shin-ichi Nitta

**Department of Medical Engineering and Cardiology, Institute of Development, Aging and Cancer; †Information Synergy Center; ‡Tohoku University Graduate School of Engineering; §Institute of Fluid Sciences; #Department of Fediatric Surgery, Tohoku University Graduate School of Medicine, Tohoku University, Sendai, Japan*

Abstract: Tohoku University has developed various artificial organs over the last 30 years. Pneumatic driven ventricular assist devices with a silicone ball valve have been designed by the flow visualization method, and clinical trials have been performed in Tohoku University Hospital. On the basis of these developments, a pneumatic driven total artificial heart has been developed and an animal experimental evaluation was conducted. The development of artificial organs in Tohoku University has now progressed to the totally implantable type using the transcutaneous energy transmission system with amorphous fibers for magnetic shielding. Examples of implantable systems include a vibrating flow pump for ventricular assist device, an artificial myocardium by the use of shape memory alloy with Peltier elements, and an artificial sphincter for patients with a stoma. An automatic control system for artificial organs had been developed for the ventricular assist devices including a rotary blood pump to avoid suction and to maintain left and right heart balance. Based upon the technology of automatic control algorithm, a new diagnostic tool for evaluating autonomic nerve function has been developed as a branch of artificial organ research and this new machine has been tested in Tohoku University Hospital. Tohoku University is following a variety of approaches aimed at innovation in artificial organs and medical engineering fields. **Key Words:** Vibrating flow pump—Artificial sphincter—Transcutaneous energy transmission system—Shape memory alloy—Artificial myocardium.

Tohoku University has been involved in artificial organ research for over 30 years. The first case discharged from a hospital in Japan wearing a ventricular assist device (VAD) was achieved by Tohoku University Hospital in 1985. Various artificial organs are currently under development at Tohoku University.

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Address correspondence and reprint requests to Dr. Tomoyuki Yambe, Department of Medical Engineering and Cardiology, Institute of Development, Aging and Cancer, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-77, Japan. E-mail: yambe@idac.tohoku.ac.jp

PNEUMATICALLY ACTUATED VENTRICULAR ASSIST DEVICE

Circulatory support devices are necessary in some patients with severe congestive heart failure. However, some ventricular assist devices are too expensive, especially for patients in developing countries. We succeeded in reducing the cost by adopting silicone ball valves. Clinical application of our pneumatic ventricular assist device was performed, and about 30% of patients were discharged from the hospital after weaning. Figure 1 shows the Tohoku University type pneumatic VAD.

PNEUMATIC TOTAL ARTIFICIAL HEART

Development of the pneumatic total artificial heart (TAH) was carried out in our laboratory based

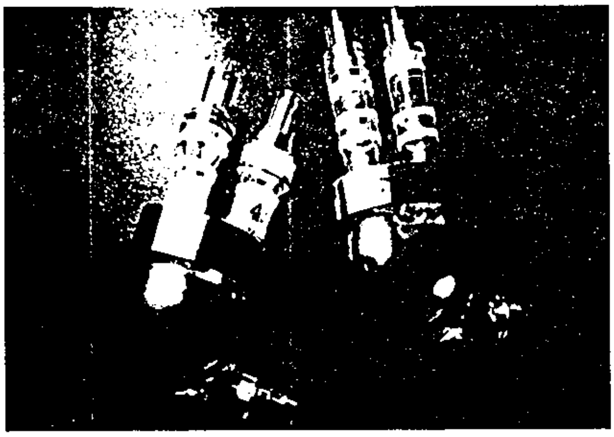

FIG. 1. The Tohoku University type pneumatic ventricular assist device is shown.

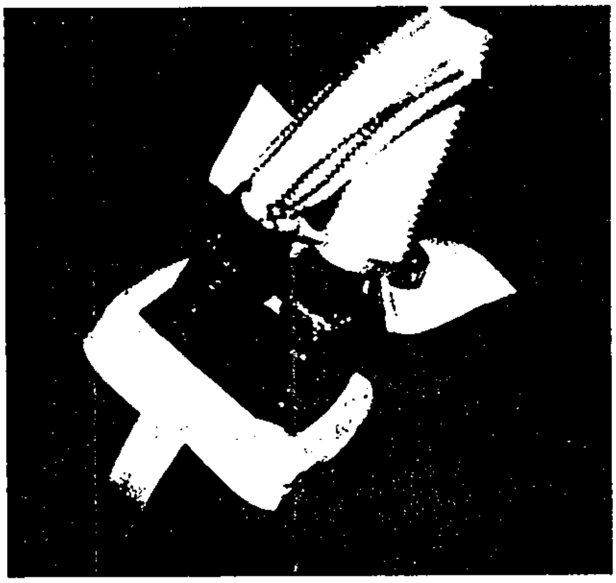

FIG. 2. The Tohoku University type pneumatic total artificial heart is shown.

on the development experiences with the VAD. To reduce cost and improve durability, silicone ball valves were adopted in our TAH system. The basic material of this TAH was designed using a polyvinyl chloride paste, and the inner surface of the inner sac was coated with polyurethane to prevent thrombus formation. To test this pneumatic TAH, a fitting study into the chest cavity of adult goats was conducted (Fig. 2).

VIBRATING FLOW PUMP

Small size implantable ventricular assist device

The size and weight of implantable devices is so important that various investigators have taken various developmental approaches. We aimed to solve the problem by increasing the drive frequency of the ventricular assist device. A vibrating flow pump, and small stroke volume with high driving frequency enabled us to realize a small and lightweight implantable ventricular assist device.

The weight of actuators has recently been lessened by adopting a cross-slider mechanism. Miniaturization was successful compared with a linear motor drive (Fig. 3).

High frequency oscillated blood flow made by vibrating flow pump (VFP) is so unique that influences on the cardiovascular system might be needed. We evaluated the effect of oscillated assist flow with VFP upon renal circulation using near infrared spectroscopy in animal experiments on adult goats. During oscillated assist flow, oxygenated hemoglobin in the kidney tended to increase. This finding will be useful when considering the clinical application of VFP.

TRANSCUTANEOUS ENERGY TRANSMISSION SYSTEM

Energy transmission is an important issue in the development of internal artificial organs. To maximize energy transmission we developed a transcutaneous energy transmission system applying amorphous fibers for magnetic shielding, and achieved over 90% energy transmission efficiency (Fig. 4).

APPLICATION OF THE SHAPE MEMORY ALLOY FOR ARTIFICIAL INTERNAL ORGANS

Development of a small, lightweight actuator is the most difficult challenge for totally implantable artificial organs because space in the body is limited.

FIG. 3. The photograph shows a vibrating flow pump, implantable ventricular assist device.

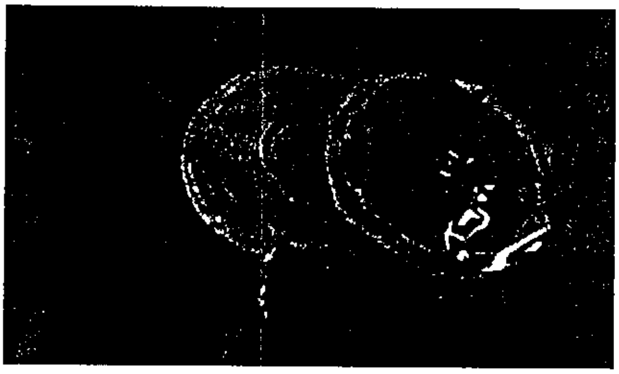

FIG. 4. A transcutaneous energy transmission system using amorphous fibers is illustrated.

Shape memory alloy (SMA) is a high-efficiency material. Input energy into SMA becomes very efficient actuating power.

Saywer et al. reported on the development of an SMA actuator for a TAH (1). They attached a large quantity of SMA to an artificial ventricle, which added contraction power to the ventricle. However, the drive speed of SMA was too small compared with the heart rate. Nitta et al. and Hayashi et al. reported on a VAD actuated with SMA (2,3). However, the drive speed was insufficient for the heart rate. Other researchers proposed various applications that attracted the attention of some research teams, such as valves for the urinary tract and stoma (4,5).

Recently, we invented the Peltier-SMA actuator for assisted circulation. This article reports and discusses the feasibility of SMA in artificial organ research.

ARTIFICIAL MYOCARDIUM

Bridging use of ventricular assist systems in heart transplantation may become necessary for a long time because of the shortage of donated hearts. In this situation, the quality of life of the patients waiting for a donor heart becomes increasingly important, so development of a totally implantable system is highly desirable (6–11). Toward this end, miniaturization of actuators is fundamental, especially for people with small physiques such as average Japanese people (6–8). The blood chamber in a natural heart is formed by myocardium. Therefore, a chamber is equal to an actuator; however, it is not so with the artificial heart, unfortunately.

Constituting an artificial heart is not the final goal of our studies; in fact, we are aiming to develop artificial heart muscle. Artificial heart muscle would be sewn onto the ventricle to support the contraction power of the natural heart ventricle. Since SMA is a highly efficient material, an actuator made of SMA can be miniaturized. Furthermore, since the drive mechanism is simple, an SMA actuator is expected to be durable.

However, the most important limiting factor of an SMA actuator is its drive speed because of the cooling time (1–3). We focused our attention on Peltier elements, which are the most suitable for rapid cooling. Electric energy becomes the movement of the heat in Peltier elements, as we have shown in Fig. 5. In other words, heat is moved from one side to another side, thus one side is heated and the other side cools down rapidly.

We utilized these characteristics in this study. Peltier elements were attached to SMA and record-breaking rapid cooling of SMA was achieved (1–3). As shown in Fig. 6, Peltier-SMA can actuate both ventricles of an artificial heart if the Peltier-SMA is installed in the ventricular septum. The Peltier-SMA may be an ideal drive mechanism candidate for a total artificial heart.

First, we induced an electrical current into a Peltier element attached to the SMA. Electrical current induced the heat transfer from one side to the other side. Then, heat was moved from the heat sink to the SMA. Thus, the SMA was heated and driven. After that, the electrical current was inverted. Then, the heat was moved from the SMA to the heat sink. Thus, the SMA was cooled and driven to the opposite side.

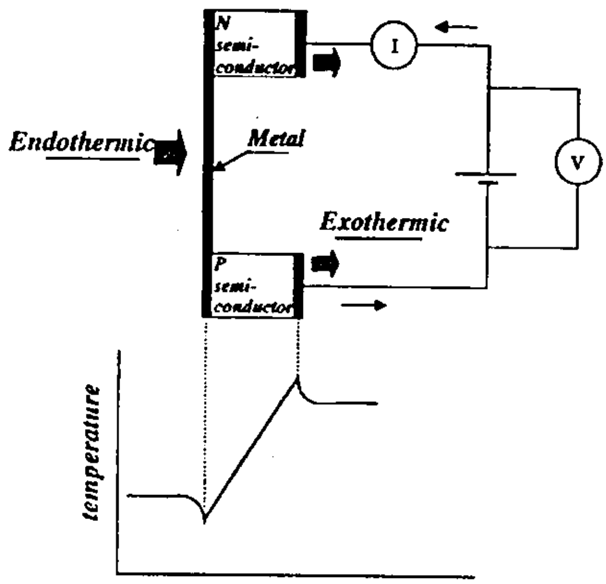

FIG. 5. Heat transfer in the Peltier element is shown.

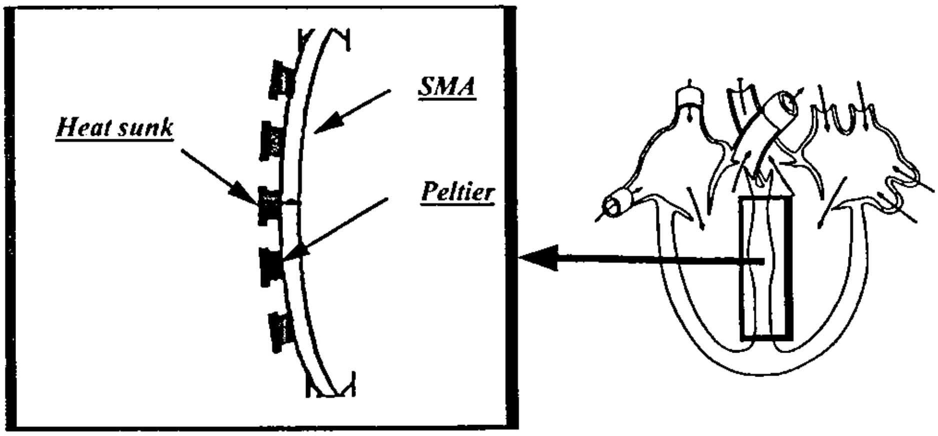

FIG. 6. Peltier-shape memory alloy (SMA) actuator for total artificial heart is shown.

FIG. 7. A goat with pneumatic artificial myocardium is pictured.

We developed an artificial muscle to support the right ventricle that was pneumatically actuated. The moving patch actuator was sewn into the right ventricle. This device was designed to support patients with right heart failure such as pulmonary hypertension, several kinds of abnormalities, and so forth. We succeeded in prolonging the survival of goats for three months using right ventricular supporting artificial myocardium, as shown in Fig. 7.

The design of artificial myocardium for right heart support is based on our previous studies. Figure 8 shows our Peltier-SMA right heart supporting artificial myocardium on a plastic model of a heart. We are currently conducting the animal experiments.

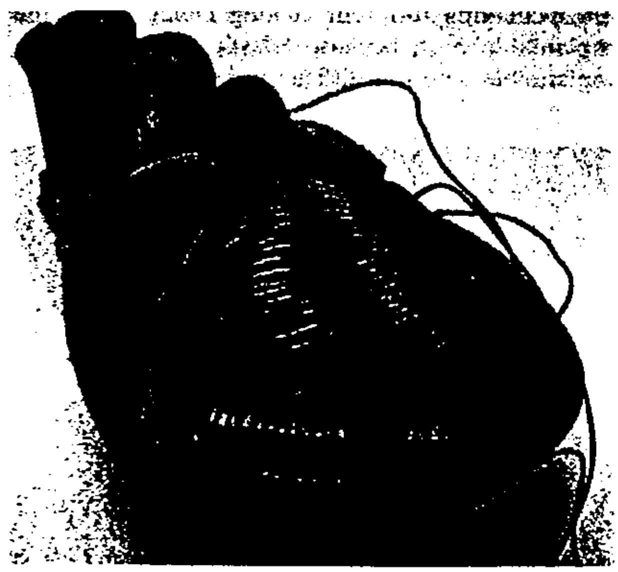

FIG. 8. Peltier-SMA artificial myocardium on a plastic model of a heart is shown.

ARTIFICIAL SPHINCTER

After an operation for rectal cancer or colon cancer, some patients require stoma and this adversely affects their quality of life.

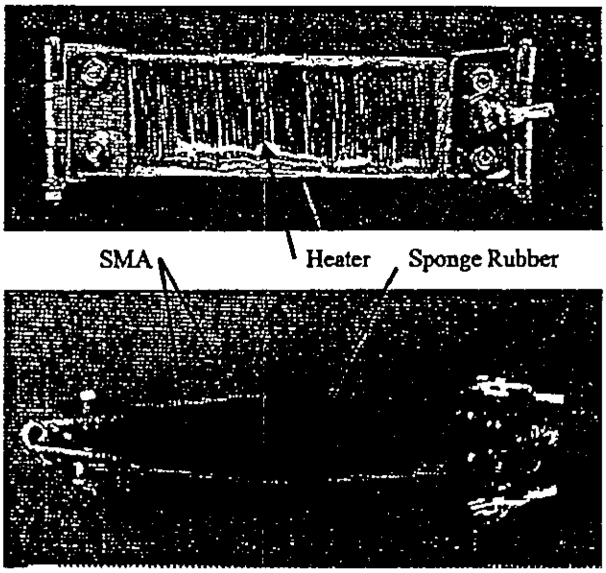

FIG. 9. Shown is a prototype artificial sphincter.

We developed an artificial sphincter to meet this need using an SMA to the stoma as shown in Fig. 9 (4). When the temperature is raised by electricity, the artificial sphincter opens, which allows patients to control their evacuations. A photograph of a prototype artificial sphincter is shown in Fig. 9. Long-term animal experiments are now being conducted on this device.

Electric power was supplied to the artificial sphincter by the use of the transcutaneous energy transmission system (TETS) as shown in Fig. 4.

Basic performance of this artificial implantable device is now under discussion. However, we are still evaluating different coating materials for the implantable part, because Silastic material for an implantable device is difficult to import.

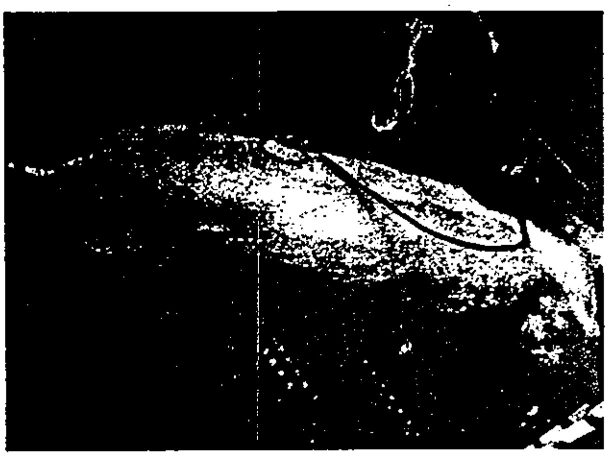

FIG. 10. A pig with artificial sphincter is shown.

The objective of the design concept is to enable patients to go to the bathroom whenever they choose. And then, when ready, they would take the TETS and attach it to their abdomen so that they would be able to control the implanted sphincter easily.

At present, the development of an artificial sphincter is at the stage of long-term animal experiments. Figure 10 shows a pig with a stoma and artificial sphincter. We are currently conducting a long-term endurance test for an artificial sphincter with TETS. When this test is completed we aim to begin preclinical trials.

CONCLUSION

This article reports on various artificial organs developed by Tohoku University and evaluates them for clinical applications.

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Original article

Artificial myocardium with an artificial baroreflex system using nano technology

Tomoyuki Yambe [a,*], Yasuyuki Shiraishi [a], Makoto Yoshizawa [b], Akira Tanaka [c], Ken-ichi Abe [c], Fumihiro Sato [c], Hidetoshi Matsuki [c], Masayoshi Esashi [c], Yoichi Haga [c], Shigenao Maruyama [d], Toshiyuki Takagi [d], Yun Luo [d], Eiji Okamoto [e], Yutaka Kubo [f], Motohisa Osaka [g], Shunsuke Nanka [a], Yoshifumi Saijo [a], Yoshiaki Mibiki [a], Tasuku Yamaguchi [a], Mune-ichi Shibata [a], Shinichi Nitta [a]

[a] *Department of Medical Engineering and Cardiology, Institute of Development, Aging and Cancer, Tohoku University, 4–1 Seiryo-machi, Aoba-ku, Sendai 980–8575, Japan*
[b] *Information Synergy Center, Tohoku University, Sendai 980–8575, Japan*
[c] *Graduate School of Engineering, Tohoku University, Sendai 980–8575, Japan*
[d] *Institute of Fluid Sciences, Tohoku University, Sendai 980–8575, Japan*
[e] *Faculty of Engineering, Hokkaido Tokai University, Sapporo, Japan*
[f] *Tokyo Dai-ni Hospital, Tokyo Women's Medical University, Tokyo, Japan*
[g] *Institute of Gerontology, Nippon Medical School, Kawasaki, Japan*

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Abstract

Where is the place which should be helped in a patient with congestive heart failure? The answer may be contraction of the heart. At Tohoku University, development research of "the artificial myocardium" has been conducted, using a ball screw type electromagnetic motor. Furthermore, super-miniaturization is being attempted at present. Thus, a system with shape memory alloy is being developed. The cooling speed problem was solved by the application of the Peltier element. A drive at a speed equal to that of a heartbeat was realized by the application of this system. At present, a ventricular assist device is used for patients waiting for a heart transplant in Japan. An air driven type system disturbs a patient's QOL remarkably because it is connected to the drive device. With our concept, energy is provided by using the electromagnetic force from outside of the body by the use of transcutaneous energy transmission system. Magnetic shielding by amorphous fibers was used at Tohoku University to improve the total efficiency. A natural heart can alter the cardiac output corresponding to the demand. Artificial internal organs must participate in the system of the living body, too. Tohoku University has developed a resistance based artificial heart control algorithm, which simulated a baroreflex system to cope with every demand. Nano level sensing equipment is now under development at Tohoku University. At present, development is being conducted aiming at an "intelligent artificial myocardium".

Keywords: Intelligent artificial myocardium; Nano technology; Artificial baroreflex; Transcutaneous energy transmission; Shape memory alloy

1. Introduction

Heart transplant facilities have recently been expanded in Japan. Everybody hopes transplant procedures in this country will reach a satisfactory level [1–4]. However, the shortage donor hearts is a serious problem. A ventricular assist device is used as a bridge to transplantation [5,6].

Pneumatic driven ventricular assist devices such as Xemex and Toyobo have been playing a very important role [2–6]. According to the increase in the waiting period for a donor heart, the realization of a totally implantable artificial heart is becoming increasingly important. After going back to basics, reconsideration was given to the principles [7–11].

Where can most assistance be given to a patient suffering from congestive heart failure?

The answer may be the contraction of the heart.

* Corresponding author. Tel.: +81-22-717-8517; fax: +81-22-717-8518.
E-mail address: yambe@idac.tohoku.ac.jp (T. Yambe).

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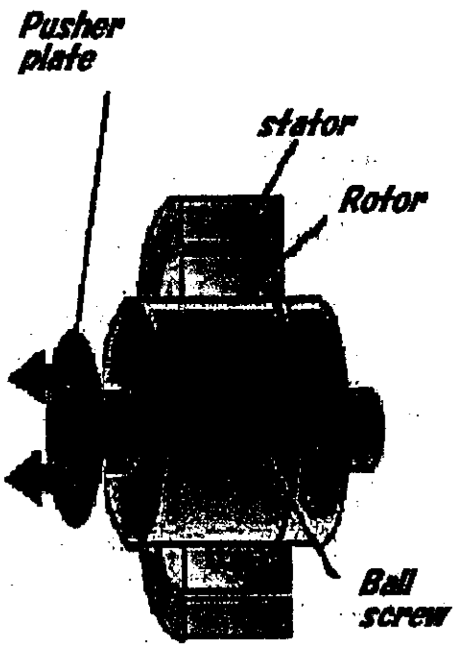

Fig. 1. Schematic drawing of the ball screw magnetic motor for implantable artificial myocardium..

If we consider the principle of heart massage, cardiac output is supported by pushing a ventricle. Based on this idea, a system was devised by which the ventricle was pushed. This system is sewn onto the ventricle and assists the contraction power of the natural heart.

Development research of "the artificial myocardium" has been conducted in Tohoku University for many years. Air pressure drive type artificial myocardium research in chronic animal experiments had already proven successful and the supporting effect of the artificial myocardium was confirmed in chronic animal experiments over 3 months.

So, from this, obtaining an improved implantable artificial myocardium in QOL was planned. This year, with a Grant in aid for scientific research, and Science research-funds from the Ministry of Welfare, Labor, a new development project was commenced. The most advanced sensor and actuator nano technology was applied, aiming for the development of a super-miniature device, which exceeds retrogenerative medicine.

2. Actuator for an artificial myocardium

The challenge was to find a miniature motor with high torque from among all the miniature motors available throughout the world. A ball screw type electromagnetic motor, which was adopted in the robot arm in the space shuttle, was used [12–16] (Fig. 1). This motor was applied to the animal experiment, and at present, its effect on heart assistance is being confirmed.

Furthermore, as super-miniaturization is also a goal, a system with shape memory alloy is also being developed at present. Regarding the shape memory alloy, the rise in temperature by the thrown energy is directly related to the drive [17,18]. Therefore, the energy efficiency is high. However, an important problem is the drive speed. Cooling down the shape memory alloy is difficult. This problem was solved at Tohoku University by the application of the Peltier element (Fig. 2). The Peltier element is a semiconductor element, which moves heat. The settlement side is refrigerated due to the movement. A drive at a speed equal to a heartbeat was realized by the application of this system and currently, research aiming at the improvement of the durability is being conducted.

Fig. 2. Photograph of an example of a candidate for an implantable artificial myocardium using shape memory alloy with the Peltier element.

This system also aims at the development of a super-miniature micro system. The development of a micro actuator for holding nano level structure development is indispensable. Various kinds of nano actuators are now under development at Tohoku University. These nano–micro systems are expected to become the key technology for artificial myocardium.

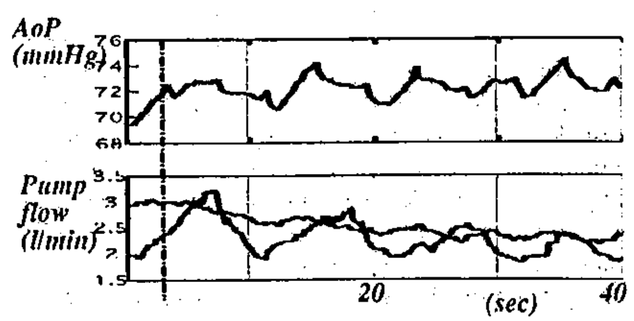

Fig. 3. Time series data of an artificial baroreflex system with biventricular rotary blood pump assistance with ventricular fibrillation. During increase of the blood pressure by drug administration, the drive speed of RP was automatically controlled to be decreased. This control algorithm can be used in the artificial myocardium system.

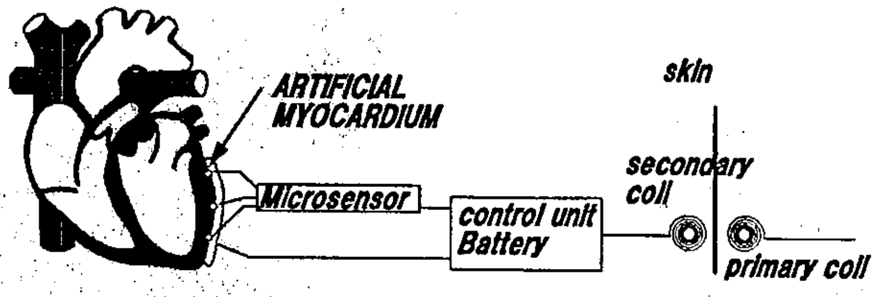

Fig. 4. Schematic illustration of the total system of an implantable artificial myocardium.

3. Energy supply system

At present, an assistant mechanical heart is used for patients waiting for a heart transplant. Only an air pressure drive type system is covered by insurance in Japan. An air driven type system disturbs a patient's QOL remarkably because it is connected to the drive device. So, a totally implantable system is necessary to improve the patient's QOL.

With our concept, energy is provided to the artificial myocardium using the electromagnetic force from outside the body. Such a system has been developed all over the world. Magnetic shielding by amorphous fibers was used in Tohoku University to improve the total efficiency [9,10]. Amorphous fibers are attached outside the coil, which is placed on the skin to prevent the leakage of magnetic power. Therefore, the efficiency of the energy transmission between the coils is improved.

Power generation equipment, to which nano technology was applied, is currently being developed at Tohoku University. This system can improve the efficiency of the energy use. As a comparison, this system resembles that of a hybrid car. The energy of the actuation part is used, and the generation of electricity is achieved.

4. Artificial myocardium control algorithm

A natural heart can alter the cardiac output corresponding to the demand. Artificial internal organs must participate in the system of the living body, too. Therefore, artificial internal organs must maintain pace with the actions of the living body, and must cope with the total system. Tohoku University developed a resistance based artificial heart control algorithm, which had a simulated baroreflex system to cope with every demand [19,20]. A total artificial heart, a ventricular assist device, cardiopulmonary bypass, percutaneous cardiopulmonary support system (PCPS) and a rotary blood pump can be controlled with this automatic control system [19–21]. Fig. 3 shows time series data of biventricular total nonpulsatile artificial circulation with resistance based control algorithm simulating the baroreflex function. According to the increase of blood pressure with drug administration, the drive speed of the rotary pump was automatically controlled to be decreased. Since it can be calculated at the microchip level, it can be implanted in the control microchip for an artificial myocardium (Fig. 4).

The sensing device is, of course, important in the automatic control system. Nano level sensing equipment is now under development in Tohoku University. It can sense hemodynamic pressure, blood flow and several hormonal factors. A chronic durability animal experiment has already been completed with the micro sensors. More miniaturization is planned to build this into the nano level structure.

Development aiming at an "intelligent artificial myocardium" is being conducted at present.

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