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Micro-Robots in Medicine: From Concept to Clinical Reality Review

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Abstract: Microrobots are under investigation for biomedical purposes such as drug delivery, biological carrier transportation and minimally invasive surgery. However current work is dominated by the development of proof-of-concept microrobots made of non-translatable materials in a "design and apply" paradigm, which hinders clinical applications. While proof-of-concept studies were instrumental in the advancement of micro-robotics, we believe that it will be through a "design by problem" approach, where unsolved problems dictate the design of the microrobots for functional use, that the unique properties of micro-robots can be most effectively introduced to the patient. The judicious application choice, enhanced consideration of delivery requirements, and logical selection of translation-ready biomaterials can thus serve to increase the efficiency and reduce the burden to the patient while revolutionizing therapeutic agent efficacy for challenging diseases.

Keywords: micro-robotics, medicine, biomedical engineering, Artificial Intelligence, micro-manipulation.

I. Introduction

Microrobots are micron sized objects capable of performing programmable functions such as sensing [1], manipulation [2] and targeted navigation [3], operated by means of an external field or an environmental energy source. The propulsion methods commonly used for microrobots rely on external fields (magnetic [4], acoustic [5], electric [6] or environmental sources such as chemicals [7-9] and biological signals [10]. Due to their programmable nature and tiny dimensions, microrobots can be employed in notoriously difficult-to-access regions in the human body such as the blood vessels, cavities and porous regions (e.g., cortical bone [11], mucus [12], extracellular matrix [13]. Force exerted on external field actuated microrobots are significantly higher than those affecting nano-particles, ensuring their travel to designated target locations effectively [14-16]. These properties have made microrobots capable of revolutionizing both minimally invasive medicine and targeted delivery of therapeutic agents.

Despite the exceptional promise for medical micro-robots, few such devices have translated from the laboratory setting to pre-clinical and clinical environments. We attribute this trend to the fact that the majority of researchers focus on the subset of challenges of this emerging technology and refrain from addressing practical concerns critical for clinical use. While advanced robot intelligence, advanced materials and high-resolution imaging are often identified as the primary obstacles, focusing on the latter challenges typically results in the development of lab-specific tools for irrelevant clinical problems. Furthermore, this approach leads to proof-of-concept research that can result in impressive demonstration of microrobot functionality (e.g., Enhanced maneuverability) yet fail to achieve practical application in settings such as remote surgery, in situ sensing and biopsy extraction.

Although proof-of-concept studies are vital to expand knowledge, demonstrate microrobot capabilities and build a foundation for future advancement, we believe it is imperative to shift focus towards addressing diseases with no effective treatment options. This will require (i) directing scientific endeavor toward practical applications, (ii) formulating and addressing the need for delivery of the microrobots, and (iii) using materials suitable for clinical deployment (e.g., biocompatibility, biodegradability, and interactions with the immune system). Moreover, constant communication with clinicians and end-users must occur to aid the progression of medical micro-robots from the lab to the bedside to improve patient outcomes.

1. Fundamental Challenges

At the micro scale, gravitational, inertial and buoyancy effects are insignificant. Surface tension, adhesion, fluid viscosity, friction, Van der Waals forces, electrostatic and capillary forces are dominating effects [17]. Van der Waals forces are always present at the micro-scale while other forces become significant depending on the material and environmental conditions [18].

These dominating physical effects mean that the models typically used to control macro-scale robots do not apply for the micro-scale. Non-linearity introduced by micro-scale physics makes precise and flexible micro-manipulation of biological micro-objects difficult since the size, geometry and material type of biological micro-objects will significantly influence the resulting force and torque of the manipulated object, while these parameters can also change depending on the condition of the target objects. Additionally, micro-robotic systems are highly sensitive to environment factors like humidity, temperature and surface chemistry. These effects are exacerbated in vivo where the micro-robotic system is subjected to varied physiological conditions (e.g., Varying blood and soft tissues) and unexpected biological events. This dictates the modification of standard physical models in the design of micro-robotic systems based on the exact operating conditions to achieve effective operation.

2. Practical Challenges

In addition to fundamental physical issues, several practical challenges need to be addressed in micro-robotic system construction. These include efficient actuators, sensors and controls. Actuators, sensors, power sources and controllers are all required on board the micro-robots and these must all be built on a microscopic scale where conventional methods are often not feasible. Research into new fabrication techniques is required, coupled with innovative ways of dealing with the power and sensing systems on-board micro-robots. New actuation schemes must also be explored as will new ways of sensing in the challenging environments that micro-robots will be required to operate in, along with effective control strategies taking into account multi-material processing.

To bring the capabilities of micro-robots to fruition, novel micro-fabrication methods are urgently required coupled with a re-design of the micro-robotic power system that must lean on new material designs and smart structural methods [19]. Because micro-robots are too small to contain typical electronic circuitry, established methods using electronic computing and software will not work. New strategies will have to be implemented in constructing advanced micro-robots using new materials, novel fabrication techniques, actuation capabilities built using new mechanisms and on-board sensors also based on novel mechanisms.

Apart from micro-robot fabrication, micro-manipulation presents further obstacles. Adhesion forces at the micro-scale mean that objects are frequently attracted to either the gripper or the main body of the robot itself. Various techniques to overcome this challenge have already been employed, including using dynamic effects [20], adhesive glues [21], physical release [22], gas injection [23] and varying the contact angle of the liquid bridge via electrowetting [24]. New design concepts for reducing the contact area between object and end effector by modifying micro-gripper geometry have also been developed [25].

3. Clinical Challenges

Further hurdles are faced when transitioning the techniques developed in the laboratory to real clinical applications [26]. While laboratory-based methods are now quite advanced, they are nearly always confined to a homogenous Newtonian fluid under optical microscopes and additional challenges need to be solved.

Micro-robots for applications in medicine offer the ability to target disease sites more precisely and could be engineered with sensing and control abilities [27]. There are three classes of micro-robots used to target diseases such as cancer; synthetic, biological, and biohybrid (containing a mixture of biological and synthetic components) [28,29]. Active locomotion in each category can be utilized to increase accumulation and penetration in tumor tissues, although they can also be used to target diseases through delivering therapy drugs to specific sites in various ways (e.g., chemically or enzymatically actuated mechanisms are used) [30]. This differs from the use of such robots in the laboratory where in vitro studies offer easy access to information at a microscopic level. The use of these robots in vivo poses specific obstacles.

One problem of particular interest in the medical domain is tracking of micro-robots within the human body using medical imaging devices [31]. The development of suitable medical imaging techniques will be of critical importance in this area [32]. Biocompatibility and biodegradability must also be considered for materials used to build micro-robots to be introduced into the body [33] while removal of degraded or malfunctioning units after use remains a challenge [34]; hence developing retrievable micro-robots is a requirement [35].

Medical micro-robots are most commonly deployed in homogenous Newtonian fluids during laboratory testing. In contrast, biological fluids are far from being homogeneous and Newtonian fluids. Therefore, propulsion systems designed to operate in a controlled lab setting are unlikely to function correctly when used in vivo and would require significant modification based on the specific properties of, and conditions associated with, their environment [36]. While some progress has been made in overcoming these factors, it should be emphasized that it is the characteristics of these biological environments that provide an impetus for the continued development of micro-robotics. Biological barriers, particularly those of high tightness, are typically present at the point of entry into target tissues, posing obstacles to mobility [37].

The host immune system can interact with micro-robots in the body to trigger an innate immune response, and efforts are ongoing to combat this effect using zwitterionic coatings which inhibit phagocytosis [38]. Use of biohybrid micro-robots also offers the potential to limit adverse interactions and increase possible functionality; a micro-robot's structure, morphology and surface chemistry can all be modified to reduce their immunogenic properties [39]. Alternatively, micro-robots could be engineered to augment immune responses in order to provide enhanced immunotherapy. Ethical concerns, and risks associated with performing invasive interventions on the human body directly, will have to be investigated and regulatory requirements concerning safety and clinical validation passed [40,41].

4. Applications of Medical Micro-robots

Medical micro-robots can be used to carry out various tasks ranging from diagnostic tests such as isolating pathological agents and measuring tissue properties to therapeutic interventions such as targeted drug and cell delivery and microsurgery at remote sites of the body, potentially overcoming the limitations associated with catheters and conventional surgical tools.

5. Cell Characterization and Pathogen Sensing

Single-cell characterization represents a crucial application of micro-robotics as it allows researchers to probe cells in greater detail for new drug discovery and other biomedical purposes. This can largely be categorized as an in vitro application where experiments take place outside the human body [42] Researchers have been successful in characterizing single-cell responses to mechanical stimulation through the quantitative evaluation of the response of Pleurosira laevis to external forces [43], and detection and capture of tumor cells using magnetically actuated untethered micro-robots [44].

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Cell characterization can also be extended to determining the mechanical properties of cells as micro-robots offer better throughput and repeatability than manual techniques. An example includes the development of a force-controlled micro-robot capable of precise single cell positioning for accurate force sensing [45], while magnetic actuation of micro-robots was also used to study the response of Pleurosira laevis to varying forces [43].

Pathogen identification can also be facilitated by micro-robots to enable early interventional therapies. Fluorescent magnetic spore-based micro-robots (FMSMs) have been synthesized and used to detect toxins secreted by Clostridium difficile (C. Diff) by immobilizing sensing probes on their surface [46] while biohybrid magnetic microrobots capable of targeting biofilms and killing E. Coli through localized drug delivery were also developed [47].

6. Biopsy and Pathogens Collection

Tissue biopsy coupled with histopathologic examination remain the gold standard for diagnosis of inflammatory diseases, and tumors among other diseases [48], and thus untethered microscopic endoscopes were developed to assist in collecting tissue for pathological assessment.

Micro-robots have shown utility in performing biopsy both in vitro and in vivo. Responsive micro-grippers for cell removal were developed for in vitro biopsy of tissues at the end of capillary tubes that could be actuated remotely via chemicals or temperature [49]. For in vivo use, magnetically actuated untethered soft capsule endoscopes containing thermo-sensitive grippers for gastrointestinal biopsy were created [50], and stimulus-responsive drug releasing grippers for biopsy coupled with treatment delivery in breast cancer cells were designed [51].

Micro-robots have also been used to sample motile pathogenic microbes such as those present in body fluids. A novel onion-inspired structure with a hollow internal section can capture target microbes and was shown to function for collecting motile pathogens [52]; however, preservation of sample integrity and sterility in such an environment remain a challenge.

7. Drug and Cell Delivery

Due to their tiny size and flexibility, medical micro-robots hold tremendous promise for drug and cell delivery. A review of the application of stimuli-responsive soft untethered grippers to drug delivery was recently published [53], where one can find detailed discussions on their performance. In one approach dual-action micro-daggers could be used to deliver drugs at the cellular level [54], while electromagnetically actuated micro-robots are currently being developed to target cancer cells for therapy [55], capable of controlling drug release kinetics via acoustic bubble oscillations.

An in vivo study of chemically-actuated micro-motors showed that drugs carried by them could be safely delivered and automatically released within the human body as the microrobot dissolved [56]. The motion of large swarms of micro-swimmers have been visualized in deep tissue via magnetic fields using fluorescent tracking [57], suggesting great potential for targeted drug delivery.

Magnetic field-driven porous spherical micro-robots were demonstrated as delivery vehicles for hippocampal stem cells capable of differentiation and proliferation for effective treatment and regeneration purposes [58]. Self-folding micro-robots have also been demonstrated to successfully deliver cells to desired locations through microchannels mimicking blood vessels [59] demonstrating their potential to treat conditions requiring targeted stem cell transplantation [60] and also act as 3D scaffolding for in situ cell growth and tissue regeneration.

8. Tissue Penetration and Microsurgery

The ultimate aim in microsurgery will be the development of untethered soft micro-grippers due to their inherent advantage of soft motion and capability to handle sensitive tissues [61]. Such devices are capable of transporting cargo and navigating through anatomical complexity in real-time and dynamic physiological conditions where anticipated events can occur. Ultrasonically powered micro-robots actuated through acoustic droplet vaporization-ignition mechanism are capable of achieving very high speeds, potentially beneficial for procedures requiring tissue ablation and deep penetration [62]. Untethered magnetic micro-robots used as implantable devices have also been demonstrated for applications in ophthalmology where it could be introduced into the eye with a micro-needle and navigated using an ophthalmoscope and an on-board camera [63]. A similar approach, used to treat tumors, was shown to exhibit both diagnostic and therapeutic effects [64].

9. Future Outlook

Intelligent medical micro-robots hold great promise for a variety of healthcare applications, although clinical feasibility and monitoring and control remains an issue. To exploit the full potential of this technology more capabilities, such as the smart material properties, wireless untethered power systems and enhanced reliability are needed. At present, research on the design, actuation and sensing strategies for micro-robots must be carried out using a materials approach where smart materials can potentially provide inherent intelligence and programmability without need for electronic components. Biology, in the form of "living micro-robots" made from living cells, is now emerging as a potential technology that can provide useful capabilities through self-propulsion and the ability to naturally target diseases such as cancer [65,66]. While significant challenges lie ahead in precisely controlling and safely utilizing such self-replicating systems [67], external signals like light and magnetic fields can already direct cell movement [68-71], as well as innate capability of cells to target cancerous environments for drug delivery [72-73]. Cybergenetic platforms offer another area their intrinsic targeting ability has also been recognized [for future development that can guide these cell robots in real time [74,75]. Challenges with biological robots such as the response to the host immune system and potential proliferation control remain, however it may be that a fusion of living and synthetic components will provide the most useful way to construct intelligent programmable micro-robots in the future [76,77]. As more sophisticated individual micro-robots become available, it will become important to understand how swarm behavior [78] can be exploited, as many biomedical treatments require large numbers of cells to be targeted, consequently a similar number of robots will be required to be effective. As our computational capacity increases, the use of digital twins for simulating medical conditions and testing micro-robots will become increasingly useful to accelerate innovation and tailor devices for individual use.

II. Conclusion

Recent breakthroughs in intelligent medical micro-robotics provide promise for the development of a more effective future healthcare system. The last three decades have led to significant advancements in micro-robotics research with considerable promise in the medical arena; fundamental, practical and clinical obstacles associated with micro-robots are discussed here. Several classifications of micro-robotics systems are introduced and state-of-the-art technology for ongoing research is explored. Primary applications in early diagnosis and treatment are presented and the general trajectory of micro-robotics research is mapped out.

While the fields of micro robotics and medicine have become increasingly intertwined due to the unique abilities of micro-robots to precisely deliver treatments and obtain diagnostics at the microscopic level, challenges remain. Significant progress has been made, and this article illustrates several opportunities that necessitate the cooperation of researchers from disparate disciplines to overcome remaining obstacles. With time and effort, we believe that micro-robots can deliver immense societal value. They are likely to have an immediate impact on diagnostics and treatment in the coming years. The greatest barrier to widespread clinical application remains regulation and market demand. The earliest market opportunities must first be explored by addressing specific unmet needs in current medical practices to gain initial clinical validation before wide scale adoption.

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Conflict of Interest

All authors declare no conflicts of interest.

Author Contribution

Authors have equally participated and shared every item of the work.

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