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Potential therapeutic use of magnetic nanocarriers in brain tumors

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Summary. — Nanobubbles with polymeric membrane containing fluids with high oxygen solubility and able to deliver drugs can be stably coated with superparamagnetic iron oxides nanoparticles (SPIONs) and acquire suitable magnetic properties to allow driving toward targeted tissues by magnetic fields generated by external permanent magnets. Tumors close to the walls of the cerebral ventricles could be reached by nanobubbles injected into the cerebrospinal fluid and properly guided, in order to release locally their contents in a sustained and continuous manner, allowing the optimization of the radio-chemotherapy treatment of these aggressive tumor forms. To validate this approach, a laboratory setup aimed to simulate the brain environment and supported by *in silico* modelling of magnetic fields is proposed.

1. – Introduction

Tumors of the Central Nervous System (CNS) are still poorly treated due to the difficulty to reach their site without seriously damaging the surrounding structures. Both surgery and less invasive approaches are critical because the presence of very selective membranes (such as the Blood-Brain Barrier) restricts the passage of drugs and substances. Since the main therapeutic approaches, such as radiotherapy and chemotherapy, are not enough effective individually, it may be favorable to identify alternative approaches inducing a synergistic effect of multiple therapies and taking into account the specific complexity of the CNS.

Nanomedicine has the potential to drastically improve the diagnosis and treatment of many diseases including cancer. The nanometric size of a material is the same scale of several biological mechanisms allowing nanoparticles and nanomaterials to potentially cross the biological barriers to access the sites of delivery and to interact with DNA or small proteins at different levels, in blood or within organs, tissues or cells [1]. Theranostic nanomedicine is a novel and fast-developing concept involving the integration of diagnostic imaging with therapeutic intervention in a single platform using nanomaterials. Magnetic nanoparticles (MNPs) made of iron oxides exhibit special properties, including high surface-to-volume ratio and high magnetic moment, allowing potential manipulation by an external magnetic field, gaining a great interest in several biomedical applications [2]. In our previous studies, we developed a novel multipurpose theranostic carrier designed as Magnetic Oxygen Loaded Nanobubbles (MOLNBs), able to be physically drivable and loadable with therapeutic drugs. MOLNBs are composed by a

perfluoropentane core, a shell of biocompatible material (dextran) and are covered with superparamagnetic iron oxide nanoparticles (SPIONs), conferring them proper magnetic properties. MOLNBs are potentially able to cross brain barriers when injected in the systemic circulation and enter the CNS due to their non-toxic interplay with the BBB cells and also to be magnetically guided using external permanent magnets [3]. Due to the fact that the nanovectors can lose part of their cargo in the systemic circulation before overcoming the BBB, a possible alternative is the intravertebral injection in the cerebrospinal fluid (CSF), in direct contact with the brain parenchyma. Several studies evaluated the administration route via CSF rather than systemic delivery, investigating the distribution of intrathecally injected nanoparticles within the CNS [4, 5].

Therefore, due to their properties, MOLNBs may be magnetically driven towards target membranes, for instance the one separating CSF and the interstitial fluid of the brain located in the choroid plexus in the brain ventricles, to deliver oxygen and chemotherapy drugs to brain tumors. This new approach consisting of MOLNBs locally administrated via intravertebral injection in the CSF, allows monitoring of their concentration by Magnetic Resonance Imaging (MRI) or sonography and exploiting their magnetic properties to precisely direct them to their target. Tailoring the driving magnetic field based on the position and dimension of the brain tumor and the brain membranes to be crossed is a very challenging goal. To validate such application, in this work we present a setup aimed to simulate the brain environment and the motion of MOLNBs inside brain fluids in the presence of magnetic fields in different configurations (*e.g.*, generated by magnets positioned on the skull), monitored by Ultrasound (US) imaging and supported by *in silico* models.

2. – Setup

2˙1. *Magnetic field.* – Suspension of MOLNBs were injected in a plastic cylinder and sonicated. Permanent cylindric magnets (diameter = 6 mm, height = 0.75 mm, Br = 1.17–1.21 T) of neodynium covered with Ni-Cu-Ni (`https://calamite.org`) were positioned on the cylinder wall in different configurations (fig. 1) to generate the magnetic fields. The value of residual magnetization is in the range of 860–915 kA/m. Simulations of magnetic field lines were obtained using the Python package Magpylib [6].

2˙2. *US imaging monitoring.* – B-mode US imaging was carried out to study the response of MOLNBs to the external magnetic field due to their excellent echogenicity. MOLNBs were injected in the plastic cylinder containing demineralized water by means of a syringe passing through a glass tube. The experiment was performed at a temperature

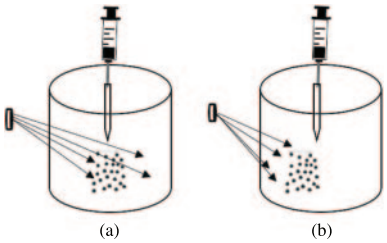

Fig. 1. – A sketch of the setup used to investigate the response of MOLNBs to magnetic fields generated by two different configurations of magnets positioned on the cylinder wall: (a) Four magnets at distance 4 cm each other in symmetric position with respect to the cylinder axis; (b) four magnets positioned in the left side of the cylinder at distance 2 cm each other.

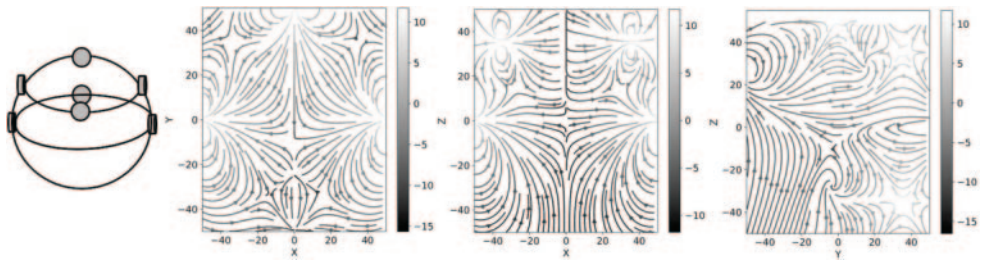

Fig. 2. – Seven magnets ideally located on the wall of a sphere (5 cm radius): three magnets located in the equatorial plane, and four magnets located in a fixed plane at the top of the sphere. Simulations of magnetic fields were performed revealing the direction of magnetic field.

of a 25 °C. MOLNBs were sonicated by an US clinical equipment (MyLab^{TM} 25Gold Esaote, Genova, Italy), connected to a linear array transducer (LA523, 7.5 MHz central frequency, Esaote, Genova, Italy) operating in B-mode with the use of the small parts imaging preset. B-mode cineloops (30 seconds) were acquired and recorded. Snapshots from cineloops were extracted at different time frames (5, 15, 30 s) after the initial injection and compared in the different conditions.

3. – Results

Firstly, we present simulations of magnetic fields generated by seven magnets, located on the wall of a sphere of 10 cm diameter as described in fig. 2, since the sphere might be considered as an ideal reproduction of the brain.

Using the setup described in the previous section, snapshots at different time inter-

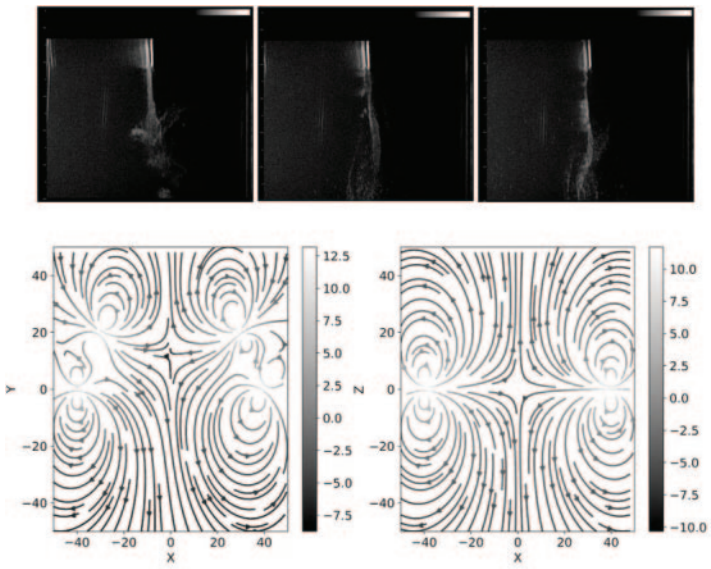

Fig. 3. – Snapshots from US imaging of MOLNBs in the magnetic field generated by four magnets in simmetric position with respect to the vertical axis. Images were recorded at different time frames (5, 15, 30 s) from the injection. Projection of magnetic fields lines in the XY and XZ plane were visualized.

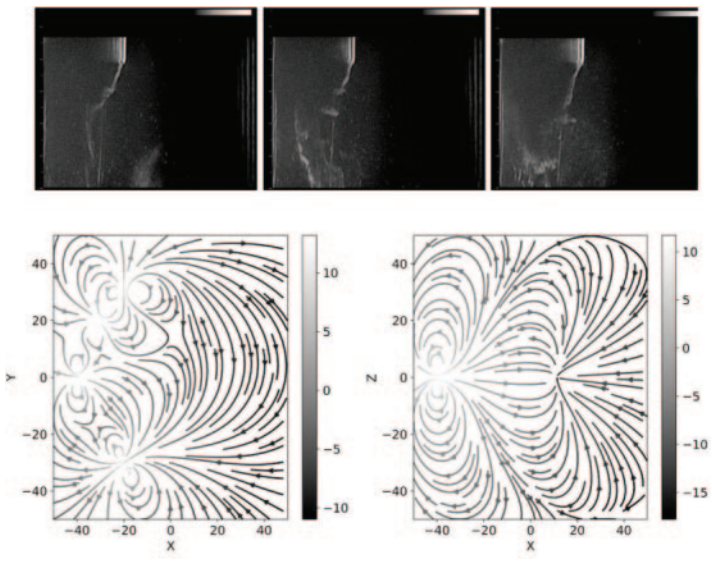

Fig. 4. – Snapshots from US imaging of MOLNBs in the magnetic field generated by four magnets in non-simmetric position with respect to the vertical axis. Images were recorded at different time frames (5, 15, 30 s) from the injection. Projection of magnetic fields lines in the XY and XZ plane were visualized.

vals from US imaging showed the flow of MOLNBs in the presence of a magnetic field generated by four magnets located in symmetric position, monitored by the US probe positioned on the cylinder wall in axial direction (fig. 3). The configuration of four magnets in non-symmetric position revealed a significant deviation of MOLNBs motion towards the magnets, confirmed the effect of magnetic fields on MOLNBs (fig. 4).

4. – Conclusion

In this paper, we propose a new potential application of physically drivable magnetic nanobubbles to precisely target brain tumors, due to the interaction with magnetic fields allowing their manipulation. A new setup was developed, with the aim to simulate brain and motion of MOLNBs inside brain fluids. These preliminary results highlighted the possibility to precisely tune the motion of MOLNBs (monitored by sonography) using magnetic fields tailored by *in silico* modelling.

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