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# A mixing-frequency magnetic particle imaging system for high-throughput in-vivo imaging

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**Abstract**

A mixing-frequency magnetic particle imaging (MPI) system is presented for high-throughput in-vivo studies. Coprime AC magnetic fields at 4.98 kHz and 97 Hz produce a field-free-point (FFP) scan in the $x$–$y$ plane, which drive the MNPs to generate rich high-order harmonics and mixing-frequency components. All the mixing-frequency spectra of the MNPs are measured for image reconstruction. Phantom experimental results demonstrate the spatial resolution better than 1.5 mm at gradients of 0.64 T/m ($x$) and 1.28 T/m ($y$), and a limit of detection of 34.9 µmol/L Fe (≈195 ng Fe). A scanning coil enables the 3D imaging speed of 0.5 min. A in-vivo murine study of cerebral blood-flow (CBF) imaging was acquired within a 30×30×30 mm$^3$ FOV with clear delineation of anatomical structures. The mixing-frequency spectra-based approach combines hardware cost-effectiveness with good imaging performance, indicating strong potential for tumor diagnosis, cerebral perfusion, and longitudinal drug monitoring.

## I. Introduction

Magnetic particle imaging (MPI) enables quantitative spatial mapping of magnetic nanoparticles (MNPs) by utilizing their nonlinear magnetization dynamics in alternating magnetic fields, providing a radiation-free imaging modality[1-4]. The mixing-frequency MPI approach drives the field-free point (FFP) with coprime AC magnetic fields, producing faster scanning along the $x$-direction and slower scanning along the y-direction to generate a dense, non-uniform trajectory[5]. The resulting MNP response contains high-order harmonics and abundant mixing-frequency components, all of which are measured and used for image reconstruction. This approach achieves a favorable trade-off between imaging performance and hardware complexity: with roughly half the hardware effort of conventional Lissajous-based trajectory, comparable imaging performance can be maintained. An MPI system was developed based on this approach, and sub-1.5 mm spatial resolution and a limit of detection (LOD) of 34.9 µmol/L Fe (≈195 ng Fe) were achieved in phantom experiments.

This work presents a 3D mixing-frequency MPI system capable of acquiring volumetric images of a 30×30×30 mm$^3$ FOV in approximately 0.5 min, suitable for both phantom and murine studies. Cerebral blood-flow (CBF) imaging demonstrates the system's high-throughput in-vivo performance, supporting potential use in tumor diagnosis, perfusion assessment, and longitudinal drug monitoring.

## II. Methods and materials

The mixing-frequency MPI system uses orthogonal drive coils ($f_H$ = 4.98 kHz, $f_L$ = 97 Hz) and a permanent-

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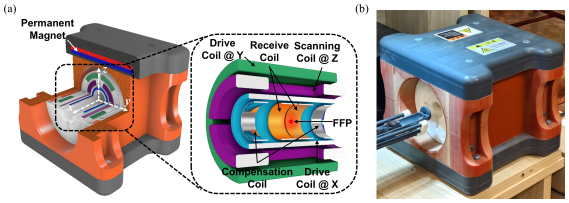


**Figure 1:** (a) The schematic and (b) the photo of the scanner of the mixing frequency MPI system.

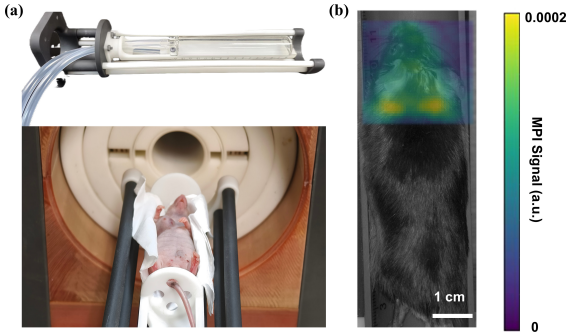


**Figure 2:** (a) The animal bed assembled with isoflurane-based inhalational anesthesia. (b) The reconstructed CBF image of utilizing the mixing-frequency MPI.

magnet gradient assembly to produce a dense, non-uniform FFP scan in the $x$–$y$ plane; 3D volumetric coverage is obtained by a slow $z$-bias via a scanning coil (see Figure 1(a) and (b)). A receive coil with low noise preamplification captures the nonlinear MNP magnetization. The analog signals are digitized and demodulated into complex mixing-frequency spectra at frequencies of $mf_H \pm nf_L$, where $m = 2,\ldots,26$, $n = -12,\ldots,+12$. A system matrix was built by mechanically moving a dot MNP sample within the FOV with a 1 mm step and was used for image reconstruction.

Based on the mixing-frequency MPI system, continuous 2D imaging at 1 frame/s and 3D volumes in $\approx 0.5$ min were supported. Image reconstruction was performed by algebraic reconstruction technique (ART) implementing Tikhonov regularization. Maximum-intensity projection (MIP) was used for visualization of volumetric datasets. In-vivo CBF imaging was performed following tail-vein injection of long-circulating synomag®-D (Surface: PEG 25.000-Ome, micromod GmbH, Germany).

## III. Results and discussion

The CBF imaging followed tail-vein administration of a fivefold-diluted MNP solution (300 mL) in a C57BL/6 mouse. An animal bed was employed to provide stable isoflurane-based inhalational anesthesia and to minimize respiratory motion artifacts during CBF acquisitions (see Figure 2 (a)). 5 min after the MNP injection, the head region of the mouse is measured and the reconstructed 3D CBF image is visualized by MIP (see Figure 2 (b)). Reconstructed CBF maps resolve vascular features that align with anatomy: bilateral common carotid arteries in the neck and paired intracranial arteries are discernible. The reconstructed CBF demonstrates the system's capability for sensitive, repeatable tumor monitoring and noninvasive cerebrovascular mapping.

## IV. Conclusion

The mixing-frequency MPI system enables high-throughput 3D in-vivo imaging with reliable performance. The CBF imaging delineated the major vascular structures under stable isoflurane anesthesia, which highlights the system's potential for preclinical tumor diagnosis, cerebral perfusion assessment, and longitudinal drug monitoring.

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## Author's statement

Conflict of interest: Authors state no conflict of interest. Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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