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Edited by
MinJun Kim
A. Agung Julius
Edward Steager

# MICROBIOROBOTICS

## Biologically Inspired Microscale Robotic Systems

Micro & Nano Technologies Series

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# Preface

Building a robotics system in the microscale is an engineering task that has resulted in many important applications, ranging from microscale assembly to cellular manipulation. However, it is also a very challenging engineering task. One of the reasons is because many engineering ideas and principles that are used in larger scales do not scale well into the small world. For example, locomotion principles in fluidic environments do not scale because of the difference in (order of) the Reynolds numbers. The use of rotational motors is also impractical, because of the challenges related to building of the components.

Similar challenges exist in the effort to realize sensing mechanisms. Macroscale positioning techniques such as global satellite positioning systems or acoustic positioning sensors simply do not offer microscale resolution. The fundamental wavelengths for such operations are much larger than the scale of the robots themselves. For vision-based sensing, components for typical on-board robotic vision are also much larger to integrate with microscale robots.

On the other hand, microorganisms have evolved various mechanisms to thrive in such an environment. Microbial cells use various structures, such as flagella and cilia, to generate motion. They have also developed various chemical receptors and cellular signaling mechanisms to detect and process sensory information from their environment. This is evident in the observed motility behavior of microorganisms, which includes phenomena such as chemotaxis, phototaxis, thermotaxis, and others.

This book covers the use of biological systems and design ideas in microscale robotics application. Three main topics that are covered are as follows:

- Fundamentals of cellular mechanics
- Theoretical microbiorobotics
- Experimental microbiorobotics

In these topics, we have solicited contributions from leading researchers in the area so as to provide a balanced treatment between the theoretical analysis and experimental results.

Microbiorobotics is a new engineering discipline that inherently involves a multidisciplinary approach (mechanical engineering, cellular biology, mathematical modeling, control systems, synthetic biology, etc). The documentation of relevant development in this field has been scattered in various journals and conference proceedings in areas mentioned above. With this book, we aim to provide the readers with a unique perspective and unified source for the fundamentals and the recent advances in the field of microbiorobotics.

This book is aimed at engineers with a background in robotics, physics, and biological systems. It is also aimed to teach graduate students about the fundamentals and the recent advances in the field of microbiorobotics.

# Acknowledgements

It is obvious that the work of editing this book does not represent solely the efforts of its three editors. Since experimental and theoretical microbiorobotics is an advanced and interdisciplinary topic, we aim to highlight some of the most innovative and powerful developments in microrobotics that have been based on biologically inspired systems and to provide a resource for research and scientists interested in learning about the techniques themselves – their capability and limitations. We owe a great debt to many who helped us in many ways, from sharing their understanding to providing original research data. We do certainly appreciate all authors for their contributions. This book would not be possible without their work. The diverse backgrounds of the authors provide multiple perspectives of microbiorobotics that we present in this book. Special thanks should be given to our reviewers for providing detailed suggestions on all aspects of this book.

Many people read and commented on specific chapters, provided figures and materials, and spent much time with us in helpful discussions. We gratefully thank Sean Brigandi and Paul Kim. We have been privileged to work with many gifted graduate and undergraduate students at Drexel University and Rensselaer Polytechnic Institute, all who contributed in part to further this research: David Casale, Jigar Patel, Dalhyung Kim, Paul Kim, Sean Brigandi, Yan Ou, Rafael Mulero, Anmiv Prabhu, Wonjin Jo, Kevin Freedman, U Kei Cheang, Gaurav Goyal, Hoyeon Kim, and Kiran Phuyal. We would also acknowledge several funding agencies such as National Science Foundation and Army Research Office for their financial support to our current microbiorobotic research programs.

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Edward Steager

# About the Editors

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Dr. MinJun Kim is presently an associate professor at Drexel University with a joint appointment in both the Department of Mechanical Engineering and Mechanics and the School of Biomedical Engineering, Science and Health System. He received his B.S. and M.S. degrees in Mechanical Engineering from Yonsei University in Korea and Texas A&M University, respectively. He completed his Ph.D. degree in Engineering at Brown University, where he held the prestigious Simon Ostrach Fellowship. He was a postdoctoral research fellow at the Rowland Institute in Harvard University. He has been investigating the integration of biomolecular motors for actuation, sensing, and transport at micro/nanoscales to develop a new class of engineered motile cellular microrobots. He is the first researcher to fully utilize flagellated bacteria as microactuators in engineering systems. Based on such research achievement, Dr. Kim was awarded the National Science Foundation CAREER award (2008), the Human Frontier Science Program Young Investigator award (2009), and the Army Research Office Young Investigator award (2010).

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Dr. Edward Steager is presently a postdoctoral fellow at the University of Pennsylvania in the General Robotics, Automation, Sensing and Perception (GRASP) Laboratory. He received his B.S. degree at Duke University and his M.S. and Ph.D. degrees at Drexel University. His research interests include automated techniques to manipulate microscale objects and single biological cells both chemically and mechanically, as well as methods to harness the power of groups of microorganisms.

PART

# Introduction

1

# Motivation for Microbiorobotics

For much of the history of robotics, research has focused on systems that have some relation in operational capability or length scale to humans. From the perspective of the layperson, the very definition of robot is most often closely tied to the subclass of robotics relating to humanoids. Perhaps this is not particularly surprising, because the methods of machining and the tools that we first developed are correlated with our ability to easily observe and manipulate objects at macroscopic length scales. That is, with the naked eye we can easily see objects down to the millimeter, and our hands are not adept at working with smaller objects. It is also not surprising that we have developed strong capabilities for developing much larger structures such as bridges and skyscrapers. In a sense, the bottom of the scale limits engineers more than the top, and we can consider the largest structures to be considered "bottom-up," a concept that is prevalent in nanotechnology. In the last decade, significant advances have been made in the field of microrobotics due to relatively recent advancements in both micromachining and microscopy. With the proliferation of several advanced tools for imaging and analysis, such as atomic force, electron, and confocal microscopies, coupled with the increasing availability of microfabrication technology, we can expect to see tighter integration between fundamental discovery and engineering applications.

Experimentalists in microscale robotics are inevitably led to consider two fundamental questions. Firstly, what can we learn from cells in terms of mimicking or integrating natural phenomena with robots? Secondly, how can we apply new microrobotic technologies to the fields of cell biology and medicine?

Cells are, in a sense, highly optimized and specialized microrobots. If we look at the function of a cell from the perspective of a beginning robotics course, we find striking analogs between cells and robots. Motor proteins perform as actuators, neurons and ion channels act as wiring, DNA and RNA act as memory and software, etc. The cellular systems are composed of elements that are self-assembled in the truest, atomistic sense from the bottom-up. Proteins are the functional subunit of the cellular machinery, assembled into myriad actuators and sensors. In the current state of micro- and nanorobotics, we either mimic behaviors that are otherwise performed by these proteins or we use whole, intact cells. For example, the behavior of the flagellum is currently replicated not by proteins, but by external magnetic fields [1, 2], and the sensing of chemical compounds may be interfaced with mechanical measurements and solid-state microelectronics [3]. In the long view, however, it is only reasonable to expect that cellular subsystems will be successfully integrated with microfabricated, inorganic elements. Indeed, there is a significant progress being made in the effort to harness the power of motor proteins as microactuators.

The branches of bioengineering related to genetic engineering and synthetic biology will also inevitably be interfaced with microbiorobotics, from both the standpoint of sensors and actuators, or even combinations. In the field of optogenetics, we see a step toward this combination, the coupling of light exposure with muscle actuation [4]. If we are willing to expand our definition of robotics, another viable option is to reprogram whole cells to suit our needs. Bacterial and yeast cells have been reprogrammed to perform basic operations such as counting and timing [5, 6].

One of the great challenges in microrobotics is expanding the current control capabilities from single- or few-robot systems to many-robot systems. Because many of the current techniques are field based, it is no small task to accomplish. That is, individual control is limited by the divergence or resolution of the applied fields. In many current systems, sensing and control are performed at a much larger scale using the microscope as an interface. Despite the current limitations on the ability to create systems of independent microrobots, it is easy to imagine how such capabilities would greatly enable otherwise difficult tasks, such as the collective propulsion of large objects relative to the robot size, or collecting data from disparate locations.

From the biomimetic point of view, multirobot systems seem like an obvious step along the continuum of technological advancement. Although there are certainly countless examples of microorganisms that go about their life cycle in a largely independent manner, there are also many examples of single-cell organisms that demonstrate collective behaviors, such as swarming bacteria [7].

Passive, circulating multirobotic systems can also easily be envisioned. Although much of the focus to date has been on actuation methods, sensing networks of passively flowing, perhaps even communicating robots. For instance, leukocytes detect and defend against infection in the human body. Although many of these cells circulate freely in the blood, they are able to sense and respond to foreign bodies. One can imagine another layer of robotic protection tasked with monitoring or even responding to disease.

As described, there are clearly myriad options for fundamental study on several levels with direct applicability to microbiorobotics. Although the fundamental research by itself serves to motivate the subject as a whole, the application of microbiorobots to cellular research, drug delivery, or as working tools for other microscale tasks should prove to be fascinating.

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# Historical Overview

In recent years, there has been an increasing interest in the development of microscale robotic systems. Researchers have explored numerous ways and techniques to provide capable systems for microscale tasks. Many microscale systems have been biologically inspired or based. For effective microscale systems, it is critical to understand cellular mechanics and its interaction with low Reynolds number environments. Cellular swimming has led researchers to mimic biological motors such as flagella for bacteria-inspired microrobots. Others have used biological phenomena and external stimuli for microscale robotic systems such as magnetotactic bacteria. Using bacteria as well as other microorganisms as a power source for a microrobot has also been investigated. Furthermore, mathematical modeling has been used to characterize cell behavior for the control of microbiorobotic systems. Microbiorbotics has vast potential for creating robust microscale robotic systems.

## Low Reynolds number swimming

The first step to building microscale robotic systems is to understand fluid mechanics at low Reynolds numbers. In low Reynolds numbers, viscosity is the dominating force, as inertia plays no role whatsoever. Motion at very low Reynolds number is entirely determined by the forces exerted on the organism at that moment and by nothing in the past [1]. Purcell's scallop theorem says that to achieve propulsion at low Reynolds numbers, reciprocal motion cannot be used. Purcell describes reciprocal motion as, "I change my body into a certain shape and then I go back to the original shape by going through the sequence in reverse. So, if the animal tries to swim by a reciprocal motion, it can't go anywhere [1]." The scallop theorem forms the basis of aquatic locomotion for microswimming devices [2].

To create efficient propulsion at low Reynolds numbers, the mechanics of biological motors such as flagella and cilia have been examined. Many bacteria, such as *Escherichia coli* and *Salmonella*, have several flagella attached at points distributed over the surface of the cell. The flagella, which are typically helical shaped, rotate in a corkscrew-like motion. While bacteria are swimming, the flagella come together in a synchronous flagellar bundle, which propels the cell [3]. For microorganisms with cilia, such as *Tetrahymena pyriformis* and *Paramecium*, the locomotive cilium motion can be described in terms of two swimming strokes, effective (forward) and recovery (back). The cilia are aligned in arrays along the cell body and beat in a phase relationship with neighboring cilia [4]. The mechanics of flagella and cilia are shown in Figure 1. These biological motors are efficient in low Reynolds number environments and are a source of inspiration for microbiorobotics.

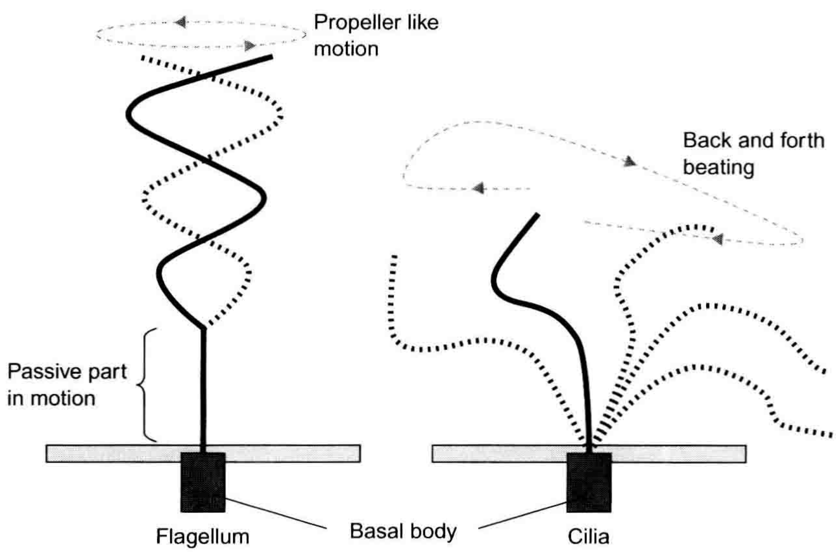


**FIGURE 1**

The swimming motion of bacterial flagellum and cilium. *Source:* Copyright from [31].

## Taxis of microorganisms

For the control of microbiorobots for microscale applications, external stimuli can be utilized. Many biological microorganisms respond to stimuli such as magnetotaxis (magnetic fields), galvanotaxis (electric fields), phototaxis (light), and chemotaxis (chemicals). Based on the characterized behavior of microorganisms, these taxes can be applied to produce a desired response from the microscale robot. Responses from microbiorobots can be used as a method for chemical detection [5] or the manipulation of objects [6].

Magnetotaxis is used to change the direction of locomotion in motile organisms by inducing a magnetic stimulus. Two different magnetotactic mechanisms, polar and axial, are found in different magnetotactic bacterial strains [7]. Strains that swim in only one direction along the magnetic field are polar magnetotactic. These magnetotactic bacteria always swim towards either the north or south direction of the magnetic field and will only reverse direction if exposed to a more powerful magnetic field. They always move in the same magnetic direction, relative to the dominant field. Axial magnetotactic bacteria move along either direction of magnetic field lines with frequent reversals of swimming direction and make no distinction between north and south poles. The magnetic field provides only an axis of motility for axial magnetotactic bacteria, whereas both an axis and a direction are specified for polar magnetotactic bacteria. These two magnetotactic mechanisms can be utilized to control microscale robotic systems.

Electrical current can be used to produce directional movement of motile cells; this is known as galvanotaxis. Bacterial strains will only swim in one direction, either towards the anode or cathode. When the electric field is reversed the cell will turn around, so that the same end of the cell is leading towards the new anode or cathode [8]. Previous researchers have determined the direction bacterial strains, *E. coli* and *Salmonella* swim, while under electrical stimulus, based on surface structure [9]. Rough bacteria swam towards the anode, whereas smooth bacteria moved toward the cathode. Galvanotaxis has been shown to be applicable to numerous microorganisms [10–12].

Phototaxis is the movement of an organism in response to light, which can vary with light intensity and direction. The organism's reaction to light can either be negative or positive. Negative phototaxis causes swimming away from the light source, while in positive phototaxis movement occurs towards light. There are two types of positive phototaxis that are observed in bacteria, scotophototaxis and true phototaxis. Scotophototaxis is a phenomenon found underneath a microscope. Once the bacterium moves outside the illuminated area, it reverses direction and re-enters the light. In true phototaxis cells follow a gradient of increasing light intensity [13]. Phototactic responses are observed in many microorganisms such as *Serratia marcescens* [14] and *T. pyriformis* [12]. Similar to phototaxis, chemotaxis can either be positive (chemoattractants) or negative (chemorepellents) based on the cell's motility response to a chemical concentration gradient. Chemotaxis is more commonly used for research in biology and medicine, as there are some disadvantages for controlling organisms as microbiorobots. There is a significant delay in response and release time when compared to taxes such as photo, galvano, and magnetic. Also, there are challenges in the introduction and removal of chemicals as well as the creation of fluidic disturbances.

## Artificial bio-inspired microrobots

Microrobots have vast potential in many engineering applications such as micromanipulation, microassembly, and minimally invasive procedures. However, locomotion at the microscopic level is challenging. One source of inspiration for microfluidic propulsion has been to found in motile organelles such as flagella [15] and cilia [16]. The capabilities of these organelles at low Reynolds numbers are intriguing to researchers in the design of microrobots.

In recent years, mimicking flagella for purposes such as biomedical applications has been studied extensively [17]. It has been shown that helical propellers can be manufactured at the microscale [18]. Attaching the propeller to a thin soft-magnetic microsphere at one end creates a helical swimmer that has comparable shape and size to bacterial flagella [19]. The helical swimmer was labeled as artificial bacterial flagella (ABF). Magnetic fields rotate the swimmer to produce propulsive forces [20]. It was found that as size decreases, swimming with a helical propeller becomes more desirable [21]. The propelling force of a single ABF is in the range of piconewtons. Swarm-like behavior has been demonstrated in which three ABF swim in a pack, showing the potential as manipulators for micro objects [22].

In another technique to mimic flagella, it was shown that a chain of magnetic particles linked by DNA and attached to a red blood cell could act as a flexible artificial flagellum [15]. The chain of magnetic particles forms a filament. The filament aligns with an external uniform magnetic field and bends from side to side by an oscillating field. The magnetic field induces a beating pattern that propels the structure. The velocity and direction of motion can be controlled through the external fields [15]. A model was derived for the dynamics of the driven filament and from it; design principles were determined for constructing the fastest possible microswimmer of this type [23].

## Biological microrobots

The creation of artificial microrobots creates many challenges for engineers. Due to the differences between the physics of the macro- and microscale, it is difficult to design and manufacture microrobots. The costs are great for the microrobots that can be constructed. Also, there is a lack of sufficient power sources for microrobots making them unsuitable for time-consuming tasks. Some researchers have turned to microorganisms such as, magnetotactic bacteria, *S. marcescens* and *T. pyriformis* to be used as biological microrobots. Biological organisms are easily and cheaply cultured in labs with little equipment. They can draw chemical energy from their environment eliminating the need for external power sources. Microorganisms also respond to various external stimuli allowing them to be controlled as biological microrobots.

Magnetotactic bacteria (MTB) are geomagnetically sensitive and orient themselves along the Earth's magnetic field lines. MTB have organelles called magnetosomes that contain magnetic crystals, which allow them to be directed by magnetic fields. Magnetotaxis has been used to show the controllability of MTB by manipulating microbeads [24, 25]. MTB has been proposed as a microcarrier, as individual MC-1 bacteria were measured to produce a thrust of 4 pN [26]. Designs to utilize the thrust from a swarm of MTB to provide propulsion and steering for a microrobot have also been presented [27, 28]. In this case, MTB are embedded in special reservoirs within the microrobot structure. An embedded microcircuit powered through photovoltaic cells is used to control the swimming direction of the bacteria and consequentially the microrobot.

Another method for using flagellated bacteria as microrobot has been shown using *S. marcescens*. Negative photoresist SU-8 microstructures were fabricated using simple microfabrication techniques. *S. marcescens* are then blotted on the surface of the microstructure, allowing the flagella to randomly propel and rotate the structure without stimulus. Phototactic control is demonstrated by exposing ultraviolet rays to localized regions of the swarm bacteria [14]. Within a few seconds, exposed areas become inactive, eliminating random motion. When combined with galvanotaxis, the microbiorobot's position and orientation can be controlled [11]. The microbiorobot could then be utilized for applications such as single cell manipulation [6].

Eukaryotes that are significantly larger than bacteria such as *T. pyriformis* have also been employed as cellular microrobots. *T. pyriformis* uses locomotive cilia for propulsion. Galvanotactic and phototactic control have been validated in the past research [12]. *T. pyriformis* is also capable of internalizing magnetic iron oxide particles using oral cilia located at the anterior part of the cell [29]. After magnetization of the particles, the cell's swimming direction can be controlled using magnetic fields. Using magnetotaxis feedback control with real-time path planning was implemented for microscale tasks such as object manipulation or transport [30]. This validates *T. pyriformis* as a useful cellular microrobot.

## Conclusion

Much effort has been put into the study of biologically inspired microscale robotic systems. To design a robust system, it is important to understand cellular mechanics as well as the stimuli needed for control of microbiorobots. Both artificial bio-inspired and biological microrobots exhibit great promise. Microbiorobots have the potential to revolutionize many research disciplines including biology and medicine.

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# About this Book

With this book, we present the reader with a mosaic of topics that cover multiple aspects of microbiorobotics research. The chapters in this book are independently written by the authors. Together, they cover the two sides of microbiorobotics research, theory and experiments. Although most chapters are not exclusively theoretical or experimental, we can roughly outline their contribution to each side as follows.

## Theory

There are two main theoretical themes that we cover in this book: the physics of microscale bio- and bio-inspired actuation, and the mathematical models for a large number of actuators. Most of the undergoing research in microbiorobotics involves bio- and bio-inspired actuation in a fluidic environment. In relation to that, several chapters in this book are devoted to the physics and mathematical models of swimming cells. Chapter 1 by Fu addresses the interaction between hydrodynamic forces and flagellar shapes for swimming cells. Chapter 2 by Shum and Gaffney reviews some mathematical and numerical methods used for simulating flagellated bacteria swimming. In Chapter 7, Peyer et al. discusses a mathematical model for the actuation of swimming microrobots in low Reynolds number fluidic environment. Their approach is inspired by flagellar propulsion, and is confirmed by experimental results. Dreyfus, in Chapter 9, presents some mathematical models for swimming in low Reynolds number fluidic environment using flagella-like actuators, and demonstrates its use in manipulating red blood cells.

One of the benefits of using live cells as microscale actuators is the fact that they can be produced relatively cheaply and easily. The main challenge in utilizing such actuators is to control them. Direct control at the cellular level is typically impractical or infeasible. Therefore, in many cases, these actuators are deployed in large numbers, where control is performed at the "colony" level. In Chapter 4, Ueda and Asada present an analysis of a "broadcast control", where control commands are issued to a large group of independently operating actuator units. The behavior of each actuator is stochastic, whereas their statistical properties are regulated through the broadcast control. Julius et al., in Chapter 5, review several mathematical models for random behaviors in cellular biology and discuss how a control structure such as "broadcast control" can be used to regulate a macroscopic property of a colony of randomly independently operating cells. In Chapter 6, Milutinović and Lima analyze the problem of controlling a population of random agents, using stochastic differential equations and optimal control theory.

## Experiments

Microbial cells are known to respond to various stimuli, such as chemicals, light, temperature changes, and electromagnetic fields. There is a large number of works in microbiorobotics that use electromagnetic field as control input to affect the cellular actuators, as presented in several chapters in this book. In Chapter 3, Kőhidai reviews the biological properties of *Tetrahymena pyriformis*, a eukaryotic microbe whose motion can be controlled using external stimuli. In Chapter 11, Kim et al. present some experimental results, in which *T. pyriformis* can be artificially magnetized and steered using an external magnetic field. The motion control of the cell is planned by using the Rapidly-Exploring Random Tree (RRT) technique. In Chapter 8, Martel uses external magnetic field to manipulate a colony of magnetotactic flagellated bacteria (MTB) to manipulate microscale objects in microassembly and medical applications. Finally, in Chapter 10, Steager et al. present some experimental results, in which a colony of swimming bacteria, *Serratia marcescens*, is used as actuators for microscale objects. These bacteria are blotted on the surface of the objects, and their motion can be manipulated using electromagnetic field and exposure to ultraviolet light.