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Strategy for haptic-based guidance of soft magnetic particles in the cochlea

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***Abstract*— In this study, a novel magnetic guidance-based drug delivery approach for the inner ear is proposed. The approach incorporates a soft microparticle navigation strategy to promote biocompatibility and mitigate corrosion risks. To avoid damage to the round window membrane, a magnetic diffusion method based on particle chain formation was implemented. This chainlets, once inside the cochlea, form a particle bolus under the presence of a converging magnetic, which was guided within the cochlear canal to the target area. The guidance procedure was controlled through a haptic telemanipulation device. The particle diffusion method through the RWM was tested in an in-silico model as no realistic model to mimic the RWM exists. However, the demonstration of chainlet formation was experimentally achieved. In-vitro evaluations were conducted to demonstrate the feasibility of the proposed method, including the guidance performance of the particle bolus within a human-scale artificial cochlea. These findings lay the foundation for the potential integration of this innovative solution into clinical practice.**

***Index Terms*— Electromagnetic, Navigation, Strategy, Microparticle, Cochlea.**

I. Introduction

The method of cochlear drug delivery has undergone a transformation from systemic to local administration due to various limitations associated with the former. The blood-cochlear barrier hinders the diffusion of drugs from the blood to the cochlea, leading to the need for increased doses of oral or intravenous administration [1]–[3]. These high doses and the requirement for long-term treatment result in significant adverse side effects, further limiting the feasibility of systemic administration [4], [5]. The locally administered method involves the injection of drugs into the middle ear cleft through the tympanic membrane under local anesthesia. This allows the drug to come into contact with the round window membrane, thereby enabling its delivery into the cochlea [6]. However, the quantity of therapeutic agents delivered into the inner ear remains poorly controlled, and the diffusion beyond the basal turn is limited due to the negligible perilymphatic flux [7], [8].

Recent research has demonstrated the feasibility of controlling the navigation of magnetic particles in the cochlea using a combination of permanent magnets [9]–[11]. The proposed four-permanent-magnets-based actuator offers the advantage of pushing and pulling microrobots, unlike single-permanent-magnet systems that only provide pulling forces. The magnetic particles used in this system are spherical NdFeB magnetic balls, which raise questions regarding their integration and safety in the medical context due to potential corrosion and toxicity issues.

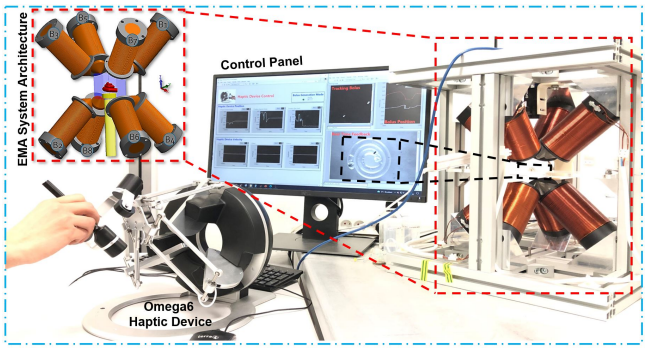

FIG. 1. Microrobot manipulation platform integrating the electromagnetic actuation system [12].

For the manipulation of magnetic particles and for reasons of magnetic power, we have chosen to use a magnetic actuator based on an electromagnetic coil. The use of such a system allows us to turn on and off the magnetic field, which is essential for the rest of our work. The proof-of-concept microparticle navigation system demonstrator, shown in Fig.1, was developed in our laboratory [12].

This demonstrator includes eight electromagnets placed in 3D around the workspace. It was designed to generate a magnetic field of up to 0.15 Tesla in a central volume of $100\text{mm} \times 100\text{mm} \times 90\text{mm}$ by controlling the eight electric currents flowing through the coils of the electromagnets. In addition, the electromagnets are composed of expandable cylindrical soft magnetic cores which focus and enhance the magnetic field strength and gradients in the central area of the working space. The soft magnetic core was chosen due to its ability to easily magnetize in the presence of an external magnetic field and to quickly demagnetize as soon as the currents of the electromagnets are switched off. The maximum magnetic field generated by the eight electromagnets (up to 0.15 T) was sufficient to exert the necessary forces on the particle to accurately guide it to the desired area [12].

Magnetic particles subjected to a magnetic field tend to aggregate and form either a bolus or chains of magnetic particles depending on the behavior of the magnetic field

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(uniform, converging, diverging, etc.). Each of these particle forms (bolus or chain) can be used depending on the environment and intended application. For example, a chain of particles is suitable for crossing a biological membrane (cell, round window, etc.), while a bolus can be used for navigation in a fluidic channel (blood vessel, cochlear channel, etc.).

In this work, our primary contribution is to develop an interventional procedure for the treatment of the cochlea using magnetic microparticles. We will use soft microparticles to address biocompatibility and patient safety. A haptic system will also be used to integrate the operator into the control loop and to allow for different modes of magnetic system use depending on the medium in which the particles are found. Finally, a navigation strategy will be established to manage the entire procedure from particle injection to target area delivery.

Our navigation strategy enables the navigation of middle ear microparticles by safely crossing the round window membrane (RWM) and delivering drugs to the target area while ensuring their diffusion. To avoid RWM perforation, we have proposed a method to align the particles in chain form, reducing the size of the surface in contact with the RWM and facilitating penetration. To guide the particles to the target area, we propose forming a bolus of particles inside the cochlea and then transporting it to reach the target area.

Due to the various particle shapes (bolus and chain) proposed within our strategy and the need to change modes of magnetic system use, implementing a closed-loop control presents challenges in terms of convergence and continuity. To address these challenges, we propose integrating a human operator (doctor) into the control loop. This is made possible by incorporating a haptic device to improve usability and leverage the doctor's expertise and in-depth knowledge of the cochlear environment. Including a human operator in the procedure increases responsibility, safety, and acceptability.

II. Drug Delivery Strategy

The objective of this work is to propose an efficient strategy to transport and guide magnetic particles from the outside of the cochlea (middle ear) through the membrane of the round windows, and then guide them into the cochlear canal until reaching the target area to ensure their local distribution. To guarantee patient safety, it must be ensured that the procedure takes place without the risk of perforation of the membrane. This therefore consists, from a practical point of view, of avoiding the formation of agglomerates of particles outside the cochlea. Conversely, to efficiently guide the magnetic particles into the cochlear canal, it is preferable to form a bolus of particles inside the cochlea. This bolus must be dispersed once in the area to ensure the diffusion of the particles (drug). In this section, we will present how to implement this strategy using the magnetic system presented in the introduction. As presented in Fig.2 the strategy unfolds in four steps :

A) Chain generation : Diffusion of particles through the round window ;
B) Bolus generation : Particle bolus formation ;

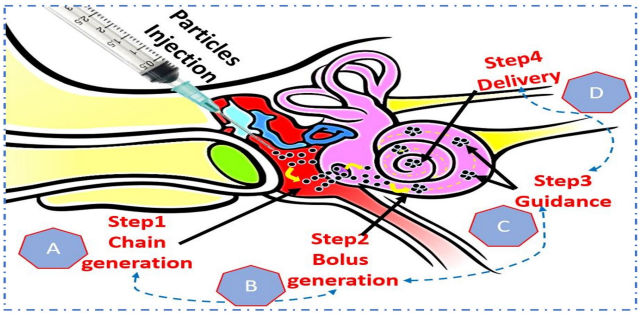

Fig. 2. Navigation strategy protocole.

C) Guidance : Bolus navigation ;
D) Delivery : Particle dispersion ;

A. diffusion of a particle through the round window

In this part, our hypothesis concerns the ability of magnetic particles to penetrate the membrane without being influenced by repulsion forces related to the stiffness of the membrane. Carry out the diffusion of the particles through the RWM, we must minimize the size of the agglomerate and be able to carry out this step in a minimum of time which is currently estimated in hours. For this, our contributions focus on two important aspects : the first consists in using particle chains instead of agglomerates in order to be able to reduce the size of the agents which cross the RWM. The second, consists in modeling the diffusion of the particles through the round window to estimate the magnetic gradient making it possible to accelerate the process of diffusion.

1) Particle chain creation: After the deposition of the particles at the level of the RWM, the latter are dispersed on the membrane. Having the ability to be magnetically actuated, these particles can form a chain of particles when subjected to a uniform and aligned magnetic field in the workspace.

According to the simulation results presented in Fig.3, we can understand that following the use of the magnetic actuation system we are able to generate a uniform magnetic field in the workspace. Following the application of magnetic field the particles align themselves in the working space and therefore the surface of the agglomerate in contact with the RWM becomes very weak and similar to that of a single particle. The second advantage is that by increasing the intensity of the magnetic field we will help the particles to cross the RWM more quickly, for this in the next part we seek to estimate the magnetic force allowing to reduce the time of the process.

2) Modeling the diffusion of a particle through the RWM: the work of Professor Chen's team [13] stipulates that below a certain volume, magnetic particles are not able to interact with the elastic part of the membrane because proteins and other macromolecules have the same dimensions as the magnetic particles. Our model Fig.4 assumes that the latter are of negligible size compared to the macromolecules of the human membrane, and navigate through the latter in a viscous liquid. The particle is then subjected to a driving

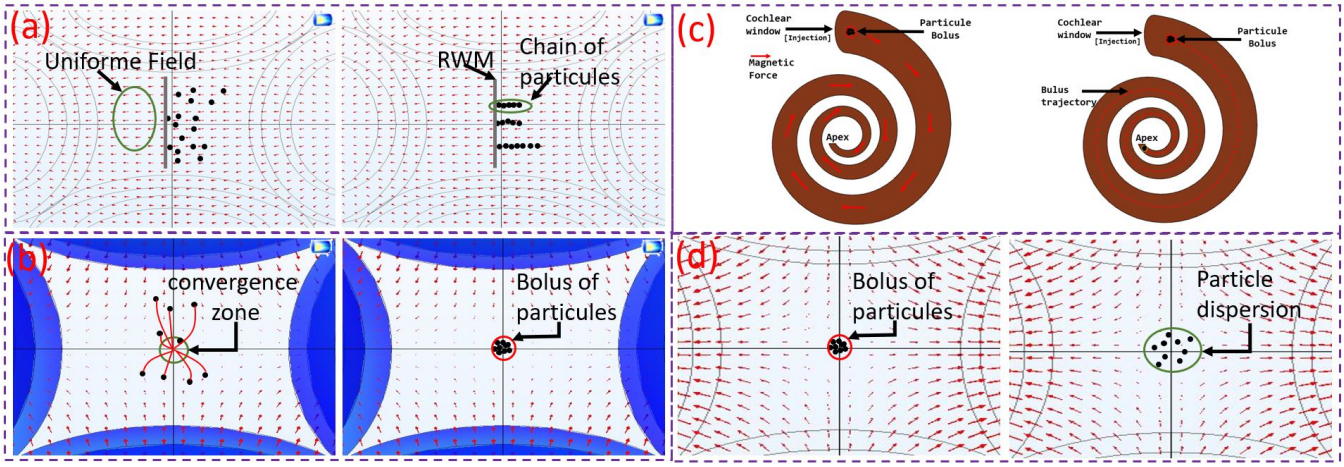

FIG. 3. Navigation strategy for magnetic particle in the cochlea : a- Chaine generation process. b-Bolus formation. c-Particule guidance in the cochlea. d-Dispersion of particle in the reached area

force, as well as to its own weight given by the following relation :

$$\Sigma\vec{F} = \vec{f_m} + \vec{f_d} + \vec{f_g} \tag{1}$$

The driving force being a magnetic force, the dynamic equation is written :

$$\gamma + \frac{6\eta\pi r}{m}\upsilon = \frac{V(M.\nabla)B}{M} + g \tag{2}$$

At equilibrium, the acceleration γ vanishes and the result is given by :

$$\upsilon = \frac{2\rho(M\nabla)r^2}{9\eta}B + \frac{mg}{9\eta\pi r}B \tag{3}$$

It is then observed that each magnetic force applied to the particle affects the movement of the particle. Knowing the thickness of the round window, we can easily deduce the travel time of the particles from this equation :

$$t = \sum_{i=1}^{3} \frac{e_{rwmi}}{\frac{2\rho(M\nabla)r^2}{9\eta_i} + \frac{gm}{6\eta\pi r}} \tag{4}$$

Figure 4 illustrates the speed of magnetic particles as a function of their position in the round window membrane. We find an average speed of $63.3nm/s$ on the outer and inner layers, and a speed of $0.88nm/s$ on the middle layer. This speed is conditioned by the application of a constant magnetic field gradient of $1T/m$ over the entire trajectory. It can be seen that the reduction in the travel time is conditioned by an increase in the magnetic field gradient. Thus, we can determine the minimum magnetic gradient required to allow particles to penetrate the round window membrane in 20 minutes, at most. We thus find an average speed of $37.9nm/s$, which corresponds to an average gradient ∇B of 0.53 T/m.

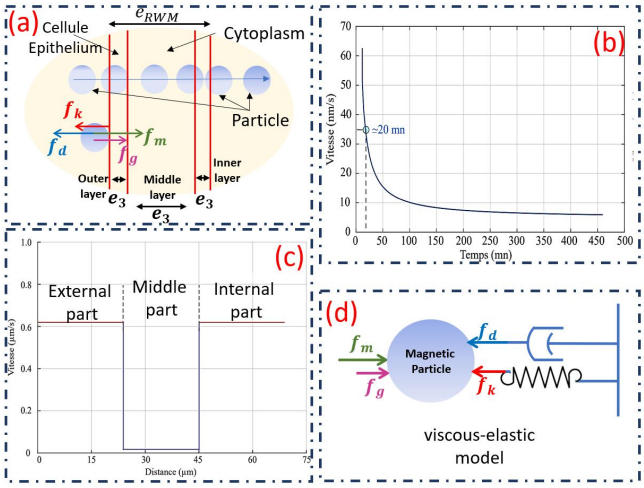

FIG. 4. Simulation of particle diffusion through the round window membrane : a- presentation of the particle path in the three layers of the RWM. b- simulation of the particle displacement velocity during time simulation. c-Simulation of the velocity regarding the distance traversed. d-Viscous-elastic model.

B. *Particle bolus formation*

After the penetration of the round window, the particles are found inside the cochlea in the perilynphatic liquid. To be able to guide them in the cochlear canal our solution is to form a particle bolus to be able to transport the maximum number of particles.

Knowing that the magnetic field makes it possible to magnetize the particles, then a force of attraction exists between the particles. Our solution consists in generating a converging magnetic field in an area to be able to form the bolus.

More precisely, and as presented in Fig.3, the magnetic field generated by the magnetic actuation system converges towards the central area of the workspace, in fact, the particles follow the lines of fields and converges towards the central zone. The fact that the particles are found in the

central zone and thanks to the force of attraction we can form a particle bolus.

C. Bolus navigation

The strategy adopted in part of the navigation requires actuation by magnetic push called *bead pulling*. This mode of magnetic actuation consists of inducing driving magnetic forces via magnetic field gradients. Indeed, in the presence of a magnetic field $\vec{B}$, a magnetic dipole is subjected to a magnetic force $\vec{f_m}$ and a magnetic torque $\vec{t_m}$ given by :

$$\vec{f_m} = V_m.(\vec{M}.\nabla).\vec{B} \tag{5}$$

$$\vec{t_m} = V_m.(\vec{M} \wedge \nabla.\vec{B}) \tag{6}$$

where ∇ represents the gradient operator, $\vec{M}$ is the magnetization of the magnetic body and V_m its volume. In particular, the force, $\vec{f_m}$, and the magnetic torque, $\vec{t_m}$, depend on the value of the magnetization $\vec{M}$ of the magnetic particle. This magnetization corresponds to the vector field which expresses the volumic density of the magnetic dipole moments, $\vec{m}$, permanent or induced in the material.

D. Particle dispersion

The main purpose of the magnetic bolus navigation procedure is to be able to transport medication to the target area. For this we thought about how to disperse the bolus particles for drug delivery. To carry out this step, we based ourselves on two main assumptions : the first considers that the particles lose their magnetization after the disappearance of the magnetic field, and the second consists in generating a divergent magnetic field to be able to pull the particles in several directions in the workspace

Since we are using soft magnetic particles, the first assumption remains valid. To satisfy the second hypothesis, we use the magnetic actuator with opposite electrical currents injected into the pairs of coils to generate a diverging field in the workspace, the simulation results are presented in the Fig.3.

III. Magnetic Manipulation Plateforme

A. Electro-Magnetic Actuator system

The magnetic actuation system shown in the introduction is part of a magnetic platform consisting of eight computer-controlled DC power supplies that have been specifically developed to provide the electrical currents necessary to create the desired magnetic field distribution throughout the system. central 3D workspace. These power supplies are controlled directly by a power board which converts 240V±20$\mathring{V}$/10A, 50 Hz AC input to 50V/10A DC output. The whole system is controlled by a *LabVIEW* application and runs on a Windows 10 operating system. A *PI-MOVE* positioning system to place the cochlea in the workspace and a CCD high-resolution camera (Edmund Optics, 69487 France) to provide visual feedback allowing the operator to follow the real-time evolution of the particles in the cochlear canal.

In the rest of this work, we will use the EMA system developed by [12], keeping all the components of the platform. However, to adapt the platform to our users, we want to integrate a haptic system to be able to use it in an open loop. The integration and the communication between the haptic system and the control model of the platform will be presented in this work.

When the magnetic field is generated by the system, a magnetic force is applied to the spherical microrobot. This force is given by the following equation :

$$F_{mag} = \frac{4}{3}\pi\mu_0 R^3 M(H).\nabla H \tag{7}$$

whereμ_0 is the permeability of free space, M is the net magnetic polarization, H is a magnetic intensity, and ∇H is the magnetic intensity gradient.

B. Haptic system

We are interested in this work in guiding a particle bolus with a small diameter in the cochlear canal and reaching the most difficult zone (Apex). For this, it is important to control the generation of forces in the right directions to ensure simple and efficient navigation in the cochlear environment. Due to advancements in Virtual Reality (*VR*) technologies, virtual environment simulations like the physical remote manipulation system can replicate real in vivo experiences without implementing entire hardware systems.

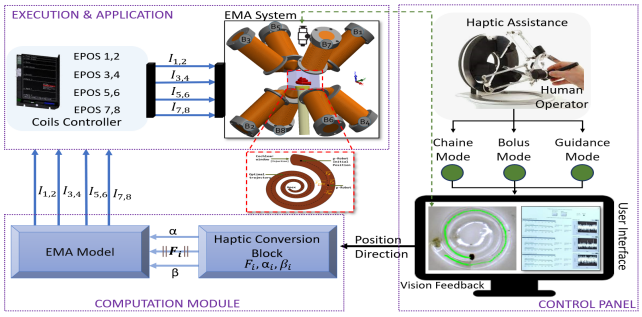

FIG. 5. Magnetic actuation system control module and control interface according to the navigation strategy.

The *Omega 6 haptic* device *by Force Dimension* can be considered as a 6-DOF haptic device which is primarily designed for very precise applications. Customization, Control and Characterization of the Omega haptic device are described in [14].

A haptic device is typically used as a position control device in which displacement of the end-effector is directly correlated to displacement of the avatar displayed on the screen. To integrate the haptic device into the guidance platform, we based ourselves on the analytical model of the actuator. This model makes it possible to generate the magnetic fields in any point of the workspace :

$$H(x,y,z) = \sum_{j=1}^{8} \widetilde{H}_j(x,y,z).I_j \tag{8}$$

$\widetilde{H}_j(x, y, z)$ is defined as the unit vector of spatial distribution, which is generated by a coil j traversed by an excitation current I_j. Knowing that :

$$F_m = (M.\nabla).H \tag{9}$$

The calculation of the axial currents I_x, I_y and I_z can be found using the pseudo-inverse of the following equation :

$$\begin{Bmatrix} H_x \\ \\ H_y \\ \\ Hz \end{Bmatrix} = \begin{Bmatrix} f(I_x) \\ \\ f(I_y) \\ \\ f(Iz) \end{Bmatrix} \tag{10}$$

The allocation of the electric current to the different coils is carried out as follows :

$$\begin{Bmatrix} I_6 = I_7 = I_x^+ \\ I_2 = I_4 = I_y^+ \\ I_1 = I_3 = I_z^+ \end{Bmatrix}; \begin{Bmatrix} I_5 = I_8 = I_x^- \\ I_2 = I_3 = I_y^- \\ I_1 = I_4 = I_z^- \end{Bmatrix} \tag{11}$$

Where I_x^+ and I_x^- are the positive and negative axial currents respectively. The current I_j is that injected into the coil j. the equation 11 presents all the combinations of currents to navigate in 3D space using the haptic system, these combinations cannot all be valid, three combinations are valid in the case where the direction of the force is 3D, two combinations in the 2D plane and 1 combination in the case where the force is axial 1D.

To illustrate the use of the platform, we have implemented an architecture to manage the interaction between the user, the haptic system, the control module and the magnetic actuation system. This architecture is presented in the Fig.5 and consists of four parts :

- First : The user chooses the desired mode of manipulation thanks to a selection button implemented in the effector of the haptic device. Selecting the warp mode automatically generates uniform field lines in the workspace to align the particles. The bolus mode must be chosen after the penetration of all the particles to be able to create a bolus of particles. The guidance mode releases the haptic system in 3-DOF to be able to guide the microrobot.
- Second : The positions of the effector of the haptic system are converted into electric currents to control the electromagnetic coils. A calibration method illustrated in Fig.6 is used to define the calibration coefficients used to convert the movements of each axis into electric currents.
- Third : The movements of the haptic system effector must be similar to the movements of the microrobot in the workspace. Indeed, a control panel makes it possible to send the converted electric current to the coils concerned according to the movement of the haptic system Fig.5. The coils receive the current and the magnetic force is generated in the workspace, this allows the microrobot to be manipulated. The operator controls the movement of the microrobot via the vision system and reacts to the haptic system to ensure the guidance of the microrobot towards the targeted area. We remind you that this manipulation requires short training so that the operator can master the use of the haptic system.
- Fourth : To simplify both joystick guidance and operator training, we have implemented a guidance vector in the control interface. This vector makes it possible to project the direction and the amplitude of the magnetic force following a movement of the haptic joystick. This strategy allows the operator to be more precise in navigation.

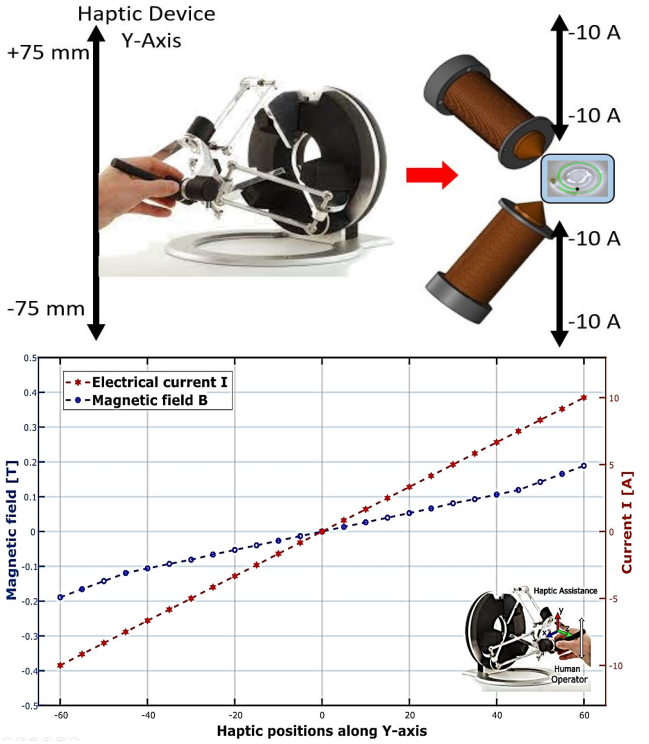

FIG. 6. Transformation of x,y,z position of the haptic system effector for controlling the intensity of the electrical current for each electromagnetic coil.

To ensure the correct functioning of the haptic system, we have set up a calibration that allows the transformation of the positions of the axes of the haptic system into current and direction. These will generate a magnetic field of a given amplitude and direction. For this, we have presented in Fig.6 the magnetic field generated by each position of the Y axis of the haptic system. We note that in the case where the position of the haptic is positive and maximum the magnetic field takes the positive direction and maximum amplitude, the reverse remains true.

IV. EXPERIMENTAL VALIDATION

In the experiments, spherical microparticles (ASIC35) of radius r = 10 to 100 μm were used as the body of the microrobot, immersed in physiological liquid, with approximately 31 L of pure water and 0.36g of chloride of sodium (NaCl). The artificial cochlea used in the experiments mimics the geometric characteristics of the real cochlea which consists of a coiled labyrinth, which is about 2.5 turns in humans [15],

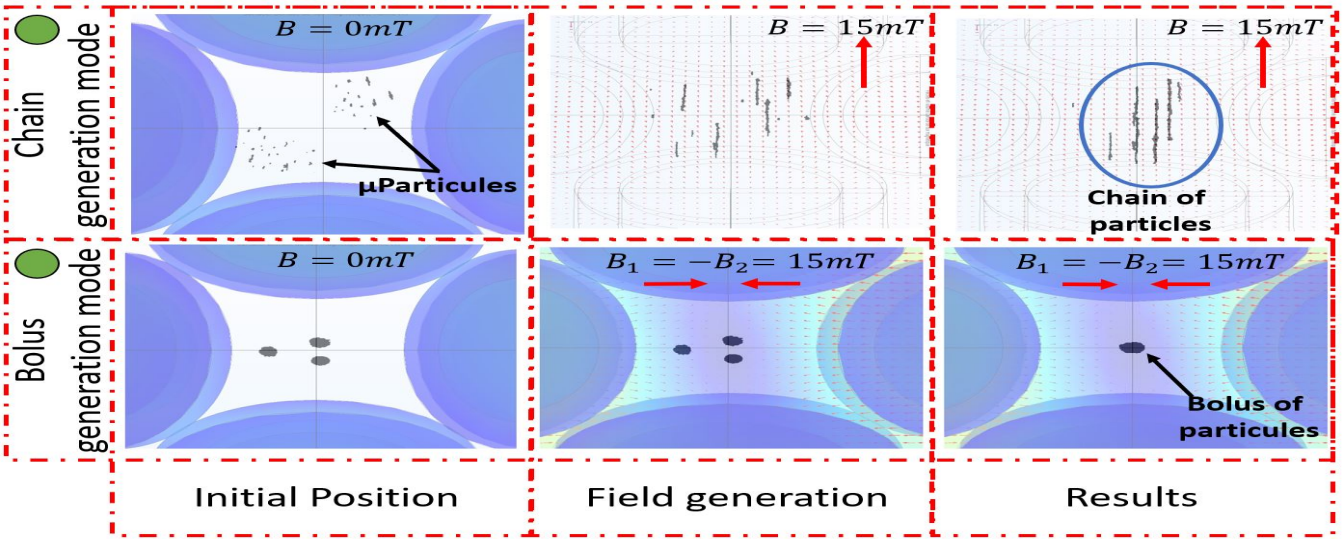

FIG. 7. Experimental tests of chain particle creation and magnetic bolus formation : the experimental tests are superposed on the magnetic field simulation tests, the chain or bolus formation results are obtained experimentally and the magnetic field direction arrows are represented from the numerical simulation.

with a radius of $2mm$ at the entrance of the cochlea to $1mm$ at the apex. See Fig.8. The inlet and outlet of the cochlea were plugged with an elastic rubber to keep the liquid under pressure. The main objective of these in-vitro tests

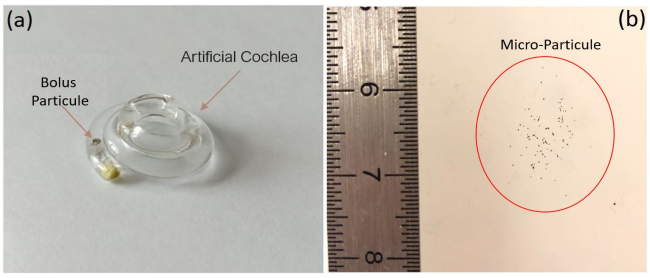

FIG. 8. (a) Artificial cochlea on a real scale; (b) Soft microparticle (ASIC35).

is to test the feasibility and efficiency of the microparticle navigation strategy in the cochlea. For this purpose, we set up three experimental tests, the first one consists in proving the method of creating a chain of microparticles for the RWM passage. The second one is to show the feasibility of converging the particles in the same point to create the bolus. The third one is to test the formation of the bolus in the cochlea as well as its guidance in the cochlear canal.

A. Chain generation experiment

To test the magnetic particle chain generation, we place the microparticles in the working space immersed in the physiological fluid. Then, we generate a uniform magnetic field in the working space similar to the one simulated in section II. As illustrated in Fig.7, the uniform magnetic field allows to align the particles in the form of chain, which proves the feasibility of the creation of the particle chains must the RWM and facilitates their diffusion through the membrane since the diameter of the particles that comes into contact with the membrane will be very small : 10 μm diameter of the particle versus 1 mm diameter of the RWM.

B. Bolus generation experiment

We have described in Section II that the creation of the magnetic bolus is important for guidance, however this bolus must be created inside the cochlea so as not to increase the membrane contact diameter (for this reason, we implemented the particle chain method).

In this experience shown in Fig.7, we place three groups of particles in an aqueous workspace and then use the magnetic system to generate a converging magnetic field. We observe that the three groups converge with the field lines to the central area of the workspace. Since the two vertical groups are very close to each other, they are the first two to converge and form a new group of particles in 17 sec. Finally, the two groups that remain horizontal converge in the same area within 31sec to form a bolus of magnetic particles.

C. in-vitro test of the navigation strategy

We wish through this experiment to test the feasibility and effectiveness of the navigation strategy we have proposed. For that, we realize an in-vitro test of the procedure in the cochlea. However, we cannot test the first step of the procedure which consists in crossing the RWM since we do not have experimental components allowing to reproduce the behavior of the RWM membrane such as stiffness, permeability and mechanical resistance. Since we have proved experimentally the possibility of particle chain creation and theoretically the reduction of time and risk of particle passage, thus combining these results with those of Professor Chen's team [13], we consider that particle diffusion is feasible. Following this last information, the protocol of the in-vitro test begins with the deposit of microparticles in the entrance of the cochlea, then formed a bolus of particle to finally guide it to the target area. Fig.9 shows globally that the formation of the bolus

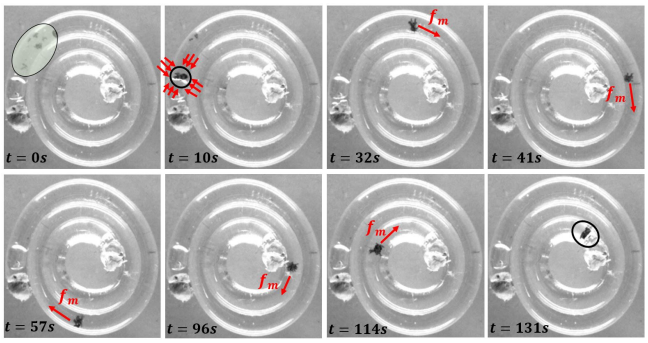

FIG. 9. In-vitro test of the navigation strategy in the artificial cochlea.

and the guidance of the latter towards the target area Apex is correctly performed inside the cochlea. More specifically, we can notice that the particles injected in the cochlea are initially formed by a group of dispersed particles. The generation of a converging magnetic field allows to form a magnetic bolus which contains about 95 % of the injected particles, the unformed particles remained stuck either at the entrance or on the wall of the cochlea. Finally, the guidance of the bolus was achieved within 131 sec from the entrance of the cochlear canal to the Apex. During the guidance of the bolus we noticed that the shape of the bolus changes by varying the magnetic field allowing the guidance, this result that we mentioned in the introduction makes difficult the control in closed loop and justifies the use of the haptic system.

The experiments are mentioned in the attached video and allow to visualize in details the procedure, the tracking of the microrobot in real time as well as the cartesian positions of the haptic system during the procedure.

V. CONCLUSION AND FUTURE WORK

The navigation strategy proposed in this work makes it possible to demonstrate that it is possible to use soft magnetic particles as therapeutic agents and to penetrate the RWM without risk of performation and in an estimated time of 20 min. the use of a magnetic bolus inside the cochlea is achieved through the generation of a convergent magnetic field, thus the use of a haptic system makes navigation to the target area very simple and effective. However, we want to consolidate the results of this work by finding a solution to test particle diffusion in a real RWM. The development of a more powerful magnetic actuation system will further reduce the particle size and the navigation strategy remains valid.

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