CHAPTER 6

ROBOTICS FOR BIOLOGICAL AND MEDICAL APPLICATIONS

Yuan Zheng, George Bekey, Arthur Sanderson

BACKGROUND

This chapter describes research activities currently conducted in the world that are related to robotics for biological and medical applications. Robotics for medical applications started fifteen years ago while for biological applications it is rather new (about five years old). In this chapter, we first discuss why we need robots and automation in biology and medicine. Then we present robotic tools, devices and systems, key technologies, and fundamental research challenges that are relevant to the two applications. Research activities conducted and visited by the assessment team in the U.S., Japan, Korea and Europe are introduced.

WHY ROBOTS AND AUTOMATION IN BIOLOGY AND MEDICINE

Biological Applications

The primary purpose for use of robotics in biology is to achieve high throughput in experiments related to research and development of life science. Those experiments involve the delivery and dispensation of biological samples/solutions in large numbers each with very small volumes. Typical applications include high-throughput systems for large-scale DNA sequencing, single nucleotide polymorphism (SNP) analysis, haplotype mapping, compound screening for drug development, and bio-solution mixing and dispensing for membrane protein crystallization. Without robots and automation, biosamples/solutions must be handled manually by human hands, which is not only tedious but also slow. Various robotic systems have been developed in laboratories that are either specially developed for a particular application (Fig. 6.1) or integration of commercially available robots, general purpose tools and sensors.

The second purpose of robotics for biological applications is for effective handling and exploration of molecular and cell biology. This type of application includes immobilization of individual cells, cell manipulation, and cell injection for pronuclei DNA insertion. Special tools fabricated using different technologies have to be developed such as lasers for microsensing and manipulating, electroactive polymer for cell manipulation, and microneedles for cell penetration.

Another interesting area of application is robotics-inspired algorithms for molecular and cellular biology. This includes the work for predicting protein folding, and for structural biology (Zheng and Chen, 2004).

Medical Applications

Research on robotics for medical applications started fifteen years ago and is very active today. The purpose is three-fold. First it is for robotic surgery. Robotic surgery can accomplish what doctors cannot because of precision and repeatability of robotic systems. Besides, robots are able to operate in a contained space inside the human body. All these make robots especially suitable for non-invasive or minimally invasive surgery and for better outcomes of surgery. Today, robots have been demonstrated or routinely used for heart, brain, spinal cord, throat, and knee surgeries at many hospitals in the United States (International Journal of Emerging Medical Technologies, 2005). Fig. 6.2 shows doctors performing knee surgery using a robotic system. Since robotic surgery improves consistency and quality, it is becoming more and more popular.

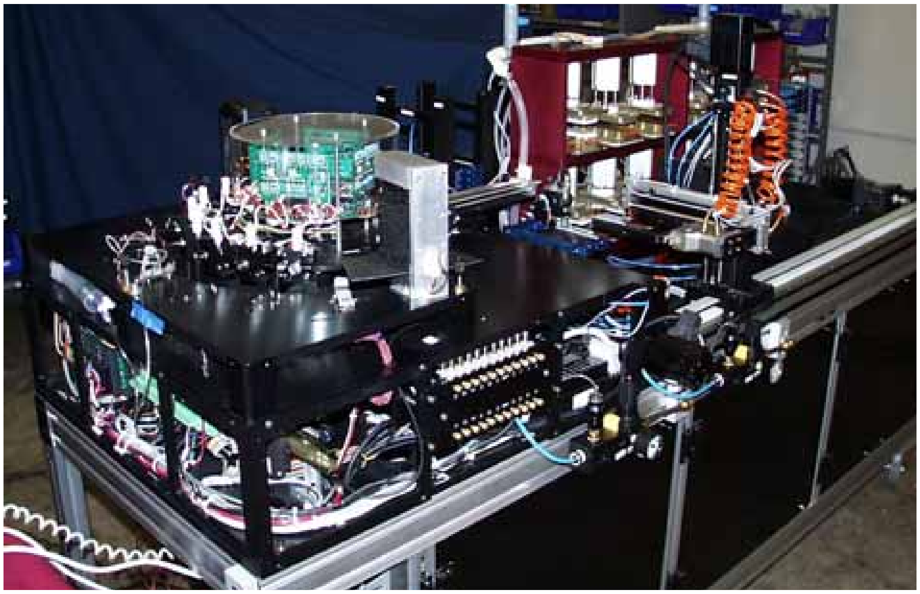

Figure 6.1. High-throughput systems for DNA sequencing (U. Of Washington) (Meldrum and Kavraki, 2004).

Figure 6.2. Doctors perform knee surgery using a robotic system (Taylor, 2004).

The second use of robotics in medicine is diagnosis. Robotic diagnosis reduces invasiveness to the human body and improves the accuracy and scope of the diagnosis. One example is the robotic capsular endoscope that has been developed for non-invasive diagnosis of gastrointestinal tract by Polo Sant'Anna Valdera of the Sant'Anna School of Advanced Studies in Italy (Fig. 6.3).

The third use of robotics is for providing artificial components to recover physical functions of human beings such as robotic prosthetic legs, arms and hands. For example, at the Technical University of Berlin there is work on powered leg orthoses using electromyographic signals for control (Fig. C.71) and on prosthetic hands (Fig. C.72). The latter is basically an exo-skeleton for a non-functional hand. Prosthetic hands are also being developed at University of Tsukuba in Japan. In addition, rehabilitation robotics can help patients recover physical functions more effectively after injury by replacing or supplementing the work of physical therapists. Robotic devices and systems can also help elderly people move around; this includes intelligent wheeled chairs, walking-assistance machines, and limb-empowering robotic devices. For example, a new type of powered walker was developed at Waseda University. It is capable of sensing pressure from both the left and right arms (see Figure 6.6 on page 68).

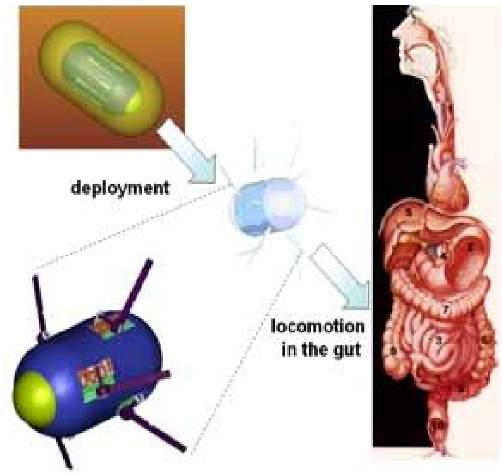

Figure 6.3. Robotic capsular endoscope for examination of gastrointestinal tract (Polo Sant'Anna Valdera of the Sant'Anna School of Advanced Studies, 2005).

In addition, rehabilitation robotics can help patients recover physical functions more effectively after injury. Robotic devices and systems can also help elderly people move around; this includes intelligent wheeled chairs, walking-assistance machines, and limb-empowering robotic devices.

Robotic Tools, Devices and Systems

Robotics for biological and medical applications uses many tools, devices, and systems of both general-purpose and specially designed types. The former includes robot manipulators for picking and placing, and microactuators for dispensing biosamples/solutions such as the one shown in Fig. 6.4. Another example is the system developed by the Novartis Research Foundation's Genomics Institute, which includes standard industrial manipulators for high-throughput screening of compounds up to 1 million samples per day (Meldrum and Kavraki, 2004). In robotic surgery, commercially available robots are often a part of an integrated system.

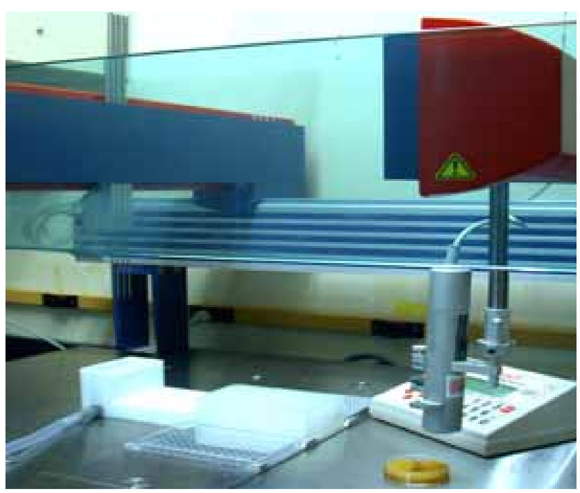

Figure 6.4. Off-the-shelf robot is a part of a biosolution dispensing system (Ohio State U.).

Special-purpose devices and systems come in many varieties depending on the purpose of applications. For example, special systems are developed for high-throughput preparation of bio-solutions such as the one developed by the University of Washington, shown in Fig. 6.1. Special purpose sensors have even more types including visual, force, and neuro-sensing. Biosensors often are very small and so microelectromechanical systems (MEMS) technology is used to fabricate such elements as the microforce sensor from the University of Minnesota and ETH-Zürich shown in Fig. 6.5. Special tools using non-traditional principles are also developed to handle bio-solutions or to manipulate cells. For example, Nagoya University in Japan used local photo polymerization on a chip to immobilize individual cells.

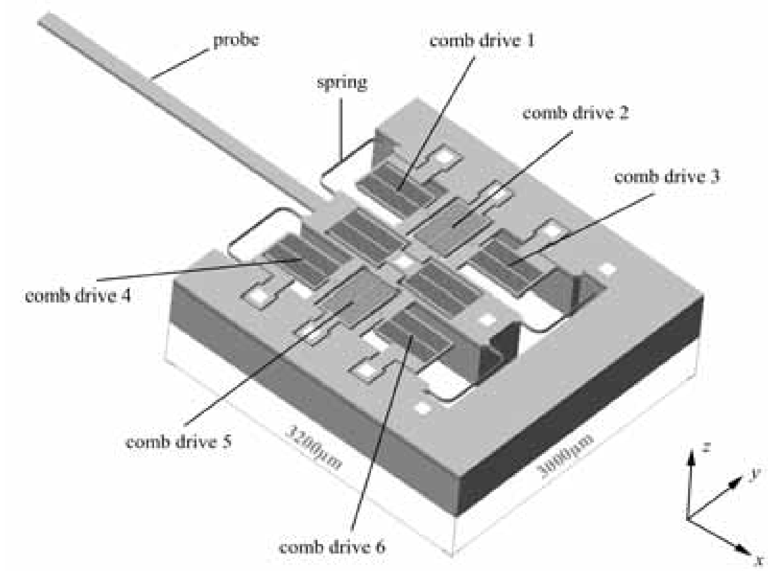

Figure 6.5. Microforce sensor using integrated circuit (IC) fabrication technology, U. of Minnesota (Nelson and Zheng, 2004).

Besides tools and devices, software and algorithms are also an important part of robotics for biological and medical applications. In robotic surgery, for example, effective algorithms for modeling and analysis of human body components are an important topic of research. The purpose is to develop patient-specific models for performing precise surgery.

Key Technologies

Key technologies for robotics in biological and medical applications include the following:

a) MEMS technologies that can fabricate tools and devices suitable for microsensing, microactuation and micromanipulation of biosamples/solutions and bio-objects such as cells. These technologies use either IC-fabricating methods or use micromachining methods.

b) Special robotic systems that can perform surgery precisely and at low cost. The challenge is to program motion of robots efficiently based on patient-specific modeling and analysis.

c) Modeling and analysis algorithms that are precise and fast for individual patients.

d) Reliable and efficient system integration of off-the-shelf components and devices for specific biological and medical operations.

e) Engineering modeling of biological systems. The purpose is to develop mathematical models for explaining the behavior and structure of biological systems as engineers do for artificial physical systems. This has been proved extremely challenging because of the complexity of biological systems.

f) Solid understanding of life science. To develop an effective robotic or automation system for biological and medical applications, it is necessary for engineers to have a deep understanding of life science.

From the above, one can see that robotics for biological and medical applications covers a wide scope of technologies from conventional robots and sensors to micro sensors and actuators, from tools and devices to algorithms. For molecular-level study of biological systems, nano-devices and actuation are key technologies as well.

Fundamental Research Challenges

There are a number of fundamental research challenges in robotics for biological and medical applications that can be summarized as follows. First and foremost, technologies for biological and medical applications are not mature, especially for biology. There is still a lack of effective tooling and sensing technologies to deal with massive and tiny bio-objects and biosamples/solutions. In particular, the following issues in biological research are still not resolved:

- Automated cell handling and operations (probing and sensing) is extremely challenging because of the tiny size of the cells.
- Automated protein characterization and functional analysis is extremely difficult because finding protein structure is slow and costly.
- Automated protein crystallography including protein crystallization, crystal harvesting, and X-ray detection is still not possible because protein crystals are so small that they are difficult to detect using vision sensors, and there are no effective tools for picking and placing.
- Automated DNA sequencing is still slow and expensive.
- Automated DNA and protein chip production and analysis are still expensive and slow, although technologies have been improved constantly.

For medical applications, Russell Taylor of the Johns Hopkins University summarized core challenges in three areas: modeling and analysis, interface technologies, and systems, which are described below (Taylor, 2004):

- For modeling and analysis, the emphasis is on developing computationally effective methods for patient-specific modeling and analysis.
- For interface technology, the emphasis is to fundamentally extend the sensory, motor, and human-adaptation abilities of computer-based systems in an unusually demanding and constrained environment.
- For systems, the emphasis is on developing architectures, building blocks and analysis techniques that facilitate rapid development and validation of versatile computer integrated surgery (CIS) systems and processes with predicable performance.

In general, robotics for biological and medical applications is still new, and relevant technologies are immature, especially for biological applications. Consequently methods of robotics and automation are often ad hoc, and systems developed for a particular application are evolutional, not revolutionary (Meldrum, 2000). For medical applications, robotic methods are more systematic, but not necessarily a matter of science yet. Furthermore engineers of robotics and automation have limited knowledge of life science. As a result, engineers have difficulty developing effective tools, devices and systems in an efficient way for both biological and medical applications. Collaboration between engineering and biology is still rare, although that between engineering and medicine has a longer history.

REGIONS VISITED BY THE ASSESSMENT TEAM

The assessment team visited two regions in addition to the workshop held in the United States last July, which reported research results by U.S. researchers. The countries in the two regions are Japan, Korea and a number of European countries.

United States

The U.S. workshop was attended by U.S. researchers of academia, research laboratories, and industries. Three presentations related to robotics for biological and medical applications were:

a. Deirdre R. Meldrum (U. of Washington) and Lydia E. Kavraki (Rice U.) on the topic of robotics and robotics-inspired algorithms for molecular and cellular biology: diagnostics, genomics, proteomics.
b. Brad Nelson (U. of Minnesota and ETH-Zürich) and Yuan F. Zheng (Ohio State U.) on the topic of status of robotics in the U.S.: Bio/Pharmaceutical.
c. Russell Taylor (Johns Hopkins U.) on the topic of medical robotics and computer integrated surgery.

It should be noted that the number of U.S. organizations involved in robotics for biological and medical applications mentioned by the three presentations is more than thirty. Some of the research activities performed by these organizations have been described earlier in this chapter. In biological applications, for example, the U.S. is particularly strong in developing robotic systems for high-throughput handling of biosamples in life science, such as gene-sequencing and protein crystallization. In medical applications, the National Science Foundation has funded Johns Hopkins University for the Engineering Research Center for Computer-Integrated Surgical Systems and Technology, which has a focus on robotics in medical applications, especially robotic surgery.

In terms of commercial applications, the U.S. has a very successful system called *Da Vinci* which is designed to assist surgeons with complicated medical operations. The system has been purchased by many hospitals in the U.S. (in the world as well) for robotic knee replacements and prostate and heart surgeries.

Japan and Korea

In Japan, the assessment team visited in Japan Nagoya University, Waseda University, and ATR Computational Neuroscience Laboratories; in Korea KIST (Korea Institute of Science and Technology) and Seoul National University, among others. The organizations mentioned here performed research on robotics for biological and medical applications. Nagoya University studies non-contact cell manipulations using lasers, and intravascular surgery based on 3D-reconstructed cerebral arterial model using CT images and an *in vitro* model of human aorta.

Figure 6.6. The walking-assistance device by Waseda University.

Waseda University is well known for its research on legged locomotion. In recent years, Waseda has also been active in the research on robotic surgery and walking-assistance devices for elderly people (Fig. 6.6).

ATR studies brain function using a special computational approach called, "understanding the brain by creating one." In Korea, Seoul National University studies MEMS and nanotechnologies for bio-applications, and KIST studies advanced techniques for cell handling.

Europe

Research on robotics for biological and medical applications has been active in Europe for a long time. There are many institutions involved, of which the assessment team could visit only a few in the limited time period. The team visited the group at the ETH Swiss Federal Institute of Technology, which is led by Dr. Brad Nelson, who is also with the University of Minnesota. Dr. Nelson's group studies MEMS technologies for tools for cell manipulation and operation. The University of Zurich's Artificial Intelligence Laboratory studies the evolution of artificial cells whose purpose is to mimic biological growth. At the University of Genova in Italy, scientists study haptic control mechanisms of human arms, and control mechanisms of human eyes. At the Technical University of Munich, Dr. Alois Knoll leads a research group that develops surgical robots. Researchers there use haptic approaches based on force feedback and touch sensing for surgery and skill transfer. The advantage is to scale robot motions to non-human-sized situations to improve accessibility and range of distance, dexterity and speed for applications as minimally-invasive heart surgery.

Polo Sant'Anna Valdera of the Sant'Anna School of Advanced Studies in Italy is one of the largest groups, which performs research on robotic for biological and medical applications. The group consists of eight laboratories and centers which are: a. ARTS Lab (Advanced Robotics Technology and Systems Laboratory), b. BIO Labs (Biological Laboratories), c. CRIM (Center for Applied Research in Micro and Nano Engineering), d. PERCRO (Perceptual Robotic Laboratory), e. RETIS (Real-Time Systems Laboratory), f. EZ-Lab Research Center which focuses on technologies and support services related to longevity, g. IN.SAT (Business and Territorial Systems Innovation Laboratory), and h. Humanoid Robotics Research Center. Of the eight laboratories, ARTS and CRIM are involved in the research of robotics for biological and medical applications.

The ARTS laboratory focuses on basic research of robotics, mechatronics and bioengineering. Research projects currently going on explore biomorphic and anthropomorphic solutions for robotic devices in general, and biomechanics, neuro-robotics, and rehabilitation and assistive devices in particular. One such a project investigates implantable microdevices which can detect neuron signals from human arms to directly control robotic devices (Fig. 6.7).

The CIRM laboratory focuses on the design and development of micro- and nano-devices, but its strategy is to avoid the silicon processing method popularly used for fabricating IC devices, which includes many chemical processes such as lithography, itching, and diffusion. Instead, CRIM cuts materials, plastic, metal or silicon directly using precision machines. For that purpose, CRIM is facilitated with a set of machining equipment such as a Kern HSPC micro-computerized numerical control (CNC) machine, an electrical discharge machine, a plastic injection molding machine, and a microerosion system. The robotic capsular endoscope mentioned earlier (Fig. 6.3) was developed by the laboratory using the technologies just mentioned.

Figure 6.7. Human arm implantable microprobes.

Another large group the assessment team visited is led by Dr. Tim C. Lüth who is associated with the Medical School Charite of Humboldt University and Fraunhofer Institute for Production and Design (IPK) in Berlin, Germany. The team observed that Dr. Lüth's involvement in both sides was deep and had yielded great results. The team saw excellent facilities for conducting research on medical robots, which included a wide mix of small machine shops and integration areas, mixed with facilities for clinical trials, teaching hospital theaters, and full-time surgical suites. This vertical integration of the research, founded at IPK, is not matched in the U.S. (see Figure 6.8).

Figure 6.8. Medical robot facilities at the Berlin Center for Mechatronical Medical Devices (Charite and IPK).

Dr. Lüth leads a group called Berlin Center for Mechatronical Medical Devices, which focuses on three areas of surgerical robots, namely navigation, robotic, and navigation control. Navigation is to develop mechanisms for leading the tip of a medical instrument to precise positions and orientations with respect to a patient's tissue structure, Robotic is to develop devices for carrying the tip to the desired positions and orientations, and Navigation Control is to actively constrain the instruments' power during operations. The group has studied extensively the navigation mechanisms for various types of operations including neurosurgery, knee replacement, dental implantology, radiation therapy, radiology, etc. Multiple generations of navigation systems have been developed in house. The latest generation has reduced the required inter-ocular baseline to a small distance (~0.4m). This is mounted on a small roller mount that takes up only a small amount of floor space. Many types of surgeries have been performed by these navigation systems, which are by no means less than what we have seen in the U.S.

QUANTITATIVE AND QUALITATIVE OBSERVATIONS

Quantitative Observations

In terms of quantity, the U.S. is leading the world in both the number of organizations and the types of applications for both biological and medical applications. As mentioned earlier, in the U.S. there are at least thirty research organizations performing research on robotics for biological applications. The U.S. is leading the world in the following areas: DNA sequencing, cell manipulation, protein crystallography, DNA and protein chip production and analysis, and computational biology, and bioinformatics.

For medical applications, there is a National Science Foundation Engineering Research Center (NSF/ERC) at the Johns Hopkins University, named the NSF/ERC Computer Integrated Surgical Systems and Technology. The center has over $5 million of support per year, not counting numerous small research groups in the U.S. Many university hospitals study and perform robotic surgery on hearts, brains, knees, prostates, or spinal cords, etc., (often sponsored by the National Institutes of Health) including Johns Hopkins University, University of Southern California, CMU, Ohio State University, University of California at Berkeley, and University of Illinois at Chicago, among many others. Many non-university hospitals routinely use robotic devices for minimally invasive surgery.

There is no doubt that the U.S. is leading the world in the research of robotics for biological and medical applications. However, other countries are catching up; the assessment team saw many organizations in Japan, Korea and Europe actively participating in the research and more of the others are joining, such as the Chinese University of Hong Kong (Dr. Wen J. Li's group, which will be mentioned later).

Qualitative Observations

Research on robotics and automation for biological and medical applications is still young. However, many quality results have been generated by the scientists in the United States and all over the world. The maturity of new robotics technologies vary from laboratory demonstrations to reliable applications. It is fair to say that quality of research in the U.S. is as good as any other country in the world. For biological applications, the U.S. is clearly leading the world in the areas of DNA sequencing, protein crystallography, drug discovery, and cell operation. Other countries are also producing promising results, such as the best paper award of the IEEE 2003 International Conference on Robotics and Automation, which went to Dr. Wen J. Li of the Chinese University of Hong Kong for his outstanding work on electroactive polymer cell manipulation.

In spite of great progress, there are still obstacles and challenges. First, approaches are still ad hoc, i.e., no systematic theory governs the area as mentioned earlier. Secondly, progress in this area heavily relies on the development of MEMS and nano technologies, which unfortunately have proved slow. Finally, collaboration between engineers and biologists is still new and challenging. For medical applications, the U.S. is most active for robotic surgeries. The U.S. is also leading the world in the development of robotic tools and systems for medical applications.

The leading position of the United States in both quantity and quality is not a surprise since the country invests the most in the two areas. As other countries are now putting in more resources, the U.S. government has to maintain the level of investment or to invest even more to keep the leading position.

Conclusions

Research on robotics for biological and medical applications is still young. Scientists in the U.S. are more active in identifying and developing new applications of robotics for the two applications. Many significant results have been achieved, and some have been commercialized to become useful devices and systems such as the *da Vinci* surgical system (International Journal of Emerging Medical Technologies, 2005). In the U.S., the number of institutions involved in the research of robotics for both applications is significantly higher than any other country while the quality of research is equally good.

On the other hand, approaches for robotics for biological and medical applications, especially for the former, are evolutionary, not revolutionary. Still there are many opportunities for collaboration between engineers and biologists, and between engineers and doctors. It is believed that any new breakthrough in biology and in medicine may need revolutionary tools, perhaps in robotics, to take place. Although the U.S. is still leading the world in the two applications, more and more countries are participating and making impressive progress. After all, the field has potential to bring great economic impact.

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