Monitoring and Imaging of Magnetic Nanoparticles: state-of-the-art and prospective

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Abstract. This paper describes the most common techniques to monitor magnetic particles and perform magnetic particle imaging (MPI) for biomedical applications. Then a new and innovative device is present which is able to enhance the image quality of magnetic particle. It will be also discussed how to ensure tracer stability and biocompatibility acting on the tracers’ properties and by understanding in depth the physics of tracer response. Furthermore, it is highlighted that to achieve its full potential the following parameters: MPI sensitivity, signal-to-noise ratio (SNR) and spatial resolution must be optimized. Finally, it will be shown how the use of high-quality iron-based tracers with tailored magnetic and surface properties is able to enhance the performance for both detection and imaging.

1. Introduction

Magnetic Particle Imaging (MPI) is a technique introduced in 2005 by Gleich and Weizenecker that directly images the intense magnetization of superparamagnetic iron nanoparticles (SPIOs) rather than indirectly detecting SPIOs via magnetic resonance imaging (MRI) signal dropouts [1]. This technique produces quantitative images of the tracer materials distribution (SPIOs) without interference from the anatomical background of the imaging objects, such as tissues, bones and organs [2]. Indeed, since no biological tissue contains a magnetic signature similar to magnetic tracers, the background signal in MPI is virtually absent, unlike other nuclear medicine techniques and fluorine MRI. Specifically, MPI has the advantage of three-dimensional visualization with very high sensitivity, temporal and spatial resolution [3] and the absence of hazardous ionizing radiation. It exploits the unique characteristics of superparamagnetic nanoparticles and is the first medical imaging method in which the nanoparticles are not just supportive contrast agents but the only source for signal and therefore the only visualized element. This is why they are referred to as “tracers”; MPI visualizes anatomical structures only if they are labelled by the tracer. As a result, MPI is an emerging imaging technique with promising applications in diagnostic and guided therapy [4] e.g. vascular imaging and ultra-sensitive cancer therapeutics, using advanced manufacturing methods, that can be scaled up to mass production.
2. Operating principles

The main purpose of the use of MPI scanner with high resolution, sensitivity and signal-to-noise ratio (SNR) is the unique feature of magnetic materials called magnetic hysteresis, which make magnetic nanoparticles ideal nanotherapeutics [5] [6]. Magnetic hysteresis [7] represents a sort of energy loss that inevitably is dissipated in the environment as thermal energy when magnetic materials are subjected to alternating magnetic field. Though for many industrial applications this energy loss represents a disadvantage, in biomedical field it is indeed a great opportunity. In fact, this phenomenon is the base of classic hyperthermia against, e.g., cancer diseases [8]. This elevation in the temperature (up to 45-47 °C) may kill cancer cells directly or render them more susceptible to other kind of treatments [9]. However, classical hyperthermia based on the use of magnetic nanoparticles still presents some drawbacks. Among them, two are the most critical: I) lack of specificity to discriminate tumor tissue surround by health tissue; II) moderate effect on cell viability when used a solely therapeutic regime. As it has been shown in 2016 by Hristoforou et al. over-hyperthermia is a tool for precise cellular ablation that does not suffered of the above mentioned drawbacks. As it has been demonstrated, this method generated high temperature elevation that caused an efficient cell death by provoking holes in the cell proplasm, figure 1 [10].

Figure 1: Over-hyperthermia resulted in detrimental effects to the cell cytoskeleton (Picture from Hristoforou et al. 2016, [10]).

Except for magnetic hysteresis, MPI scanners will track the electron paramagnetic resonance (EPR) of magnetic tracers instead of their magnetic moments (Gleich, B. & Weizenecker idea, [1]) that requires ad hoc magnetic scanners. It is known that magnetic moments of magnetic nanoparticles are much bigger than those of protons. In magnetic fields of 1.5 to 3 Tesla (T) we could modify an MRI machine to detect EPR in order to track magnetic tracers, especially those made of pure iron (Fe), because iron oxide nanoparticles have lower magnetic moments than pure Fe.

Electron paramagnetic resonance is a method for studying materials with unpaired electrons. The basic concepts of EPR are electron spins that are excited instead of the proton spins of atomic nuclei. EPR measurements are made with microwaves in the 9000–10000 MHz (9–10 GHz) region, with fields corresponding to about 3500 Gauss (G) (0.35 T). The ferromagnetic resonance frequency of Fe is 9-23 GHz, so there is a net absorption of energy when Fe-based tracers are used. Another advantage is that microwaves are able to reach deeper in patient’s body giving high resolution and good quality images of tissues and cells [11]. As mentioned above, like protons also electrons have a spin, which gives to them a magnetic property known as magnetic moment. When an external magnetic field is supplied, the paramagnetic electrons can either orient in a direction parallel or antiparallel to the direction of the magnetic field. This creates two distinct energy levels for the unpaired electrons and measurements are taken as they are driven between the two levels [12].

EPR spectroscopy is the measurement and interpretation of the energy differences between the atomic or molecular states. These measurements are obtained thanks to the relationship between the energy differences and the absorption of electromagnetic radiation. To acquire a
spectrum, the frequency of the electromagnetic radiation is changed and the amount of radiation which passes through the sample is measured with a detector, which detects the spectroscopic absorptions.

In addition, to further improve the sensitivity of magnetic tracers for certain tissues (e.g. cancer), magnetic nanoparticles can be decorated with specific ligands, e.g. antibodies and non-antibody scaffold [13], [14] able to find specific cell-type.

3. Development of the method

The development of MPI scanner as a reliable and inexpensive device for monitoring the spatial distribution of Super-Paramagnetic Nanoparticles (SPANs) in the body [15] of patient affected by disease such as cancer is based on the attachment of SPANs to the cancer cell surface through the binding of specific protein molecules involved in cancer development (with overexpressed receptors on the cancer cell membrane). The sensitivity of the method could touch the limits of single-cell measurement under given conditions, which is very important for the diagnosis of micro-metastases. Thus, measuring the density and the distribution of density of SPANs into the body, the recognition of early stage malignancies may be possible [16]. The better the magnetic sensitivity of the device is, the earlier the malignancy recognition in the body. The main target is to obtain the highest possible sensitivity in the measurement of SPANs with the minimum possible cost.

Furthermore, apart from an early stage tumour diagnosis tool, the device will offer a staging method for malignancies, with simultaneous killing of the cancer cells applying inductive heating techniques. Possible applications could be breast and prostate malignancies. This process can be feasible by controlling the rate of temperature increase; this can be achieved by controlling the structure and composition of the SPANs [17].

The motivation of the MPI scanner is the development of a novel diagnostic/therapeutic technique for the reliable diagnosis and treatment of malignancies. The novelty of the method is based on the suggested magnetic imaging technique, accompanied by the selective coating/decorating of SPANs with the appropriate protein which targets to specific cell categories and the consequent inductive heating, which may be effective due to the temperature gradient caused by the SPAN [18].

The magnetic imaging device and method are mapping SPANs distribution in space. This identification of magnetic dots reveal the existence of cellular areas with high number of bound magnetic nanoparticles and as a result the presence of a malignancy, offering possibly the ability of detecting one single malignant cell. Consequently, high inductive heating is destroying the malignant cells (ΔΤ>50°C), without being able to destroy the healthy ones due to the very small increase of temperature to them (ΔΤ<2°C) [19].

4. Conclusions

Magnetic resonance imaging (MRI) is an imaging technique used primarily in medical settings to produce high quality images of the soft tissues of the human body. MRI employs powerful magnets which produce a strong magnetic field (in clinical diagnosis, magnetic fields of 1.5 or 3 T are usually used) that forces protons in the body to align with that field. When a radiofrequency (5–100 MHz) current is then pulsed through the patient, the protons are stimulated, and spin out of equilibrium, straining against the pull of the magnetic field. Major drawbacks are associated with voluntary or involuntary (heart beating, bowel movement, e.g.) patient’s movements, use of contrast agent for high quality images of soft tissues and MRI may not always distinguish between cancer tissue and fluid, as well as small tumours surrounded by healthy tissues. Even though, some of these drawbacks (movements) are efficiently controlled, and in same case eliminated, by professional MR technologists, it is unquestionable that others, such as the ability to discriminate tumour tissues surrounded by
the healthy one or few cancer cells, need to solved. In fact, it takes millions of cells to make a
tumour big enough to show up on MRI test.
The development of the innovative magnetic measuring (and heating) device capable of
measuring the distribution of SPANs with sensitivity quite better than 1 µm (sub-micron
tumour cell diameter) could be considered as a universal breakthrough in tumour diagnosis. In
addition, the development of the structurally well controlled biocompatible SPANs decorated
with the appropriate ligands would permit for targeted SPAN delivery and subsequent
immediate killing of the cancer cells by applying controlled inductive heating techniques.

5. References

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