Biomedical microrobotics: Small sizes, large applications

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In the recent decade, the confluence of high-resolution manufacture, micro/nano-materials and devices, soft robotics and biobots propels the rapid development of novel microrobots with unprecedented functions and capabilities. Biomedical microrobots with micrometer or submicrometer sizes emerge as a paradigm shift in modern medical science and technology. In particular, magnetic soft microrobots have distinct advantages, for example, untethered and precise manipulation and control, and thus hold promises for diverse technologically significant applications in disease diagnostics, targeted drug delivery, and minimally invasive surgeries.

MAGNETIC SOFT BIOROBOTS

Soft microrobots are usually made of smart or multifunctional hydrogels, and other artificial and biological materials, with embedded devices for sensing, signaling, transduction, and actuation. They are advantageous in superior biocompatibility, deformability, and adaptability, and thus could access small regions in the human body, such as blood vessels, intestines, lung, brain, and even the eye. They can bring medicines to the unprecedented small-size regions and make minimally invasive surgeries. They perform more gentle interactions with biological entities compared to rigid counterparts, making them indispensable in diverse laboratorial and *in vivo* biomedical applications. For wide applications in cell research and disease diagnostics, their intrinsic pliability proves invaluable for intricate cellular interventions, delicate manipulation and control, efficient drug selection and injection.

In our bodies, there are many different types of intelligent microrobots, including DNA motors, ATP synthases, myosin and dynein motor proteins, each performing vital biological functions. These microrobots are involved in various biomechanical functions, including cell migration and sensing.[2] Inspired by these biorobots and other biological machines (*e.g.*, bacteria), various responsive actuation and transformation mechanisms have been proposed for biomedical microrobots used in confined spaces. Thereby, they hold the promise of reaching challenging anatomical locations, enabling dynamic interactions, including potential on-demand cargo transport and drug release. Their adaptability to ever-changing microenvironments establishes them as dynamic problem-solvers responsive to physiological and pathological cues. In the small lumens consisting of biological fluids, such as blood vessels, these robots showcase not only efficiency but also a reduced risk profile, rendering safe and effective drug transport.

Distinct from microrobots relying on stimuli like pH, temperature, pneumatics or light, which may concurrently interact with cells or their surrounding environments, purely magnetic microrobots offer notable advantages. These include high tissue penetrability and safety, consistent performance in biological fluids, minimized heating issues, and non-invasive long-range control. The success of magnetic microrobots is evident in achieving specific transportation of cells, showcasing particular value in anti-tumor applications.[3] However, transport methods based on fluid traps are susceptible to external interferences like fluid dynamics and obstacles, leading to potential sample loss midway. As a comparison, a tetrapod-like microstructure with four flexible arms was employed to ensnare a sperm, releasing it upon encountering the targeted barrier. Despite its efficacy in capturing and releasing sperms, this reactive-force-based trigger can only passively transport cells without selectivity and is limited in handling multiple cell types due to its high elastic modulus.[4] A grand challenge in this field revolves around the development of magnetic microrobots that are sufficiently small and soft, enabling multiple-degree-of-freedom control.

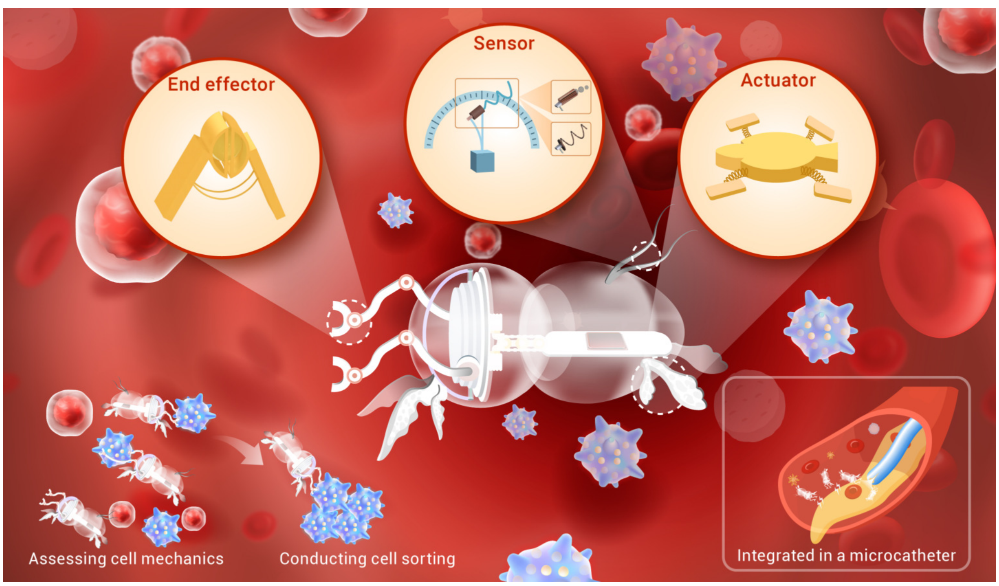

Figure 1. Advanced soft microrobot equipped with on-board sensors, actuators and end effectors for cell mechanics research and minimally invasive surgery. Images of the sensors, end effectors and actuators were reproduced with permission from Xu *et al.*[1] Copyright 2024, Nature Nanotechnology.

MICROROBOTS WITH CHIRAL STRUCTURES

Chirality is a common and intrinsic feature of almost all microscale organisms and specialized motile cells. Springs and other chiral structures such as DNA and molecular motors endow the biological systems with efficient functions of sensing, signaling, actuation, and transductions. This also indicates a novel game-changer technology for developing versatile soft microrobots. Very recently, Xu *et al.* constructed a 3D-nanofabrication strategy, enriched with the precise programming of elastic modulus (E) of each 3D-fabrication voxel (x, y, z) — a leap into a new type of 4D-nanofabrication technology (x, y, z, E). They introduced an extra fabrication degree of freedom through laser power, enabling the precise definition of elastic modulus.[1] By incorporating magnetic nanoparticles, the fabricated microrobots are capable of performing shape morphing as desired under specifically programmed magnetic fields. Leveraging this technology, they achieved a breakthrough in integrating picoforce nanosprings (picosprings) as on-board actuators and sensors for soft microrobots with programmable elasticity and magnetization distributions (Figure 1). Such picosprings enable the control of micrometer-scale deformations under piconewton-scale forces. This infusion has not only enhanced the precision and sensitivity of force measurements but has also bestowed unprecedented control in single-cell manipulation. It is expected that microrobots with various chiral structures will be designed and fabricated for medical applications.

FORCE SENSING MICROROBOTS

Though atomic force microscopy (AFM) has been well developed to measure the elastic and viscous mechanical properties of cells, the big sizes and complicated manipulation of the instruments limit their applications for *in vivo* measurements in the human body. We expect that micro- or even nano-sized robots would be the most promising techniques for this aim. By exploiting the correlation between picospring deformation and output elastic force, Xu *et al.* have crafted a tool that simplified and refined force measurement at the cellular level.[1] Their microforcemeter, with its remarkable sensitivity to 0.5 pN, signifies a departure from conventional bulky instruments, offering a more intuitive approach to exploring ultralow forces in single cells. The microforcemeter has the capability to accurately reflect the microswimmer propulsion forces in specific media, which reveals the nuanced interplay between microswimmers and potential physical obstacles. The achievement is demonstrated not only in the numerical precision but also in the newfound ability to visually discern the *in-situ* response of microswimmers with negligible viscoelastic drag in real time. Therefore, this works inspires a route towards exploring the principles of mechano-bio-chemical coupling dynamics of molecules, cells, and tissues in physiological and pathological conditions.

MAGNETIC MICROROBOTS WITH PICOSPRING ACTUATION

Besides the fabrication and sensing technology, another challenging issue of microrobots for medical engineering applications is their precise control and actuation. Magneto-elastomeric materials enable the integration of picosprings into magnetic microrobots, leading to a new era of controlled and efficient locomotion at the microscale. Xu *et al.* produced a micropenguin and a microturtle, which showcase the soft actuation ingenuity controlled by only an external magnetic field free of other harmful stimuli[1]. [1] The motion modes are orchestrated by the balance between magnetic and elastic forces. The forward movement achieved under specific magnetic field conditions signifies a controlled and purposeful motion free of continuous rotation. The micropenguin, a mere 20 μm in length, is propelled forward by its coil springs and magnetic flippers in an orientation-switching strategy, with a grace that belies its size. The microturtle, with four independent spring linkages and inhomogeneous magnetization distributions, allows for controllable propulsion with only 2D morphing modes in a plane. These inspiring microrobotic choreographies with well-controllable locomotion stem from a convergence of soft robotics and magnetic control. Microrobots with different sizes, shapes, and functions could also be driven to work in collective manners and even assembled into more complicated systems for specific purposes, *e.g.*, surgeries.

MICROROBOTICS FOR CELL MANIPULATION

3D printing of cells can make some simple biological structures.[5] However, it remains a challenge to manipulate cells precisely. One of the most promising facets of this research lies in the development of purely mechanical microgrippers with adjustable gripping power. Such a microgripper could delicately grasp and release sensitive microscale biological samples with different shapes and mechanical properties. The deformed picospring, a soft actuator in this context, serves as the initiator, providing adjustable stresses ranging from 0 to 34.7 mPa[1]. This delicacy is crucial when handling susceptible cells, eliminating the need for additional stimuli like pH or temperature changes. Furthermore, the microgripper exhibits six-degree-of-freedom locomotion controlled exclusively by magnetic fields, a feat of practical significance for biomedical operations. In essence, the microgripper represents a fusion of finesse and function, where the softness of picosprings meets the high precision of magnetic control.

PERSPECTIVES

Magnetic soft microrobots show a great promise for diverse biomedical applications, for examples, cellular biomechanics assessment in tissue engineering, cell sorting for bio-marked or transgenic cells, and drug delivery for cancer therapeutics. Their high adaptability and precision make them valuable tools across various domains of biomedical research. The achievements of such techniques are not confined to the laboratory but would benefit clinical applications in the near future. It opens an avenue for controlled, non-invasive manipulations at the cellular level, with implications reaching the realm of microsurgery and targeted drug delivery. Novel minimally invasive or even noninvasive soft microrobotic instruments are expectable to revolutionize such tasks as fertilization, clot removal, and neurointervention in small body lumens.

Yet, the path to practicality for magnetic soft microrobots is strewn with multifaceted challenges. While issues like biocompatibility and deep-tissue imaging are acknowledged in the realm of *in vivo* applications of microsystems, the realization of microrobotics with high precision necessitates dedicated research in smart sensors, micro-sized motors, automatic control, and precision manufacturing technology as well. The integration of visual, electromechanical, and magnetic systems at the micro scale is a critical yet challenging task. In this rapidly advancing field, the design and fabrication of microrobots with desired configurations need a focused and specialized approach. Much efforts are also deserved in the innovation of new materials and manufacturing strategies for medical microrobots. Additionally, the seamless integration of these microrobots with conventional minimally invasive surgical instruments, enabling cross-scale transportation and task execution, stands out as a formidable hurdle. Miniature machines featuring intricate architectures confront the challenges posed by the complex physiological or pathological environments in the human body. Navigating such terrain heralds a new era where the amalgamation of soft robotics and precision medicine may not only address current challenges but reshape the landscape of possibilities in healthcare and biomedical research, marking a transformative stride into the future of medical interventions.

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DECLARATION OF INTERESTS

The authors declare no competing interests.