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MAGNETIC PARTICLE IMAGING SYSTEM FOR CANCER DIAGNOSIS: AN OVERVIEW

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ABSTRACT

Medical diagnosis over the last decades have been reformed by tomographic imaging and has become a vital tool for diagnosis of several diseases. Magnetic particle imaging (MPI) as a new quantitative imaging method, uses the nonlinear re-magnetization behavior of magnetic nanoparticles to determine their local concentration. This paper presents an overview of a proposed method to design and construct an MPI scanner that will diagnose cancer. It is expected at the end of the research to come up with an extremely sensitive scanner that will detect the position of magnetic nanoparticles (MNPs) used as tracers in diagnosing cancer by producing a high temporal and spatial resolution images.

Keywords: magnetic particle imaging, nanoparticles, superparamagnetism, harmonic signals, cancer diagnosis.

INTRODUCTION

Magnetic particle imaging (MPI) is a novel imaging modality that accomplishes a direct measurement of the magnetization of ferromagnetic nanoparticles to calculate their local concentration. Superparamagnetic Iron oxide nanoparticles (SPIONS) are usually employed as tracer material in MPI, due to their small size and exhibit Superparamagnetism. These SPIONs are injected into a target area, then excited by an external magnetic field (Drive field) and the response of the particles is recorded which is proportional to the concentration of the SPIONs.

MPI technique was invented in 2001 by Bernhard Gleich and Jürgen Weizenecker, who first reported on it in *nature* in 2005 (Gleich and Weizenecker, 2005). MPI offers a unique combination of capabilities that sets it apart from other established modalities for medical imaging. An essential theory for describing the magnetic behavior of superparamagnetic particles is the Langevin theory, which is defined under the assumption that the particles are always in thermal equilibrium. (Gleich *et al.*, 2012) reported that MPI usually aims at applications requiring fast, dynamic imaging, such as blood flow visualization in the case of coronary artery diseases. Furthermore, future applications may be in cancer diagnosis, sentinel lymph node biopsy or any application where tracers are used for diagnosis today (MRI, PET, and SPECT).

The aim of this research is to design and construct a magnetic particle imaging system (scanner) for cancer diagnosis. This will be achieved by exposing the sample containing the MNPs and the cancer cells in a magnetic field produced by the drive coil. The magnetization of the MNPs will induce a voltage signal in the pickup coil that is being detected in the form of harmonics. These harmonics will be amplified and acquired using appropriate data acquisition hardware and software to produce tomographic images of the tracer material used.

METHODOLOGY

The spatial distribution of MNPs used as tracer material can be determined by measuring the change in the magnetization of the tracer material in a time-varying magnetic field. Figure-1 shows the relationship between the external magnetic field applied to the MNPs and their response magnetization. This is as demonstrated by the M-Hcurve in the upper left part of Figure-1. The dynamic region of the magnetization curve is non-linear when a field of A to -A is applied, while the saturation area started when the field-applied is beyond A. No further magnetization is made and this results in the occurrence of harmonics in the received signal. These harmonics are used to reconstruct the images that reveal the presence of magnetic material.

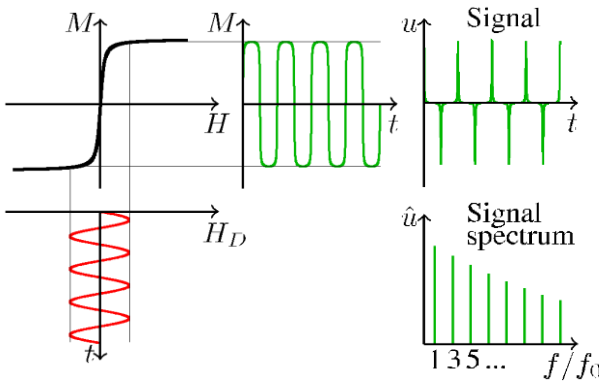

Figure-1. External magnetic field applied to the MNPs and their response magnetization.

MPI takes advantage of the non-linear magnetization behavior of SPIOs used as tracer material, to detect their spatial and temporal distribution within a target cancerous tissue (Othman *et al.*, 2014). Equation (1) gives the magnetization behavior of these particles, which be approximated by the Langevin function.

$$M_D(t) = m_s c\ (\coth(\xi))-1/\xi). \quad (1)$$

The magnetization of a distribution of particles of diameter D is described by M_D while $m_s=(\pi D^3 M_s)/6$ denotes the magnetic moment at saturation. The saturation magnetization M_s is a material constant. The particle concentration is given by *c*, and the Langevin parameter is given as:

$$\xi = (m_s \mu_0 H(t))/(K_B T_P). \quad (2)$$

$$H(t) = \sqrt{2} H_{ac} \sin(wt) + H_{dc}\ . \quad (3)$$

In which *H(t)* is the outer magnetic field, k_B is the Boltzmann constant, T_P is the temperature of the magnetic material, and μ_0 is the permeability of vacuum (Buzug *et al.*, 2012). Using a sinusoidal external magnetic field, entitled drive field H_{dc}, with frequency f_0, a non-sinusoidal oscillation of the particle magnetization M is brought due to the non-linearity of the Langevin function. In Fourier space, this deformation can be detected as higher harmonic frequency components (Othman *et al.*, 2014).

MAGNETIC NANOPARTICLES: STRUCTURE AND SYNTHESIS

Magnetic nanoparticles (MNPs) are a class of nanoparticle which can be manipulated using a magnetic field. Nanoparticles possessing magnetic properties offer significant advantages in that they can provide selective attachment to a functional molecule, confer magnetic properties to a target, and allow manipulation and transportation to a desired location under the control of a magnetic field produced by an electromagnet or permanent magnet (Wadajkar, Menon, Kadapure, Tran, and Yang, 2013). MNPs are agents that are superparamagnetic and consist of a central core of iron-oxide, surrounded by a carbohydrate or polymer coat. The size, physical properties and pharmacokinetics of MNPs make them highly suited for cellular and molecular imaging of atherosclerotic plaque and myocardial injury (Sosnovik *et al.*, 2008).

The physical and chemical properties of magnetic nanoparticles largely depend on the synthesis method and chemical structure. In most cases, the particles range from 1 to 100 nm in size and may display superparamagnetism (Morishige *et al.*, 2014). This superparamagnetic possession of materials is useful in that individual particles become magnetized only when exposed to an external magnetic field, but exhibit no remnant magnetization when the field is removed (Issa, Obaidat, Albiss, and Haik, 2013). Magnetic nanoparticle carriers consist of three functional parts: a magnetic core, a surface coating, and a functionalized outer coating (Pantic, 2010). Magnetic iron oxide particles (ferromagnetic magnetite-Fe_3O_4 and maghemite-Fe_2O_3), on the other hand, are highly biocompatible, because the iron uptake, excretion, and storage are well controlled, and the iron excess is efficiently cleared from the body without grave consequences to human health (Miller, 2013). Most synthesis procedures for medically applicable nanomaterials are inexpensive and based on simple chemical reactions. Meanwhile, nanoparticles at the target site, even with their small size, do not enter into biological systems easily, many investigators suggest that it is indispensable to design approaches that enable nanoparticles to identify the surface molecules/receptors of the target cells and, therefore permitting nanoparticles to enter the cells and their organelles (Yan *et al.*, 2006).

Various types of nanoparticles have been developed for application in cancer diagnosis/therapy: inorganic (iron based (magnetic) and other inorganic nanoparticles) and organic nanoparticles (Ishihara *et al.*, 2013). Organic Nanoparticles are those prepared with organic polymers, with examples such as liposomes, dendrimers, and carbon nanotubes. According to (Akhter *et al.*, 2011), Inorganic, on the other hand, is those prepared with inorganic elements. Examples are magnetic nanoparticles (iron oxide nanoparticles), gold nanoparticles, and quantum dots. Today, there are several commercially available contrast agents for MRI. These include Resovist (Schering), Fluid MAG-D and Nanomag-D.

APPLICATIONS OF MAGNETIC NANOPARTICLES IN BIOMEDICAL FIELD

Magnetic Nanoparticles may provide advanced biomedical research tools based on polymeric or inorganic formulations or a combination of both. They have the potential to be used in many different biological and medical applications as in diagnostic tests assays for early detection of diseases, to serve as tools for non-invasive imaging and drug development, and to be used as targeted drug delivery systems to minimize secondary systemic adverse effect. These applications fall broadly into two categories: those involving the use in-vivo and those involving the use of magnetic particles in-vitro.

i. Imaging

For many years, superparamagnetic nanoparticles have been used in diagnostics as contrast agents in magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and magnetic particle imaging (MPI). MNPs are considered as promising contrast agents in cancer diagnosis because they have much greater magnetic susceptibility than traditional magnetic contrasts, such as

gadolinium. Other advantages of using MNPs in cancer diagnosis include; they are nontoxic, biocompatible and affordable.

Magnetic particle imaging (MPI) is proposed as a new imaging tool to overcome the limitations of CT, MRI, and SPECT by employing the magnetization response of SPIO nanoparticles to generate a tomographic image. The image is characterized qualitatively by high spatial resolution that is comparable to that of CT image, and high sensitivity as good as PET image.

ii. Drug delivery

In magnetically targeted therapy, a cytotoxic drug is attached to a biocompatible MNP carrier. These drug/carrier complexes-usually in the form of a biocompatible ferrofluid, are injected into the patient via the circulatory system. When the MNPs have entered the blood vessel, high-gradient magnetic fields are externally applied to concentrate the drug or carrier compound at a particular target site within the body. Gene delivery has been done using viral or non-viral carriers for the past two decades. However, their use has some limitations and severe side effects. MNPs are non-viral tools, complemented with DNA, plasmids or interfering RNA for gene transfer.

Chomoucka *et al*. (2010) reviewed the parameters influencing drug delivery efficiency and functionalization of MNPs for targeted drug delivery. Constraints such as the physiochemical properties of the drug-loaded MNPs, field strengths and geometry, depth of the target tissue, rate of blood flow and vascular supply, all play a role in determining the effectiveness of the drug delivery.

iii. Immunoassay

An immunoassay is a biochemical investigation used in a wide field of biotechnology measurement, e.g. for the detection of pathogens and cancer cells, DNA gene analysis, detection of environmental toxins, and immune response. The immune response is obtained by measuring the binding reaction between a particular bio-substance to be measured, referred as antigen, and the diagnostic reagent that selectively bind to that antigen, applied as an antibody. Immunoassay relies on the ability of the antibody to recognize and bind a specific antigen to measure the type and amount of the antigen in vitro.

Magnetic immunoassay is a novel type of diagnostic immunoassay using the magnetic marker as label instead of other conventional labels. This assay involves the particular binding of an antibody to its antigen, where a magnetic label is conjugated to one element of the pair. The presence of magnetic beads is then detected by a magnetic reader that measures the magnetic field change induced by the beads. The signal measured by the magnetometer is proportional to the analyte quantity in the initial sample.

iv. Hyperthermia

MNPs have been used significantly in cancer therapy, particularly in magnetic target hyperthermia. Hyperthermia is a type of medical treatment of localized heating the body tissue to 42-46°C using MNPs to kill or damage tumor cells. This is achieved by injecting nanoparticles into a target site and the exposed to a magnetic field. The nanoparticles convert the electromagnetic energy into heat, thereby heating the target tissues without affecting other nearby tissues. Huang and Hainfeld (2013) carried out research on intravenous magnetic nanoparticles cancer hyperthermia. MNP was injected intravenously to the target tumor areas to achieve tumor concentration of 1.9mgFe/g tumor in a sub-cutaneous squamous cell carcinoma mouse model. With the applied field of 38 kA/m at 980 kHz, the tumor cells were heated at 60°C in 2 minutes and were ablated with millimeter precision, without affecting surrounding tissues.

There are many types of MNPs products that have been developed for biomedical applications: Resovist® (Fujifilm RI Pharma), EndoremTM (Guerbet S. A.), Feraheme®(AMAG Pharmaceuticals), Nanotherm®(MagForce Nanotechnologies) etc. Instead of some are already commercially available on the market for clinical use. However, majorities of them are remaining at the development level.

The ongoing research is directed towards monitoring events on the physiological and molecular level so that inflammatory diseases or tumors can be detected via the accumulation of SPIONs or markers expressed on the cell surface.

CURRENT STATUS OF MPI SYSTEM

FIELD FREE POINT (FFP)

Field Free Point (FFP) is a precise position created when a gradient magnetic field is applied to MNP sample and superimposed on the selection field, generated by the selection or balancing coil. At FFP, the majority of the particles in space are saturated such that only particles in the close vicinity of the FFP respond when the applied magnetic field changes. To speed up the imaging process, one just has to break the rule that the FFP has to stay within an image voxel during one measurement. Instead, by increasing the excitation field amplitude, the FFP is moved back and forth along a line in the direction of the field vector of the excitation field.

FIELD FREE LINE (FFL)

Field Free Line (FFL) is similarly created like the FFP, by superimposing the field from the drive coil on the magnetic field generated by the selection field coils, which are not static but rotates with a particular frequency f_s. This frequency f_s is much lower than the excitation frequency of the drive coil. Therefore, FFL trajectory is

produced by the dynamic rotation of the magnetic field from the selection field.

Besides FFP imaging, Weizenecker *et al.* (2008), introduced a coil arrangement to generate an FFL that promises a higher sensitivity due to particle contribution along a line. Initially, the setup consisted of 32 coils and was unfeasible to realize. In 2010, Knopp *et al*. picked up the idea, developed techniques to generate an FFL with just eight coils and presented an efficient FFL reconstruction based on the Fourier Slice Theorem. Continuously, new MPI approaches are being shown that are related to frequency space and x-space MPI, such as narrowband MPI and traveling wave MPI (Cole, Yang, and David, 2011).

The first difference between FFP and FFL is the shape of the field-free region, i.e., the area in which SPION tracer particle contribute to the acquired signal. For FFP is a circular point while for FFL is a straight line. The second difference is that the selection field for FFP is a static while for FFL requires a rotation of at least 180 degrees.

IMAGE RECONSTRUCTION

According to the literature, there are three techniques for MPI signal reconstruction. The most published procedure is harmonic-space MPI, which uses a *system matrix* that is comprised of the Fourier components of the temporal signal for every possible location of a point source. Reconstruction is achieved through regularization and matrix inversion techniques such as singular value decomposition or algebraic reconstruction. This inversion can be complicated since the size of the *system matrix* is large and contains millions of elements. The second technique is a narrowband technique, which reconstructs harmonic images into a composite image using a modified Wiener deconvolution. The third method is x-space reconstruction. X-space offers several advantages over harmonic-space MPI matrix reconstructions. Specifically, x-space MPI is experimentally proven to generate Linear Shift-Invariant (LSI) images, as well as real-time image reconstruction speed as it involves only division by a scalar to reconstruct each point in the picture. Importantly, x-space MPI makes no attempt to deconvolve the MPI signal to improve resolution at the resolution determined by the physics of the nanoparticles and field gradient, and thus avoids the significant noise gain of deconvolution.

Buzug *et al*. (2012) described the frequency-based image reconstruction approach and the corresponding imaging devices as well as other alternative concepts like x-space MPI and field-free line imaging (FFL). Additionally, Goodwill et al. introduced a reconstruction principle in the time domain, called x-space MPI. Within the hypothesis of consistent magnetic fields, i.e. assuming a linear shift-invariant system, and conventional in the Langevin theory of paramagnetism a correlation between FFP position and induced voltage signal can be created and direct reconstruction becomes possible. The most significant advantage of x-space MPI is the omitted system matrix such that a scanner dependent calibration process is no longer necessary. Although deconvolution is not essential, it most likely improves image quality.

PROPOSED MPI SCANNER

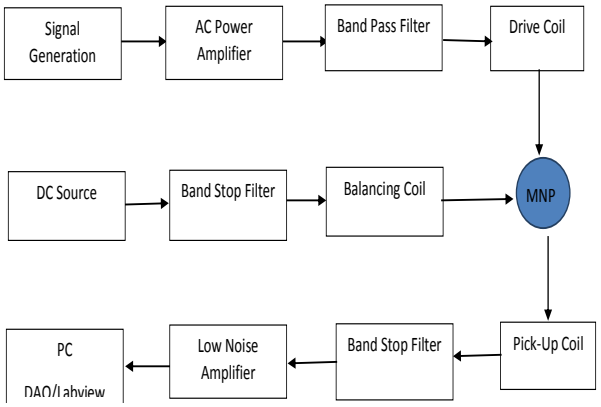

Figure-2. Proposed MPI Scanner.

The block diagram of the proposed scanner is as shown in Figure-2. The drive field signal is generated by a signal generator. The signal then passes a power amplifier for appropriate field generation. Because even high linear amplifiers generate harmonic distortions, a band pass filter is used to keep the signal on the coils clean. For this purpose, a third order Butterworth or Chebycheff II filter may be applied (Tanaka, Murata, Oishi, Suzuki, and Zhang, 2014). To obtain a purely sinusoidal signal the filter needs to be of high quality. The magnetic field generated can be described as:

$$H = hI. \quad (4)$$

Where h is the sensitivity profile of the magnetic field well-defined by the coil geometry, and I is the current. To achieve a high magnetic field strength, another magnetic field is produced by the balancing coils and superimposed on the generated drive field. This will create a field free point, where only the drive field will have an effect on the MNPs. Since the drive field signal combines into the balancing field coils, band stop filters are required to protect the DC source against the induced AC voltage. The particle magnetization changes depending on the actual resulting magnetic field, which produces a voltage signal in a receiver coil. Additionally, the received signal passes through another band stop filter to damp the fundamental frequency, which couples directly into the pick-up coil. Then the signal has to be amplified to match the dynamic range of the data acquisition hardware to achieve the highest possible resolution. The image of the

MNPs tracer is then reconstructed with the harmonics signals obtained from the low noise amplifier.

CONCLUSIONS

MPI is a promising new modality that has a lot of potential for diagnostics as well as therapy. It can be utilized to perform a quantitative detection of magnetic tracer materials based on superparamagnetic iron oxide with high temporal and spatial resolution. An overview of MPI and a proposed scanner which will be used to diagnose cancer is presented. The proposed MPI scanner will be realized by designing and constructing each component of the block diagram shown. FFP technique is going to be employed in the implementation due to its simplicity, and a harmonic space MPI reconstruction method is going to be adapted. Finally, Resovist nanoparticle will be used as a tracer material and the sample will be prepared and experimented in-vitro, where the sample mixture containing SPIONs, cancer cells, and healthy cells will be inserted into a cell culture flask.

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REFERENCES

Bringout, G., and Buzug, T. 2014. Coil Design for Magnetic Particle Imaging: Application for a Pre-clinical Scanner. IEEE Transactions on Magnetics. 9464(c), 1-1. doi:10.1109/TMAG.2014.2344917.

Buzug, T. M., Bringout, G., Erbe, M., Gräfe, K., Graeser, M., Grüttner, M., Lüdtke-buzug, K. 2012. Magnetic particle imaging : Introduction to imaging and hardware realization. 22, pp. 323–334.

Chomoucka, J., Drbohlavova, J., Huska, D., Adam, V., Kizek, R. and Hubalek, J. 2010. Magnetic nanoparticles and targeted drug delivery. Pharmacological Research. 62, pp. 144-149.

Cole, A. J., Yang, V. C., and David, A. E. 2011. Cancer theranostics: the rise of targeted magnetic nanoparticles. Trends in Biotechnology. 29(7), pp. 323–32. doi:10.1016/j.tibtech.2011.03.001.

Gleich B. and Weizenecker, J. 2005. Tomographic imaging using the non-linear response of magnetic particles. Nature. 435(7046), pp. 1214–1217.

Hathaway, H. J., Butler, K. S., Adolphi, N. L., Lovato, D. M., Belfon, R., Fegan, D., Flynn, E. R. 2011. Detection of breast cancer cells using targeted magnetic nanoparticles and ultra-sensitive magnetic field sensors. pp. 1–13.

Huang, H. S. and Hainfeld, J. F. 2013. Intravenous magnetic nanoparticle cancer hyperthermia. Internationa Journal of Nanomedicine. 8, pp. 2521-2532.

Ishihara, Y., Honma, T., Nohara, S., and Ito, Y. 2013. Evaluation of magnetic nanoparticle samples made from biocompatible ferucarbotran by time-correlation magnetic particle imaging reconstruction method. BMC medical imaging. 13(1), 15. doi:10.1186/1471-2342-13-15.

Issa, B., Obaidat, I. M., Albiss, B. a, and Haik, Y. 2013. Magnetic nanoparticles: surface effects and properties related to biomedicine applications. International journal of molecular sciences. 14(11), 21266-305. doi:10.3390/ijms141121266.

Knopp T. 2011. Effiziente Rekonstruktion und alternative Spulentopologien für Magnetic-Particle-Imaging. Vieweg+Teubner.

Miller, A. D. 2013. Lipid-Based Nanoparticles in Cancer Diagnosis and Therapy.

Morishige, T., Mihaya, T., Bai S., Miyazaki, T., Yoshida, T., Matsuo, M. and Enpuku, K. 2014. Highly sensitive Magnetic Nanoparticle Imaging using Cooled-Cu/HTS-Superconductor Pickup coils. IEEE Transaction on Applied Superconductivity. 24 (4). pp 105-109.

Othman, N. B. 2014. Magnetic Nanoparticle Imaging for Biomedical Applications. IEEE Transaction on Magnetics.

Othman, N. B., Tsubaki, T., Yoshida, T., Enpuku, K. and Kandori, A. 2012. Magnetic Nanoparticle Imaging Using Harmonic Signals. IEEE Transaction on Magnetics. 48 (11), pp. 3776-3779.

Pantic, I. 2010. Magnetic Nanoparticles in Cancer Diagnosis and Treatment : Novel Approaches. 26, pp. 67–73.

Rosen, J. E., Chan, L., Shieh, D.-B., and Gu, F. X. 2012. Iron oxide nanoparticles for targeted cancer imaging and diagnostics. Nanomedicine : Nanotechnology, Biology, and Medicine. 8(3), pp. 275-90. doi:10.1016/j.nano.2011.08.017.

Sosnovick, D. E., Nahrendorf, M. & Weissleder, R. 2008. Magnetic Nanoparticles for Magnetic Resonance Imaging: agents, techniques, and cardiovascular applications. Basic Res Cardiol. 103 (2). pp 122-130.

Tanaka, S., Murata, H., Oishi, T., Suzuki, T., and Zhang, Y. 2014. 2D magnetic nanoparticle imaging using magnetization response second harmonic. Journal of

Magnetism and Magnetic Materials. pp. 1-5. doi:10.1016/j.jmmm.2014.10.005.

Wadajkar, A. S., Menon, J. U., Kadapure, T., Tran, R. T., and Yang, J. 2013. Design and Application of Magnetic-Based Theranostic Nanoparticle Systems. pp. 47–57.

Weizenecker J, Gleich B, Borgert J. Magnetic Particle Imaging (MPI), Journal of Physics D: Applied Physics. 41(3), pp. 1-6.

Yan, H., Guo, M., and Liu, K. 2006. Multifunctional Magnetic Hybrid Nanoparticles as a Nanomedical Platform for Cancer-Targeted Imaging and Therapy.

Yoshida, T., Othman, N. B., Tsubaki, T., Ogawa, K. and Enpuku, K. 2011. Detection of Magnetic Nanoparticles using the Second-Harmonic Signal. IEEE Transaction on Magnetics. 47 (10). pp 2863-2866.

Yoshida, T., Othman, N. B., Tsubaki, T., Takamiya, J. and Enpuku, K. 2012. Evaluation of Harmonic Signals for the detection of Magnetic Nanoparticles. IEEE Transaction on Magnetics. 48 (11). pp 3788-3791.