

Microdevices: tools for medical applications

Microdispositivos: herramientas para aplicaciones médicas

Microdispositivos: ferramentas para aplicações médicas

John Euler Chamorro Fuertes¹
Oscar Andrés Vivas Albán²

Received: June 10th, 2022

Accepted: August 30th, 2022

Available: September 12th, 2022

How to cite this article:

J. E. Chamorro Fuertes, O. A. Vivas Albán, "Microdevices: Tools For Medical Applications,"
Revista Ingeniería Solidaria, vol. 18, no. 3, 2022.
doi: <https://doi.org/10.16925/2357-6014.2022.03.11>

Research article. <https://doi.org/10.16925/2357-6014.2022.03.11>

¹ Universidad del Cauca. Grupo de investigación en Automática. Facultad de Electrónica y Telecomunicaciones.

Email: cfjohn@unicauca.edu.co

CvLAC: https://scienti.minciencias.gov.co/cvlac/visualizador/generarCurriculoCv.do?cod_rh=0001710693

² Universidad del Cauca. Grupo de investigación en Automática. Facultad de Electrónica y Telecomunicaciones.

Email: avivas@unicauca.edu.co

CvLAC: https://scienti.minciencias.gov.co/cvlac/visualizador/generarCurriculoCv.do?cod_rh=0000348155



Abstract

Introduction: This article reviews the literature on the latest advances in microdevices for medical applications.

Objective: The objective is to show an overview of the latest devices and their applications, as well as future development vectors in the area.

Methodology: A search of about 170 articles was performed, most of them published between the years 2015 and 2021, of which 53 were chosen as they were the most topical and impactful in the research fields referring to drug delivery, minimally invasive surgery, and cranial and vascular intromissions.

Results: It was found that although microdevices are at an advanced stage of research, they still have many challenges to be solved, which has not allowed clinical trials to be completed in many cases.

Conclusion: One of the great challenges ahead is to increase the precision in locomotion and to make the devices capable of performing more complex tasks with the help of smaller-scale electronic devices.

Keywords: microdevices, microrobots, nanorobots, minimally invasive surgery, drug delivery, cranial intrusions, vascular intrusions.

Resumen

Introducción: El presente artículo realiza una revisión de la literatura sobre los últimos avances en cuanto a los micro dispositivos para aplicaciones médicas.

Objetivo: El objetivo es mostrar un panorama general de los últimos dispositivos y sus aplicaciones, así como los futuros vectores de desarrollo en el área.

Metodología: Se realizó una búsqueda de alrededor de 170 artículos, la mayoría de ellos publicados entre los años 2015 y 2021, de los cuales se eligieron 53 al ser los de mayor actualidad e impacto en los campos de investigación referidos a la administración de fármacos, la cirugía mínimamente invasiva, y las intromisiones craneales y vasculares.

Resultados: Se encontró que, si bien los micro dispositivos están en una etapa avanzada de investigación, aún tienen muchos desafíos por solucionar, lo cual no ha permitido completar en muchos casos las pruebas clínicas.

Conclusión: Uno de los grandes desafíos futuros es incrementar la precisión en locomoción y conseguir que los dispositivos puedan realizar tareas más complejas con ayuda de dispositivos electrónicos de menor escala.

Palabras claves: micro dispositivos, microrobots, nanorobots, administración de fármacos, cirugía mínimamente invasiva, intromisiones craneales, intromisiones vasculares.

Resumo

Introdução: Este artigo revisa a literatura sobre os últimos avanços em microdispositivos para aplicações médicas.

Objetivo: O objetivo é mostrar uma visão geral dos dispositivos mais recentes e suas aplicações, bem como futuros vetores de desenvolvimento na área.

Metodologia: Foi realizada uma busca em cerca de 170 artigos, a maioria deles publicados entre 2015 e 2021, dos quais 53 foram escolhidos por serem os mais atuais e impactantes nas áreas de pesquisa relacionadas à administração de medicamentos, cirurgia minimamente invasiva e cirurgia craniana. e intromissões vasculares.

Resultados: Constatou-se que, embora os microdispositivos estejam em estágio avançado de pesquisa, eles ainda possuem muitos desafios a serem resolvidos, o que não lhes permitiu concluir ensaios clínicos em muitos casos.

Conclusão: Um dos grandes desafios futuros é aumentar a precisão na locomoção e possibilitar que os dispositivos realizem tarefas mais complexas com o auxílio de dispositivos eletrônicos de menor escala.

Palavras-chave: microdispositivos, microrrobôs, nanorrobôs, administração de medicamentos, cirurgia minimamente invasiva, intromissões cranianas, intromissões vasculares.

1. INTRODUCTION

Some advances in medicine have been driven by the integration and assistance of certain types of technological tools. The arrival of laparoscopy in the 1980s represented great progress in surgical procedures. However, although laparoscopy brought great advantages for the patient, it also brought major challenges for the medical staff [1].

Years later, robotic-assisted manipulation emerged as a means to overcome the technical difficulties of using manual laparoscopic tools, so that surgeries could be performed with much greater precision and comfort for the surgeon. These assistants were focused on translating the surgeon's hand movements into smaller and more precise movements of the surgical instruments present inside the patient's body [2]. To properly interact with the patient, several incisions in the abdomen are required to introduce the instruments necessary to perform the surgery [3].

Due to the great benefits of robotic assistants in surgery and the advantages they offer for the prompt recovery of patients after a procedure, they have become very useful tools worldwide. However, they have some disadvantages such as their lack of robustness: all their configurations imply reprogramming and reconfiguration for new procedures and of course their high cost of operation and maintenance.

Considering the problems of the surgical assistants currently in use, there are several challenges for this type of assistant in the future, which are focused on reducing their size, improving their adaptability, making the handling of the device easier, and thus reducing the learning curve for surgeons. Therefore, micro-robots are seen as a promising tool for use in medical applications.

The interest in micro-robots is centered on their ease of access to many parts of the human body, making it possible to perform surgery, diagnostics, and localized treatments with greater precision and efficiency. However, there are still no micro-robots that have been clinically tested on humans. Even the most advanced ones are still in the experimental phase.

Entry into the patient's body should be as minimally invasive as possible, either through a single port or through natural human orifices [4]. Therefore, microrobots hold considerable promise for the future to improve the treatment of a wide variety of diseases, disorders, and surgical procedures, among other types of medical uses [5] [6]. Currently, different research works are being carried out around the world to make use of the great potential that these microdevices have in the field of human health.

2. MATERIALS AND METHODS

For the present review article, a detailed exploration of the IEEE, NCBI, and Science Direct platforms was carried out. The main search string was: "microrobot AND human AND body", followed by "microrobot AND brain" and "microrobot AND vascular"; all with a date filter with which we searched for articles from 2016 onwards. We obtained 170 articles of which 53 were chosen due to their direct relationship with the subject matter. The exclusion criteria that made us discard 117 articles were:

- Publications in which the microdevice is not the focus of the research.
- Publications made before 2015.
- Publications with insufficient information.
- Articles in which the microdevice has passed at least one simulation stage and is not only theoretical.
- Studies published in languages other than English or Spanish.
- Technical laboratory reports.
- Results with lack of clarity.

Although an initial date had been established for the search for articles, some documents before that date were added due to their relevance to the subject matter.

After the search and exclusion of articles, the 4 main themes toward which the research is guided were identified. These are:

- **Drug delivery:** This application is focused on microdevices that, after entering the body, carry a drug load that must be released in a specific place.
- **Minimally invasive surgery:** These are slightly more complex devices used to perform surgeries in specific areas, in such a way that they do not compromise other organs or tissues of the body.
- **Cranial intrusions:** These are microdevices focused on performing minimally invasive procedures in the cranial cavities, brain, or nasal passages.

- **Vascular intrusions:** Micro/nanodevices that are focused on solving blood vessel clot problems.

The review is done qualitatively for each article, interrelating with the area and other research. In addition, they are organized chronologically (except for some specific cases).

3. LITERATURE REVIEW

3.1 Drug delivery

The two most commonly used cancer treatments are chemotherapy and radiotherapy. But these have a problem; in the search to attack cancer cells, they generate a high affectation on many cells that are not infected, damaging a large part of the tissues of the human body [7].

Then an alternative, of more measured and precise use, appears that can prevent other cells from being compromised; micro-robots, thanks to their ability to reach a specific location.

Among the most popular applications of micro-robots is the selective administration of drugs or "Target drug delivery" [8]. This is based on providing medicine to specific areas that are affected by cancer, thus increasing its effect on cancer cells. Micro-robots open up a wide range of possibilities to carry out this task, in such a way that other areas or tissues of the human body are not compromised, and this can be done in the least invasive way possible.

By 2014, transient micro-robots had already been developed. These are devices that are remotely controlled and, when they fulfill their task, are absorbed by the body without leaving a significant chemical footprint, due to their biocompatibility with the body [9].

For these systems to perform their task, a transmitter-receiver communication protocol is required between the microrobot and the target cells, similar to the functioning of electromagnetism. Based on [10], a research group in China proposed the analysis of a communication paradigm they called TouchCom [11]. This proposed that it was vital to calculate the drug propagation range, delay, and path loss of the microrobot, as well as the angle of arrival at the endpoint. Through simulations, good results were achieved to improve such requirements.

In targeted drug delivery applications there are different challenges. One of them is how such a small machine can transport large amounts of medicine to the target.

For years it has been seen as a possibility to take actions from nature to apply them to robots by copying its characteristics. This is the case with "steerable dry adhesion". This mechanism was developed by shaping a dry material so that it can be more easily attached to any tissue [12]. Then in [13], taking the same idea, they worked with what they called "controllable adhesion", which is based on activating a momentary force when required and then deactivating it for locomotion, thus not consuming so much energy. It was demonstrated that by building a robot from memory alloys, the structure allows it to carry 500 times its body weight. In addition, it was shown that if piezoelectric motors are used, the microrobot can reach a force equivalent to 1800 times its weight. This opens up a world of applications for micro-robotics.

In 2016 [14], a research group designed a biomimetic microrobot to manipulate and transport objects in an underwater environment. The design is inspired by the actions of octopuses. The microrobot consists of a structure on which 8 arms, shaped like human fingers, and a proximity sensor are installed to guide the grasping of objects, as shown in Figure 1. The tests were carried out successfully but with the drawback that the device is wired. It is proposed that for future applications it could be made wireless, opening up an immense world of application possibilities.

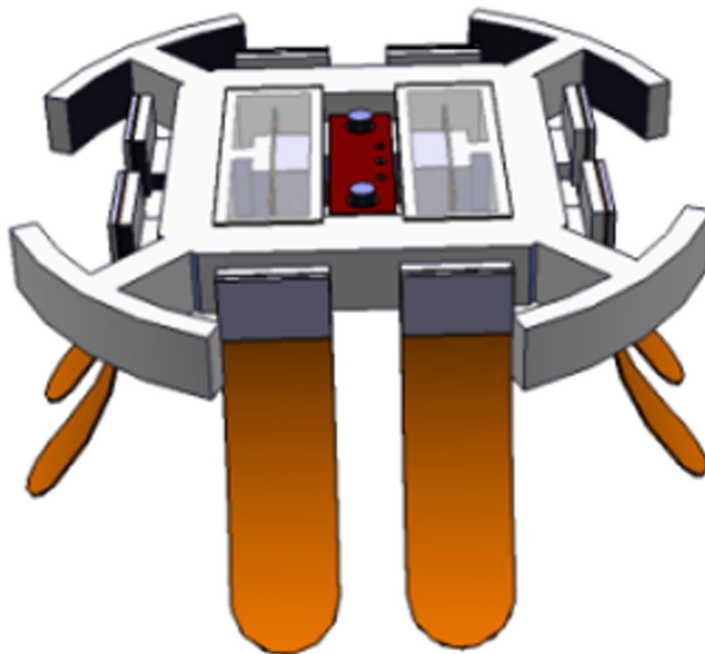


Figure 1. Microrobot structure with 8 arms.

Source:[14]

The inconvenience of wiring occurs when the devices to be used are complex and need to be energized directly electrically. However, several mechanisms have solved this problem. One of these is endoscopic capsules, which are used to perform gastrointestinal intromissions and navigate with the use of cameras. With these images, the medical professional can define the patient's possible pathologies. These mechanisms have been in operation for the last 20 years, since their introduction by Iddan [15] in 2000. Since then, many efforts have been made to improve their performance. These capsules are quite refined, so much so that some have already been approved for clinical use, including Phillcam [16]. Mechanisms have also been developed to manipulate the capsules from outside the body using electromagnetic forces [17-18]. Efforts are being made to enable these diagnostic tests to be performed in a shorter time, or otherwise, by providing larger battery sizes to the capsules so that they can perform long-lasting tests [19].

Although the external parts of these capsules are made of materials that are biocompatible with the human body, they have utensils that are not. Therefore, it becomes vital that the means of extraction can be localized and analyzed. In addition, localization increases the degree of maneuverability. A large part of the localization techniques for these devices are static methods, i.e., they only search for it when activated. In [20], a method for real-time localization during the execution of the procedure is proposed. This is made possible with the use of antennas located in certain parts of the body, which detect radiofrequency signals and, using an algorithm, calculate the location relatively precisely.

Other studies have focused on increasing the mobility and grasping ability of microrobots and have used different mechanisms to do so. In [21], a new approach to microrobots was worked on; teleoperated micro grippers. They are constructed based on up to 10 layers of microgel, which are frequently used in biomedical applications due to their compatibility with extracellular layers [22]. The tweezers are controlled by electromagnetic forces from an 8-coil system. Due to its construction, this gripper is robust enough to manipulate objects. Its structure is shown in Figure 2. The study was able to demonstrate the operation of the microgripper in 2 and 3 dimensions in grasping and levitation functions.

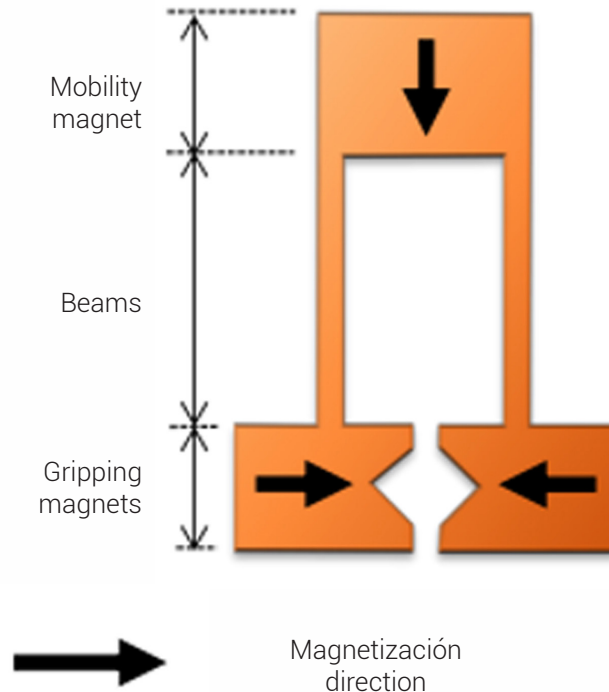


Figure 2. Teleoperated micro clamp design.

Source: [21]

Based on [21], a new locomotion mechanism is proposed to make micromanipulation tasks a reality, achieving a substantial improvement in object grasping time and also in the precision with which objects are manipulated [23].

Other microrobots have focused on improving their locomotion, inspired by nature. In [24], a tadpole-like microrobot is created with lateral flagella that allow its wave-like movement to result in the locomotion of the device. The magnetic forces are manipulated by 2 Helmholtz coils and the experiments carried out in deionized water were satisfactory, but it makes it slow. The design of this device can be seen in Figure 3. For future applications, it is proposed to test different wave types and manipulate the frequency for better displacement. This type of microrobot could carry medicine on the front of its body to the desired body part.

One of the most promising microrobots for medical applications are helical ones. These, due to their shape, can easily perforate tissues and remove obstructions using a helical blade. In [25], it was possible to increase the drilling capacity of the micro-robot, but this also caused an increase in the time required to perform it.



Figure 3. Photograph of tadpole microrobot.

Source: [24]

It has also been proposed that these mechanisms would be of great use for drug delivery tasks in a specific area. Jeon [26] proposed a double helix microrobot for this task. Although the artifact performed its locomotion task well, the drug load was falling off as the artifact moved, as it lacked a sealing mechanism for the orifice containing the load. In the end, a system for a helical microrobot was proposed in [27] that allows such a drug application to be performed without the drug falling off in transit. However, it does not have great accuracy in applying the drug as, for drug release, no independent motion is generated, which implies a negative propulsion action of the microrobot.

Then, Nam [28] wanted to unite the features of the previous works and put them into a single microrobot, which has independent motions of navigation, drilling, and drug release. This is possible because internally the microrobot has 4 fixed cylindrical magnets and 2 rotating cylindrical magnets. Two orthogonal external magnetic fields were implemented for its control. The operation of each of the functions of perforation with drug loading, closing of the storage nozzle, and opening of this in the movement for drug unloading was tested. The arrangement of the magnets inside the mechanism is shown in Figure 4.

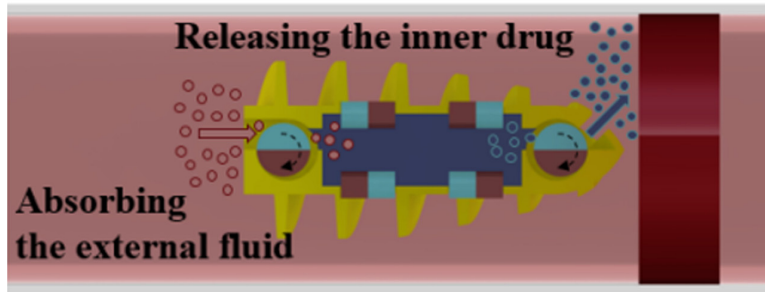


Figure 4. Schematic diagram of helical microrobot operation.
Source: [28]

In the line of tissue drilling, another mechanism has been proposed to raise the force of a small device: a magnetic hammer [29]. This device has a spring, a sphere constructed with ferromagnetic materials, and an impact rod, as shown in Figure 5. The sphere can be moved back and forth alternating the direction of the magnetic gradient of the external source. When the impact occurs on the rod it results in a pulsed force capable of penetrating tissue. Tests were performed on a lamb brain and were successful, demonstrating the potential of the tool.

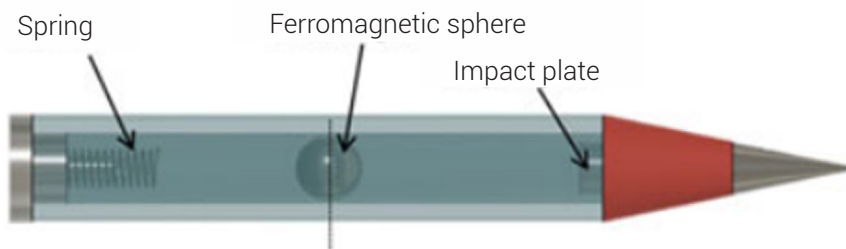


Figure 5. Structure of the magnetic hammer device.
Source: [29]

Although drug-based chemotherapy takes a high toll on the human body, it is still the most widely used tool for cancer treatment. The effectiveness increases when this drug delivery is done in a targeted manner on the tumor or affected cells [30].

Therefore, new microrobots have been developed to deliver these drugs as precisely as possible and to perform in vivo procedures. In [31], it is proposed that this drug delivery is done by cellular-type microrobots. These were constructed with magnetic nanoparticles which allow their movement to carry the anticancer drug. The drug is released upon the action of near-infrared irradiation. Although tumor suppression was achieved, the toxicity of the magnetized microrobot for clinical use remains to be evaluated.

3.2 Minimally invasive surgery

Minimally invasive surgery has become one of the main focuses of development in surgery. For example, with the advent of laparoscopy, a world of possibilities opened up for many surgical procedures. However, this practice is highly dependent on the skill of the surgeon. In [32] an origami-based structure was designed to verify its locomotion and possible applications. A continuous robot with 6 parallel modules was the focus of this research. Due to its shape, it can generate rotational movements without any problem, showing its potential in future minimally invasive interventions. Figure 6 shows its design.

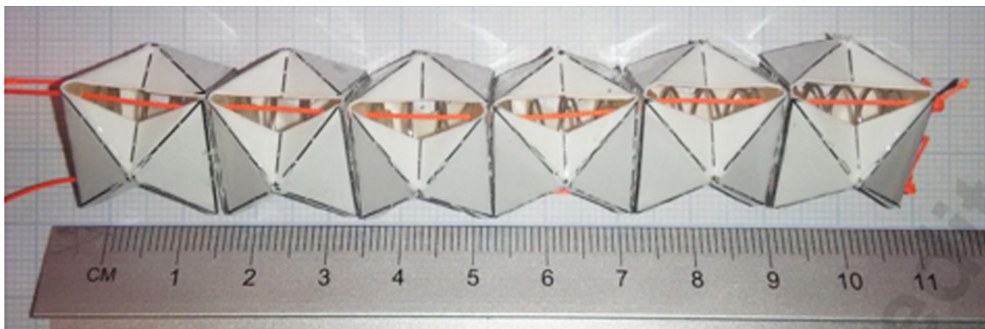


Figure 6. Origami-based structure for rotational movements.

Source: [32]

By studying the potential of origami working in conjunction with shape-memory materials, it is envisioned that these types of mechanisms would function as if they had human muscles. Therefore, in [33] the information from the previous research was taken and brought to a much smaller scale. Furthermore, by analyzing its motion, it was proposed to install a gripper with rotational movements, and thus be able to focus the device on minimally invasive surgeries. In this research, a 2 degrees-of-freedom (DoF) gripper is implemented on the 3 DoF that the module has, as shown in Figure 7. This system is on the millimeter scale; however, the authors propose that, due to its versatility, this tool can be taken to micro scales shortly.

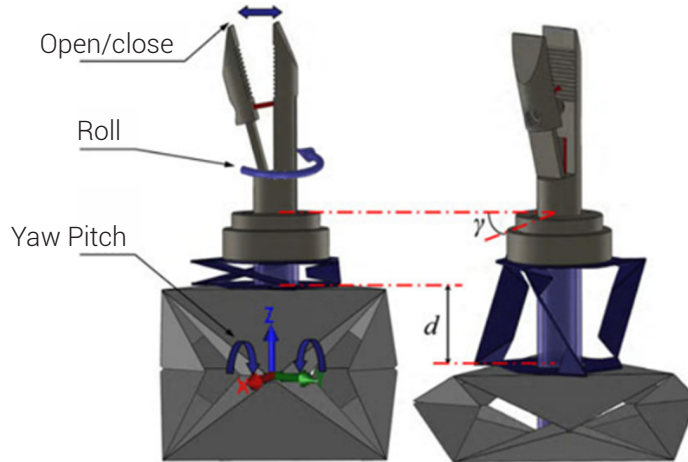


Figure 7. Movements of the origami and pincer mechanism.
Source: [33]

Robotics has always been inspired by the shapes and mechanisms that exist in nature, that is why [34] was based on the shape of octopuses to create a microrobot. Magnetic forces are applied from 4 coils that are located in such a way that they form a tetrahedron. Due to its structure, gripper shape, and good three-dimensional locomotion performance, it is proposed as a great tool for different applications; should future research lead to it being able to vary its speed and location in real-time. Its design proposal can be seen in Figure 8.

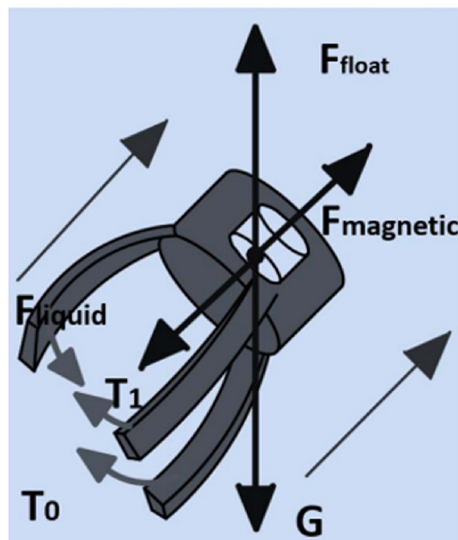


Figure 8. An octopus-type microrobot.
Source: [34]

In ocular surgery, the system called Octomag [35], which offered a great advance in this area, offers a mechanism with 5 degrees of freedom, 3 for position and 2 for orientation; enough to perform simple ocular surgeries.

When the ocular afflictions are not serious, treatments should be carried out by applying medicines. Most of these medications increase their efficacy if they are applied in specific areas of the posterior pole of the eye. The difficulty is that most eye tissues have a narrow matrix. Micro vehicles for intravitreal drug delivery are proposed in [36]. The locomotion is performed from small magnetic helices and the whole device has a liquid coating to decrease tissue adhesion. Computed tomography is used to localize the device inside the eye.

3.3 Cranial intrusions

Microrobots are becoming great tools to gain access to different parts of the body without the need for invasive procedures. Their precision makes them ideal for different applications in the internal part of the skull. On several occasions, the operation of helical micro-robots [37] has been the choice for this type of procedure.

Laliphat [38] proposed an electromagnetic system for performing brachytherapy with a helical microneedle. This system, called Hybrid, can generate uniform and gradient fields due to its 3 orthogonally placed coils, as shown in Figure 9, which generate greater maneuverability of the microneedle. Using simulation, several tests of the system were carried out, reaching the conclusion that its use inside the skull is feasible, being even more efficient than the use of Helmholtz coils for 3 dimensions.

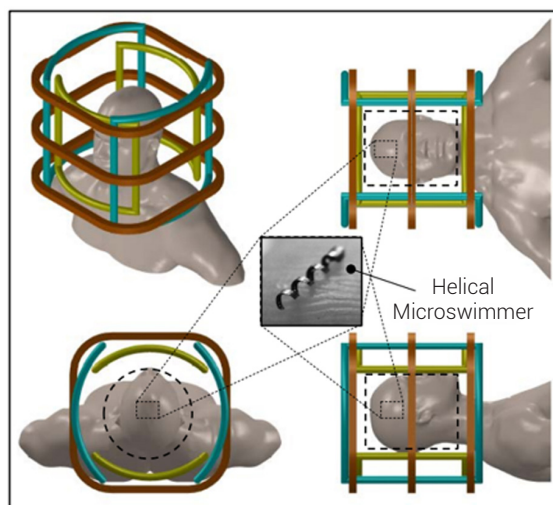


Figure 9. Coil system for microneedle control.

Source: [38]

Stem cells have the special characteristic of being able to become any type of cell. In addition, they possess neuroprotective effects. Therefore, they have been used to treat some neurological disorders and for the treatment of brain tumors [39]. To perform these procedures, it has been shown that stem cells with magnetic particles can be administered nasally and then visualized by magnetic resonance imaging. Some studies, such as [40-41], have already analyzed the possibility that these practices can be better performed using micro-robots for intranasal therapy. However, for now, these studies have been based on the definition of electromagnetic strategies for localization and not so much for stem cell implantation as such.

In contrast, Jeon [42] proposes a nasal intrusion system to reach the brain by using human nasal turbinate stem cells, in which magnetic nanoparticles called “cell-sbot” have been embedded to control their movement in the nasal cavity and then reach deeper areas. By performing an *ex vivo* experiment on a mouse, it has been demonstrated that these cells can be taken to the target and implanted in the brain tissues in a minimally invasive way.

Another of the most common affectations in humans is the presence of cerebral aneurysms. There are about 500,000 deaths per year due to this condition [43]. The current procedure is performed using a catheter-guided coil, but when there are complications, neurosurgical clipping surgery is performed. This poses a high risk as it is highly dependent on the surgeon’s skill in interventions that last hours. Therefore, in [44] they propose the use of a helical-shaped microrobot for this procedure (Figure 10). An experiment was performed on a prototype human brain aneurysm, making use of an imaging scanner to manipulate and localize the microdevice. *In vitro* experiments were performed, and it is mentioned that it is also possible to obtain an angiogram, all without the risk of radiation exposure.

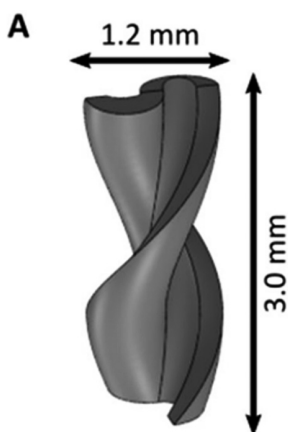


Figure 10. Helical microrobot structure.

Source: [44]

3.4 Vascular intrusions

Due to the size of the channels of the vascular system, it is common that the human body suffers faults in this system and that they are difficult to counteract. Vascular blockages are the most common and a wire with a tape tip and catheter is used to remove the blockage. This activity is difficult to perform because the blood channels (arteries and veins) have a very irregular structure. In addition, cardiologists or vascular surgeons are highly exposed to radiation, so to counteract it they wear heavy lead suits, which reduces their maneuverability [45] [46].

Micro-robots again present themselves as a great option due to their size and accuracy. Jang [47] proposed a spiral-shaped microrobot for this type of task, which would be activated by rotating electric magnets from outside the human body. The effectiveness of the microrobot was validated in a glass tube filled with water. While the microrobot has yet to be put into action with a more viscous fluid, it accomplished the task. The design is shown in Figure 11a and its operation in Figure 11b.

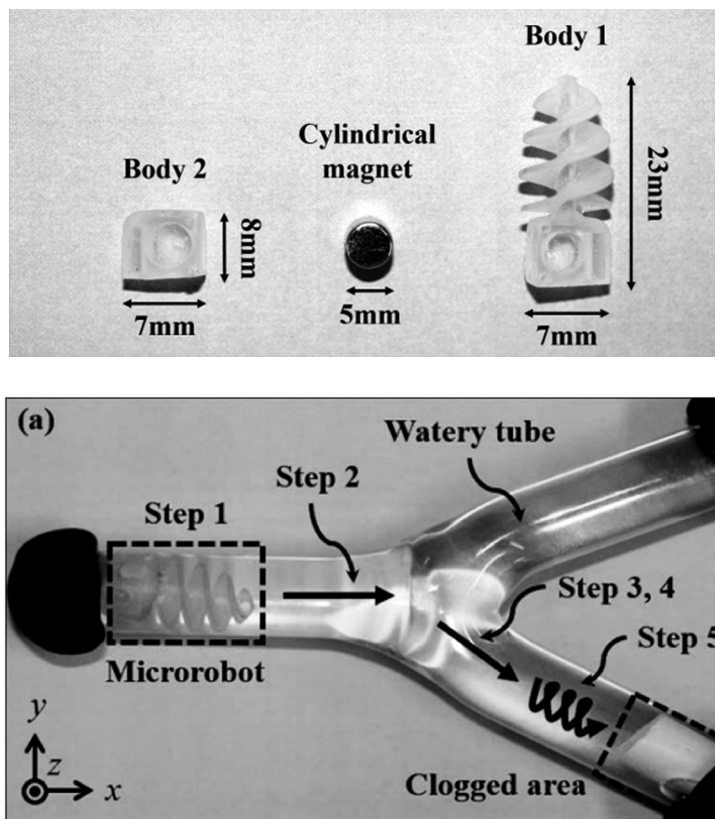


Figure 11a. Spiral-type microrobot design. **Figure 11b.** Operation of the microrobot inside a glass tube.

Source: [47]

There are different ways to move microrobots. One of the most impressive is by making use of acoustic radiation waves to convert it into motion. This is what was done in [48] to verify its range. Although it was possible to move the device, the artifact is still too large for an intrusion into the human body. As future work, the authors propose the reduction of its size, which would allow the microrobot to be used as a blood vessel restorer.

There are also other types of micro robots, which perform locomotion from monochromatic light. For Palagi [49], this is the best option for sophisticated mimetic movements. Although it works very well for complex activities, it is also difficult to synchronize the light signals received with the actions of the artifact.

For her part, Iacovacci in 2019 [50], mentions that micro-robots for vascular intrusions are already close to entering the clinical testing stage, but something very important is missing and that is their recovery. Therefore, she proposes a vascular micro-robot retrieval system based on a module installed in a catheter, which obtains signals from the site where the magnetic device is located. The model becomes a valid tool, which would soon allow for the recovery of different magnetic microactuators.

It is important in this field of study that all devices that have contact with the human body are sterilized and those that will perform intrusions must be built with biocompatible materials. Some have opted for biodegradable materials, as in [51-52], not being necessary for their extraction, but instead degrading inside the body at the end of their task.

In a study carried out about the current state of micro/nano devices [53], it is mentioned that the main areas in which they must acquire a better performance are: Miniaturization, reaching smaller scales to achieve a greater number of applications; Functionality and performance, increasing accuracy in tasks performed; Biocompatibility and biodegradability ; and Autonomy and intelligence, which is expected to improve the interaction with the environment by providing the mechanisms with the autonomy to detect, evaluate and make decisions, thus achieving tasks in dark places or with highly complex access.

4. DISCUSSION

Each specific area of microrobot research has undergone extensive development. Some proposals have already reached the stage of clinical trials and commercialization, as is the case of endoscopic capsules. These have been clinically tested for nearly two decades and research is currently underway to improve their diagnostic performance.

Other proposals are in a high degree of development but have had difficulties in accessing clinical testing stages. This is due to the fact that microdevices perform highly complex and risky medical tasks, so many measures must be taken before they can reach hospital centers.

On the drug delivery side, it is expected that the magnetic mechanisms that take the microrobot to a specific point will be improved and that, when the microdevice is not fully biocompatible, it can be removed from the body without affecting it. There is a great variety of structures and shapes that have been worked on for years and it is expected that these will be the ones that will shortly reach clinical trials. The methods that have succeeded in separating locomotion and drug release are the most promising in this field.

Minimally invasive surgery, having close contact with the tissues and sometimes also having to manipulate them, has the most complex mechanisms and are, therefore, the largest. It is hoped that they will be able to reduce their scale of work, while at the same time increase their maneuverability inside the body, to begin carrying out tests on animals.

As for cranial intromissions, the mechanisms for performing these tasks have diversified. However, it is a high-risk area in the body, so it requires extremely high precision and safety mechanisms that allow acting in case of possible minimal errors generated by the trajectories of the microdevices. Its clinical stage is farther away. Helical micro-robots are the ones currently being investigated, but it is expected that in the future the proposed mechanisms will be diversified.

Microdevices for vascular intromissions are among the most advanced, with a variety of tests being carried out in simulated environments in which they have performed satisfactorily. Future tests in animals and possibly clinical trials are expected. Helical mechanisms are the most widely used in this field and with the most promising results due to their simplicity and efficacy.

It was established in this study that there are some keywords that offer better performance when obtaining results on the desired topic, some of which are: "micro/nano-robot", "magnetic/electromagnetic", "medical" and "bio-degradable/medical/logical" are present in the majority of articles. In addition, the search string with the highest performance was "Microrobot AND human AND body", which obtained 82% of the articles referenced in this study. It is recommended to avoid "microdevices" in searches, as it considerably reduces the number of results obtained. Due to this area of research not yet being massively exploited, we recommend broad search strings in order to obtain a larger number of results. Only use specific searches such as "drug delivery" or "cranial intrusion" if necessary.

5. CONCLUSIONS

This article showed the state of the art of microdevices for medical applications, focusing on the 4 main areas that were determined based on the systematic search: drug delivery, minimally invasive surgery, cranial and vascular intromissions. From the articles investigated, some trends in each of the topics can be evidenced.

In the area of drug administration, it is evident that there is currently a large amount of research focused on improving locomotion; the future challenge is to improve the localization and controlled release of the drug.

In the area of minimally invasive surgery, small-scale devices are being sought to perform complex tasks. This has led to the constant use of electronic devices, increasing the size of the mechanisms. While this makes them more precise and adept at more tasks, it also makes them vulnerable to failure due to their electrical functions.

Micro-scale devices for cranial intromissions are still far from advanced testing. This is because it is an area of the human body that involves high risks, and this determines that errors in the exploration and experimentation phase should be minimal. In addition, the amount of research in this area is limited, so progress has been slow.

Vascular intromissions are probably the closest to clinical trials. This is because there is a great deal of research in this area, which has allowed for improvements in precision and biocompatible materials. Work is currently underway to improve post-procedure localization, although this is already at an advanced stage.

In general, helical microrobots seem to be the most versatile mechanisms as they adapt to different areas of the body and, also, to various applications. Therefore, they have been highly studied, and their close clinical application could be feasible in some of their fields of application.

6. REFERENCES

- [1] J. Shibata, S. Ishihara, N. Tada, K. Kawai, N. Tsuno, H. Yamaguchi, E. Sunami, J. Kitayama, and T. Watanabe, "Surgical stress response after colorectal resection: a comparison of robotic, laparoscopic, and open surgery," *Techniques in Coloproctology*, vol. 19, no. 5, pp. 275–280, Mayo 2015. doi: <https://doi.org/10.1007/s10151-014-1263-4>
- [2] J. Li, E. Ávila, W. Gao, L. Zhang, and J. Wang, "Micro/nanorobots for Biomedicine: Delivery, surgery, sensing, and detoxification," *Science Robotics*, vol. 2, no. 4, Marzo 2017. doi: 10.1126/scirobotics.aam6431

- [3] C. Nezhat, and N. Lakhi, "Learning Experiences in Robotic-Assisted Laparoscopic Surgery," *Best Practice & Research Clinical Obstetrics & Gynaecology*, vol. 35, pp. 20–29, Agosto 2016. doi: <https://doi.org/10.1016/j.bpobgyn.2015.11.009>
- [4] N. Simaan, R. Yasin, and L. Wang, "Medical Technologies and Challenges of Robot-Assisted Minimally Invasive Intervention and Diagnostics," *Annual Review of Control, Robotics, and Autonomous Systems*, vol. 1, no. 1, pp. 465–490, Mayo 2018. doi: <https://doi.org/10.1146/annurev-control-060117-104956>
- [5] M. Sitti, H. Ceylan, W. Hu, J. Giltinan, M. Turan, S. Yim, and E. Diller, "Biomedical Applications of Untethered Mobile Milli/Microrobots," *Proceedings of the IEEE*, vol. 103, no. 2, pp. 205–224, Febrero 2015. doi: [10.1109/JPROC.2014.2385105](https://doi.org/10.1109/JPROC.2014.2385105)
- [6] J. Wang, and W. Gao, "Nano/microscale motors: Biomedical opportunities and challenges," *ACS Nano*, vol. 6, no. 7. pp. 5745–5751, Julio 2012. doi: <https://doi.org/10.1021/nn3028997>
- [7] A. Montero, A. Hervás, R. Morera, S. Sancho, S. Córdoba, J.A. Corona, and A. Ramos, "Control de síntomas crónicos: Efectos secundarios del tratamiento con Radioterapia y Quimioterapia," *Oncología (Barcelona)*, vol. 28, no. 3, pp. 41-50, 2005. [Online]. Available: https://scielo.isciii.es/scielo.php?script=sci_arttext&pid=s0378-48352005000300008
- [8] A.I. Freeman, and E. Mayhew, "Targeted drug delivery," *Cancer*, vol. 58, no. S2), 573-583. 1986. doi: [https://doi.org/10.1002/1097-0142\(19860715\)58:2+<573::AID-CNCR2820581328>3.0.CO;2-C](https://doi.org/10.1002/1097-0142(19860715)58:2+<573::AID-CNCR2820581328>3.0.CO;2-C)
- [9] Y. Chen, P. Kosmas, and R. Wang, "Conceptual design and simulations of a nano-communication model for drug delivery based on a transient microbot system," *The 8th European Conference on Antennas and Propagation*, 2014, pp. 63-67, doi: [10.1109/EuCAP.2014.6901693](https://doi.org/10.1109/EuCAP.2014.6901693)
- [10] Y. Chahibi, M. Pierobon, S. Song, and I. Akyildiz, "A molecular communication system model for particulate drug delivery systems," *IEEE Trans. Biomed. Eng.*, vol. 60, no. 12, pp. 3468–3483, Dec. 2013. doi: [10.1109/TBME.2013.2271503](https://doi.org/10.1109/TBME.2013.2271503)
- [11] Y. Chen, P. Kosmas, P.S. Anwar, and L. Huang, "A touch-communication framework for drug delivery based on a transient microbot system," *IEEE transactions on nanobioscience*, vol. 14, no. 4, pp. 397-408, June, 2015. doi: [10.1109/TNB.2015.2395539](https://doi.org/10.1109/TNB.2015.2395539)
- [12] P. Day, E.V. Eason, N. Esparza, D. Christensen, and M. Cutkosky, "Microwedge machining for the manufacture of directional dry adhesives" *Journal of Micro and Nano-Manufacturing*, 1(1). 2013. doi: <https://doi.org/10.1115/1.4023161>

- [13] D.L. Christensen, E.W. Hawkes, S.A Suresh, K. Ladenheim, and M.R. Cutkosky, "μTugs: Enabling microrobots to deliver macro forces with controllable adhesives". In *2015 IEEE International Conference on Robotics and Automation (ICRA)* (pp. 4048-4055). IEEE. 2015. doi: 10.1109/ICRA.2015.7139765.
- [14] C. Yue, S. Guo, M. Li, and Y. Li, "Characteristics evaluation of a biomimetic microrobot for a father-son underwater intervention robotic system". In *2015 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS)*, pp. 171-176, 2015. doi: 10.1109/IROS.2015.7353370
- [15] G. Iddan, G. Meron, A. Glukhovsky, and P. Swain, "Wireless capsule endoscopy". *Nature*, vol. 405, no. 6785, pp. 417-417. 2000. doi: 10.1038/35013140.
- [16] M. Pennazio, "Capsule endoscopy: where are we after 6 years of clinical use?," *Dig Liver Dis*, vol. 38, pp. 867-878. 2006. doi: <https://doi.org/10.1016/j.dld.2006.09.007>
- [17] J.F. Rey, H. Ogata, N. Hosoe, "Blinded nonrandomized comparative study of gastric examination with a magnetically guided capsule endoscope and standard videoendoscope," *Gastrointest Endosc*, vol. 75, no. 2, pp. 373-81. doi: <https://doi.org/10.1016/j.gie.2011.09.030>
- [18] Z. Liao, X.D. Duan, L. Xin, "Feasibility and safety of magnetic-controlled capsule endoscopy system in examination of human stomach: a pilot study in healthy volunteers," *J Interv Gastroenterol*, vol. 2, no. 4, pp. 155-60. doi: 10.4161/jig.23751
- [19] M. Rahman, S. Akerman, B. DeVito, "Comparison of the diagnostic yield and outcomes between standard 8 h capsule endoscopy and the new 12 h capsule endoscopy for investigating small bowel pathology," *World J Gastroenterol*, vol. 21, no. 18, pp. 5542-7. doi: 10.3748/wjg.v21.i18.5542
- [20] H. Farhadi, J. Atai, M. Skoglund, E.S. Nadimi, K. Pahlavan, and V. Tarokh, "An adaptive localization technique for wireless capsule endoscopy". In *2016 10th International Symposium on Medical Information and Communication Technology (ISMICT)* (pp. 1-5). 2016. doi: 10.1109/ISMICT.2016.7498884
- [21] X. Dong, and M. Sitti, "Planning spin-walking locomotion for automatic grasping of microobjects by an untethered magnetic microgripper". In *2017 IEEE International Conference on Robotics and Automation (ICRA)*, pp. 6612-6618. 2017. doi: 10.1109/ICRA.2017.7989782
- [22] D. Seliktar, "Designing Cell-Compatible Hydrogels for Biomedical Applications," *Science*, vol. 336, pp. 1124-1128. 2012. doi: 10.1126/science.1214804

- [23] X. Dong, and M. Sitti, "Planning spin-walking locomotion for automatic grasping of microobjects by an untethered magnetic microgripper". In *2017 IEEE International Conference on Robotics and Automation (ICRA)*, pp. 6612-6618. 2017. doi: 10.1109/ICRA.2017.7989782
- [24] L. Zhang, H. Huang, L. Chen, X. Li, Y. Li, and J. Huang, "Amagnetically controlled micro-robot with multiple side flagella". In *2017 IEEE 12th International Conference on Nano/Micro Engineered and Molecular Systems (NEMS)*, pp. 544-549. 2017. doi: 10.1109/NEMS.2017.8017081
- [25] S. Jeong, H. Choi, K. Cha, J. Li, J. Park, and S. Park, "Enhanced locomotive and drilling micro-robot using precessional and gradient magnetic field," *Sens. Actuators Phys.*, vol. 171, no. 2, pp. 429-435, 2011. doi: <https://doi.org/10.1016/j.sna.2011.08.020>
- [26] S. Jeon, G. Jang, and W.S. Lee, "Drug-enhanced unclogging motions of a double helical magnetic micromachine for occlusive vascular diseases," *IEEE Trans. Magn.*, vol. 50, no. 11, pp. 1-4, Nov. 2014. doi: 10.1109/TMAG.2014.2320580
- [27] S.H. Kim, and K. Ishiyama, "Magnetic robot and manipulation for active-locomotion with targeted drug release," *IEEE/ASME Trans. Mechatron.*, vol. 19, no. 5, pp. 1651-1659, Oct. 2014. doi: 10.1109/TMECH.2013.2292595
- [28] J. Nam, W. Lee, J. Kim, and G. Jang, "Magnetic helical robot for targeted drug-delivery in tubular environments," *IEEE/ASME Transactions on Mechatronics*, vol. 22, no. 6, pp. 2461-2468. 2017. doi: 10.1109/TMECH.2017.2761786
- [29] J. Leclerc, A. Ramakrishnan, N.V. Tsekos, and A.T. Becker, "Magnetic hammer actuation for tissue penetration using a millirobot," *IEEE Robotics and Automation Letters*, vol. 3, no. 1, pp. 403-410. 2017. doi: 10.1109/LRA.2017.2739805
- [30] X. Wang, J. Cai, L. Sun, S. Zhang, D. Gong, X. Li, and D. Zhang, "Facile fabrication of magnetic microrobots based on spirulina templates for targeted delivery and synergistic chemo-photothermal therapy," *ACS applied materials & interfaces*, vol. 11, no. 5, pp. 4745-4756. 2019. doi: <https://doi.org/10.1021/acsami.8b15586>
- [31] Y. Feng, L. Feng, Y. Dai, X. Bai, C. Zhang, Y. Chen, and F. Arai, "A novel and controllable cell-based microrobot in real vascular network for target tumor therapy". In *2020 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS)*, pp. 2828-2833. 2020. doi: 10.1109/IROS45743.2020.9341774
- [32] K. Zhang, C. Qiu, J.S. and Dai, "An extensible continuum robot with integrated origami parallel modules," *Journal of Mechanisms and Robotics*, vol. 8, no. 3, pp. 031010. 2016. doi: <https://doi.org/10.1115/1.4031808>

- [33] M. Salerno, K. Zhang, A. Menciassi, and J.S. Dai, "A novel 4-DOF origami grasper with an SMA-actuation system for minimally invasive surgery," *IEEE Transactions on Robotics*, vol. 32, no. 3, pp. 484-498. 2016. doi: 10.1109/TRO.2016.2539373
- [34] Y. Dai, D. Chen, S. Liang, L. Song, Q. Qi, and L. Feng, "A magnetically actuated octopus-like robot capable of moving in 3D space". In *2019 IEEE International Conference on Robotics and Biomimetics (ROBIO)*, pp. 2201-2206. 2019. doi: 10.1109/ROBIO49542.2019.8961461
- [35] M.P. Kummer, J.J. Abbott, B.E. Kratochvil, R. Borer, A. Sengul, and B.J. Nelson, "OctoMag: An electromagnetic system for 5-DOF wireless micromanipulation," *IEEE Transactions on Robotics*, vol. 26, no. 6, pp. 1006-1017. 2010. doi: 10.1109/TRO.2010.2073030
- [36] Z. Wu, J. Troll, H.H. Jeong, Q. Wei, M. Stang, F. Ziemssen, and P. Fischer, "A swarm of slippery micropropellers penetrates the vitreous body of the eye," *Science advances*, vol. 4, no. 11, pp. 4388. 2018. doi: 10.1126/sciadv.aat4388
- [37] T. Xu, G. Hwang, N. Andreff, and S. Régnier, "Planar path following of 3-D steering scaled-up helical microswimmers," *IEEE Transactions on Robotics*, vol. 31, no. 1, pp. 117-127. 2015. doi: 10.1109/TRO.2014.2380591
- [38] L. Manamanchaiyaporn, T. Xu, and X. Wu, "The Hybrid system with a large workspace towards magnetic micromanipulation within the human head". In *2017 IEEE/RSJ International Conference on Intelligent Robots and Systems (IROS)*, pp. 401-407. 2017. doi: 10.1109/IROS.2017.8202186
- [39] G. Santamaria, E. Brandi, P.L. Vitola, "Intranasal delivery of mesenchymal stem cell secretome repairs the brain of Alzheimer's mice," *Cell Death & Differentiation*, vol. 28, pp. 203-218. 2021. doi: <https://doi.org/10.1038/s41418-020-0592-2>
- [40] W.S. Yun, J.S. Choi, H.M. Ju, M.H. Kim, S.J. Choi, E.S. Oh, Y.J. Seo and J. Key, "Enhanced homing technique of mesenchymal stem cells using iron oxide nanoparticles by magnetic attraction in olfactory-injured mouse models," *International Journal of Molecular Sciences*, vol. 19, no. 5, pp. 1376. doi: <https://doi.org/10.3390/ijms19051376>
- [41] Yung Jin Yoon, Yun Seop Shin, Hyungsu Jang, Jung Geon Son, Jae Won Kim, Chan Beom Park, Dohun Yuk, Jongdeuk Seo, Gi-Hwan Kim, and Jin Young Kim, "Highly stable bulk perovskite for blue LEDs with anion-exchange method," *Nano Letters*, vol. 21, pp. 3473-3479. doi: <https://doi.org/10.1021/acs.nanolett.1c00124>

- [42] S. Jeon, S.H. Park, E. Kim, J.Y. Kim, S.W. Kim, and H. Choi, "A Magnetically Powered Stem Cell-Based Microrobot for Minimally Invasive Stem Cell Delivery via the Intranasal Pathway in a Mouse Brain," *Advanced Healthcare Materials*, vol. 10, no. 19, pp. 2100801. 2021. doi: <https://doi.org/10.1002/adhm.202100801>
- [43] Aneurismas Cerebrales: Conozca la Realidad y las Opciones de Tratamiento. *Baptist Health*. [Online]. Available on: <https://baptisthealth.net/baptist-health-news/es/aneurismas-cerebrales-conozca-la-realidad-y-las-opciones-de-tratamiento/#:~:text=Anualmente%2C%20suceden%20casi%20500%2C000%20muertes,son%20menores%20de%2050%20a%C3%B1os>
- [44] A.C. Bakenecker, A. von Gladiss, H. Schwenke, A. Behrends, T. Friedrich, K. Lüdtkke-Buzug, and T.M. Buzug, "Navigation of a magnetic micro-robot through a cerebral aneurysm phantom with magnetic particle imaging," *Scientific reports*, vol. 11, no. 1, pp. 1-12. 2021. doi: <https://doi.org/10.1038/s41598-021-93323-4>
- [45] S. Saito, S. Tanaka, Y. Hiroe, Y. Miyashita, S. Takahashi, S. Satake and K. Tanaka, "Angioplasty for chronic total occlusion by using tapered-tip guidewires," *Catheterization Cardiovascular Intervent.*, vol. 59, no. 3, pp. 305-311. doi: <https://doi.org/10.1002/ccd.10505>
- [46] E. Kuon, M. Schmitt, and J.B. Dahm, "Significant reduction of radiation exposure to operator and staff during cardiac interventions by analysis of radiation leakage and improved lead shielding," *Amer. J. Cardiol.*, vol. 89, no. 1, pp. 44-49, 2002. doi: [https://doi.org/10.1016/S0002-9149\(01\)02161-0](https://doi.org/10.1016/S0002-9149(01)02161-0)
- [47] G.B. Jang, S. Jeon, J. Nam, W. Lee, and G. Jang, "A spiral microrobot performing navigating linear and drilling motions by magnetic gradient and rotating uniform magnetic field for applications in unclogging blocked human blood vessels," *IEEE Transactions on Magnetics*, vol. 51, no. 11, pp. 1-4. doi: [10.1109/TMAG.2015.2436913](https://doi.org/10.1109/TMAG.2015.2436913)
- [48] D. Kong, and M.K. Kurosawa, "A novel swimmer actuator via leaky surface acoustic wave". In *2018 IEEE International Ultrasonics Symposium (IUS)*, pp. 1-4. 2018. doi: [10.1109/ULTSYM.2018.8579910](https://doi.org/10.1109/ULTSYM.2018.8579910)
- [49] S. Palagi, A.G. Mark, S.Y. Reigh, K. Melde, T. Qiu, H. Zeng, and P. Fischer, "Structured light enables biomimetic swimming and versatile locomotion of photoresponsive soft micro-robots," *Nature materials*, vol. 15, no. 6, pp. 647-653. 2016. doi: <https://doi.org/10.1038/nmat4569>

- [50] V. Iacovacci, L. Ricotti, G. Signore, F. Vistoli, E. Sinibaldi, and A. Menciasci, "Retrieval of magnetic medical microrobots from the bloodstream". In *2019 International Conference on Robotics and Automation (ICRA)*, pp. 2495-2501. 2019. doi: 10.1109/ICRA.2019.8794322
- [51] H. Ceylan, I.C. Yasa, O. Yasa, A.F. Tabak, J. Giltinan, and M. Sitti, "3D-Printed Biodegradable Microswimmer for Drug Delivery and Targeted Cell Labeling," *bioRxiv*, pp. 379024, 2018. doi: <https://doi.org/10.1101/379024>
- [52] Wang, X.H. Qin, C. Hu, A. Terzopoulou, X.Z. Chen, T.Y. Huang, "3D Printed Enzymatically Biodegradable Soft Helical Microswimmers," *Advanced Functional Materials*, pp. 1804107, 2018. doi: <https://doi.org/10.1002/adfm.201804107>
- [53] B. Ahmad, M. Gauthier, G. Laurent, and A. Bolopion, "Mobile Microrobots for In Vitro Biomedical Applications: A Survey," *IEEE Transactions on Robotics*, vol. 38, no 1, pp. 646-663. doi: 10.1109/TRO.2021.3085245