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Introduction

Robot is a multifunctional machine that can perform tasks such as work or movement through programming and automatic control. In 1920, Karel Capek, a Czech writer, published the science fiction script “Rossum’s Universal Robots,” a classic of the world’s science fiction literature. In the play, the writer changed the Czech word “robota,” which originally meant “slave,” into “robot,” which is the origin of the word “robot.” The play tells the story of a company called Rossum that introduced robots to the market as industrial products produced by human beings and let them act as labor instead of human labor, and predicts the tragic impact of the development of robots on human society, and has attracted extensive attention.

The invention of robots is to let human beings free their hands and better improve and enjoy life. With the deepening of people’s understanding of the intelligent nature of robot technology, it began to penetrate into all fields of human activity. However, there is no unified standard for the classification of robots in the world, and there can be different classifications from different definition standards. Among them is a micro- and nanorobot defined according to the size of the robot, which has attracted more and more interest of researchers in many disciplines. It may completely change the application fields, including biomedicine, information storage, environmental detection and repair, and micro-/nanoengineering. Especially in the biomedical field, biomedical micro- and nanorobots may become an important driver for the development of this field.

1.1 Origin of Biomedical Micro- and Nanorobots

The story of biomedical micro- and nanorobots can be traced back to the famous speech “There’s plenty of room at the bottom” in 1959 (Figure 1.1). It is well known that the Nobel Prize-winning theoretical physicist Richard Feynman first proposed the idea of “nanotechnology” in his classic speech. Although he did not use the word “nano,” he actually expounded the basic concept of nanotechnology. In addition, he said, “A biological system can be exceedingly small. Many of the cells are very tiny, but they are very active; they manufacture various substances; they walk around; they wiggle; and they do all kinds of marvelous things – all on a very small scale. Also, they store information.” His smart brain began to flash, “Consider whether it’s

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There's Plenty of Room at the Bottom

An Invitation to Enter a New Field of Physics

by Richard P. Feynman

I imagine experimental physicists must often look with envy at men like Kamerlingh Onnes, who discovered a field like low temperature, which seems to be bottomless and in which one can go down and down. Such a man is then a leader and has some temporary monopoly in a scientific adventure. Percy Bridgman, in designing a way to obtain higher pressures, opened up another new field and was able to move into it and to lead us all along. The development of ever higher vacuum was a continuing development of the same kind.

I would like to describe a field, in which little has been done, but in which an enormous amount can be done in principle. This field is not quite the same as the others in that it will not tell us much of fundamental physics (in the sense of, ``What are the strange particles?") but it is more like solid-state physics in the sense that it might tell us much of great interest about the strange phenomena that occur in complex situations. Furthermore, a point that is most important is that it would have an enormous number of technical applications.

What I want to talk about is the problem of manipulating and controlling things on a small scale.

Figure 1.1 Richard Phillips Feynman (11 May 1918 to 15 February 1988), American physicist, Professor of Physics at Caltech, winner of the 1965 Nobel Prize in Physics.

possible: we can also make a little thing under our command; we can also make a thing to act according to plan on the above-mentioned small scale!" [1].

"Under our command" and "small scale," yes, this is the initial description of mini machine. In his subsequent speech, he continued, "A friend of mine (Albert R. Hibbs) suggests a very interesting possibility for relatively small machines. He says that, although it is a very wild idea, it would be interesting in surgery if you could swallow the surgeon. You put the mechanical surgeon inside the blood vessel and it goes into the heart and 'looks' around. (Of course, the information has to be fed out.) It finds out which valve is the faulty one and takes a little knife and slices it out. Other small machines might be permanently incorporated in the body to assist some inadequately-functioning organ." This is the most absurd and great idea of "swallowable surgeon".

One might ask, does this "swallowable surgeon" idea come from Albert R. Hibbs or Richard Feynman? We can't find the right answer now. But Richard Feynman praised this idea, "I can hardly doubt that when we have some control of the arrangement of things on a small scale we will get an enormously greater range of possible properties that substances can have, and of different things that we can do."

At the end of the speech, Richard Feynman offered an attractive reward of 1000 dollars to researchers who can prepare miniature books (can be read by an electron microscope) and working electric motors (only 1/64 in. cube with 1/64 in. side length) in future. The last sentence is "I do not expect that such prizes will have to wait very long for claimants".

However, he did not offer a reward to researchers who could prepare "swallowable surgeons" in the future. Maybe it's because he can't afford it, because at the critical moment, the value of a surgeon may be far more than a miniature book or a miniature electric motor. After all, who doesn't cherish life? The "swallowable surgeon" mentioned by Richard Feynman or Albert R. Hibbs is the protagonist of our book – biomedical micro- and nanorobots.

1.2 A Long Journey

The wings of artistic spirituality always lead the heavy steps of science and technology. In 1966, a novel entitled "*Fantastic Voyage*", written by Isaac Asimov, the most famous popular science writer and science fiction novelist in America, was published by Houghton Mifflin Harcourt [2]. This novel described the fantastic adventure of shrinking human beings to the size of cells through scientific means. In August of the same year, Richard Fletcher served as the director and used miniature technology to go deep into the human body to shoot the science fiction film *Fantastic Voyage* of the same name. It described, how under the background of the Cold War between the United States and the Soviet Union, five American doctors boarded a submarine reduced to a micron scale and entered the blood of a wounded Soviet diplomat. Although the blood fluctuation caused by each heartbeat kept the submarine on the verge of overturning at any time, and the antibodies in the body also took the submarine as the source of infection and madly attacked it, the heroic protagonists were still able to manipulate the submarine to avert danger in the blood and destroy life-threatening thrombus. They succeeded in saving the diplomat's life. After the final task was completed, they escaped through the eye of the diplomat. This film had a novel idea and created a new vision for the theme of science fiction films. Therefore, it won two Golden Awards, the 39th Academy Award for best art direction and best visual effect in 1967. Politics and war aside, the film has successfully triggered more imagination about micro machines (microrobots) all over the world.

The realization of dreams ultimately depends on the development of science. It has been more than 60 years since the micro- and nanorobot was developed and applied to the research of *in vivo* treatment of major diseases. The major events in the research history of micro- and nanorobots are listed in Figure 1.2 [3]. From the swimming of microscopic organisms observed by Sir Geoffrey Taylor in 1951 [4], and

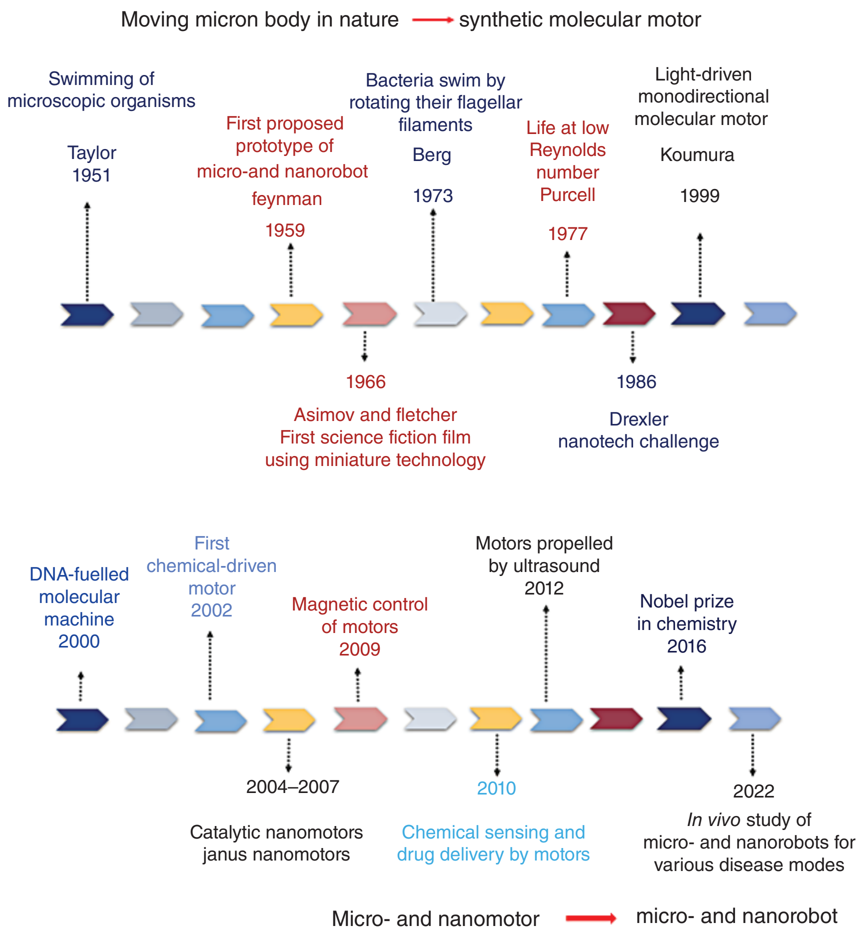

Figure 1.2 Major events in the history of micro- and nanorobot research (1951–2022). Source: Wang [3]/John Wiley & Sons.

the bacteria swimming by rotating their flagellar filaments observed by Howard C. Berg in 1973 [5], these belong to the movement of organic organisms, but they are also concerned by researchers about their internal rotating machines [6].

Researchers turned their attention to smaller molecules, which may be caused by the random motion of the molecules driven by environmental heat. At the time of Feynman's speech, chemists did not master enough synthetic technology and analytical means to create artificial molecular machines. From the 1970s to the 1980s, the rapid development of synthetic chemistry and supramolecular chemistry (which won the Nobel Prize in chemistry in 1987) provided reliable synthesis templates and strategies for the construction of artificial molecular machines. In 1991, Fraser Stoddart published an article entitled "A Molecular Shuttle," which described the earliest rotaxane-based molecular machine synthesized with a receptor template [7]. He believed that the early molecular machines only limited the random movement to a certain dimension and space. For example, the molecular shuttle limited the random movement of the macrocycle to two equivalent binding sites on one axis. Jean-Pierre Sauvage and Fraser Stoddart independently introduced the stimulus response mechanism into the design of molecular machines in 1994, realizing the control of external conditions on molecular machines [8, 9]. In 1999, Ben L. Feringa proposed the light-driven monodirectional molecular motor and described how the first molecular machine designed by him experienced two cis/trans-isomerizations of alkene and two thermal relaxation processes to realize 360° of unidirectional rotation under light. The carefully designed olefins with large steric hindrance and skillfully arranged steric hindrance groups make the thermal relaxation an irreversible unidirectional process, ensuring the unidirectional rotation of the molecular machine under light [10].

In 2000, Andrew J. Turberfield designed the first DNA-fueled molecular machine, which is different from those DNA tiles and DNA bricks prepared only using DNA as building materials, and it is a walking machine [11]. If nature mainly uses proteins as parts to build molecular machines, it is easier for researchers to program DNA to produce DNA nanorobots with different shapes and functions than proteins. These DNA nanorobots are usually manufactured as initial folding structures with DNA aptamer-based locks. The locked DNA structure can be opened by some protein mechanisms in the cell through the specific recognition of sensing chain (usually aptamer), so as to release the internal payload or form mechanical motion. In the biomedical field, these payloads can be used as drugs for disease treatment. DNA nanorobots have been proved to have the potential to target drug transport, and their targeting ability mainly depends on the protein recognition ability of aptamers, while the targeting ability of programmable energy-driven micro- and nanorobots depends on the energy supply strategy or the comprehensive effect of energy supply and site recognition [12]. Li et al. designed a DNA molecular robot that can manipulate cells by continuously activating receptor signals on cell membranes. Interestingly, this DNA molecular robot was different from the traditional DNA Walker moving on the multivalent foothold fixed on the rigid track. It can randomly cross the random diffusive receptor-anchored footholds mounted on the fluidic cell membrane, accumulate a large number of dimerized receptors, and amplify the transmembrane signal to control the cell. They believed that this strategy would potentially improve cell-based precision medicine in the future (Figure 1.3) [13].

It should be mentioned here that the emergence of DNA origami, its precise drug-loading function, and the natural affinity between DNA and cells have made it possible to promote the biomedical application of DNA nanorobots [14, 15]. However, DNA nanorobots need to be further improved in increasing the stability of nucleic acid *in vivo*, broadening the library of nucleic acid aptamers, reducing the synthesis cost, and designing a multi-in-one nanorobot with complete logic circuit [16].

1.3 Moment of Glory

The 2016 Nobel Prize in chemistry was awarded to Jean-Pierre Sauvage, Fraser Stoddart, and Ben L. Feringa for their outstanding contributions in the field of

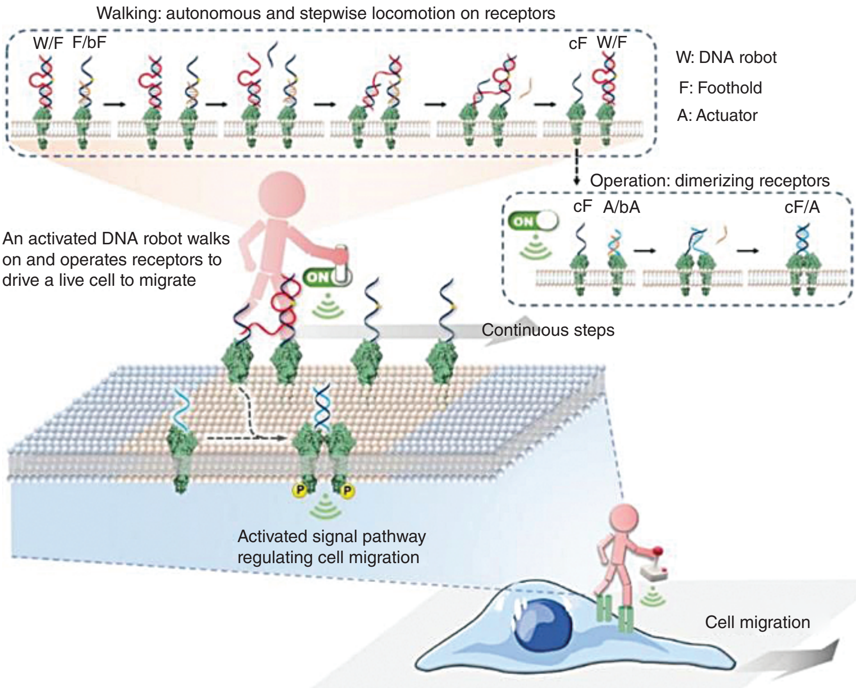

Figure 1.3 DNA nanorobot walking and operating on cell-surface receptors to activate signal pathways regulating cell migration. Source: Li et al. [13]/John Wiley & Sons.

designing and synthesizing molecular machines. Molecular machines are molecules that simulate biological macromolecular machines or macro machines in nature. Through exquisite design, scientists use organic synthesis reactions to construct these molecules that can move relatively internally, so as to realize accurate control at the molecular level.

Although these molecular machines enjoy the glory of the Nobel Prize in chemistry, they have no practical application. As David A. Leigh, the leader of molecular machines in the younger generation, lamented, "This Nobel Prize is not about curing cancer (not yet), nor making wonder materials (not yet), nor harvesting energy from the sun (not yet). It is a Nobel Prize given for tremendous scientific creativity, inspirational science, science that makes you dream 'what if.' It is a Nobel Prize about what the future may bring and a call to arms to all those who wish to accept the challenge to invent it. Feynman would surely have approved" [17].

Indeed, at present, molecular machines have not really realized large-scale practical applications to change human life, but we have to admit that molecular machines have brought human vision and thinking to another dimension, which may bring infinite possibilities to human beings in the future.

Discontent is the best wheel for mankind to move forward. The development of science often follows the law of understanding nature, simulating nature, and surpassing nature. Nature uses its own method, which scientists call "nanoengineering," to turn cheap, rich, and inanimate units containing chemical elements such as oxygen, hydrogen, nitrogen, carbon, calcium, sulfur, phosphorus, iron, and magnesium into creatures with the ability of self-generation, self-maintenance, self-repair, and self-consciousness, which can walk, twist, swim, smell and vision, even think and dream. Then, biomedical micro- and nanorobot technology should also learn from nature, try to use bionic principles and methods to design and prepare micro-/nanoscale products with biomedical functions, and finally apply them to clinical medicine.

In the past two decades, with the continuous proposal of new concepts and the emergence of real objects, such as chemical reaction-driven micro- and nanorobots, physical field-driven micro- and nanorobots, biologically driven micro- and nanorobots and composite-driven micro- and nanorobots, the research of biomedical micro- and nanorobots that can be applied to the biomedical field has officially set sail, involving micro-/nanoscience, Materials Science Physics, Chemistry, Life Science, Medicine, Electrical Automation, and many other fields are forming comprehensive interdisciplinary disciplines and rapidly becoming the forefront of biotechnology. It is providing new ideas, technologies, and methods for modern biomedical research, expanding new horizons for the solution of important biomedical problems and technologies on the micro-/nanoscale, and establishing new disease diagnosis and treatment principles and possible application modes. Based on the latest progress in biomedical micro- and nanorobots made by scientists in the first two decades of the twenty-first century, we can now be confident that they may contribute to the real realization of the wonderful vision of precision medicine.

1.4 Three Laws

It is worth mentioning that Isaac Asimov clearly put forward the famous "Three Laws of Robotics" for the first time in his work "Runaround" published in 1942. That is,

1. A robot may not injure a human being or, through inaction, allow a human being to come to harm.
2. A robot must obey orders given it by human beings except where such orders would conflict with the First Law.
3. A robot must protect its own existence as long as such protection does not conflict with the First or Second Law [18].

These were the writing techniques used to simply promote the plot. But in 1981, Isaac Asimov himself wrote in "Compute!," "Someone asked, I feel my Is it right? Three laws really can be used to regulate the behavior of robot flexible – until the degree of autonomy to choose a robot in different ways of behavior. My answer is, 'yes, the three law is a rational human to robot (or anything else) the only way'." Although a large number of skeptics of Isaac Asimov's "Three Laws of Robotics" appeared later, now in the 2020s, we will suddenly find that the laws of science fiction writer still shine in the medical application of biomedical micro- and nanorobots [19].

1. A biomedical micro- and nanorobot may not injure a human being (biosafety requirements).
2. A biomedical micro- and nanorobot must protect its own existence as long as such protection does not conflict with the First Law (avoid losing its own activity).
3. A biomedical micro- and nanorobot must obey orders given to it by human beings except where such orders would conflict with the First or Second Law (requirements of controllable behavior), or, through action, must not allow a human being to come to harm (functional requirements of treatment).

What else can we say? Pay tribute to Mr. Richard Feynman and Mr. Isaac Asimov!

1.5 Main Contents of this Book

This book will discuss the definition, classification, design, preparation, and characterization, biosafety, autonomous motion behavior, functionality, biomedical applications, and development trend of biomedical micro- and nanorobots, with special emphasis on introducing and summarizing the research progress of biomedical micro- and nanorobots in recent 20 years.

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