Localization of Microscale Devices *In Vivo* using Addressable Transmitters Operated as Magnetic Spins

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Introduction: The function of microscale wireless medical devices such as capsule endoscopes, biosensors and drug delivery systems depends critically on their location inside the body. However, existing electromagnetic, acoustic and imaging-based methods for localizing and communicating with such devices are limited by the physical properties of tissue or imaging modality performance. Here, we introduce a new approach based on concepts from MRI. We hypothesized that by designing microscale devices whose output frequency could shift with the magnetic field, they could be localized, read out and controlled with MRI-like precision (Fig. 1a). To test this concept, we developed a prototype device using a standard CMOS process. Because it operates analogously to magnetic spins, we call this technology addressable transmitters operated as magnetic spins (ATOMS).

Materials and Methods: The ATOMS chip was placed in a PCB for *in vitro* experiments and in the tip of an encapsulated 4 mm shaft for *in vivo* experiments. A transmit/receive coil was used to send the RF pulse and to pick up the chip's response. The magnetic field was generated by an NdFeB permanent magnet. A small incision of 1.5 cm was done into the skin of the shoulder area of an anesthetized mouse to insert the microchip following approved IACUC procedures. The chip's response was measured for 5 min per location, at a total of 4 locations.

Results and Discussion: The prototype chip was fabricated in a standard 180 nm CMOS process and occupies an area of 1.8 mm × 1.2 mm (Fig. 1b). We performed an *in vitro* 2-D localization experiment where two permanent magnets were used to apply magnetic field gradients in two different directions. Adding and removing one magnet at a time allowed us to apply a sequence of two field gradients, analogous to the design of pulse sequences in MRI. We tracked the location of an ATOMS chip while translating it in space to write the letters C, I, and T. The three letters can be clearly identified (Fig. 1c), with a localization error of less than 250 µm. To establish the feasibility of ATOMS technology within the context of *in vivo* biological tissue, we localized our ATOMS device following subcutaneous implantation in an anesthetized mouse. We moved the chip to four different locations on a single axis and recorded its response. The power spectral density of the received signals exhibited four different peaks corresponding to the target locations (Fig. 1, d-e), with a localization error of less than 500 µm (Fig. 1, f-g).

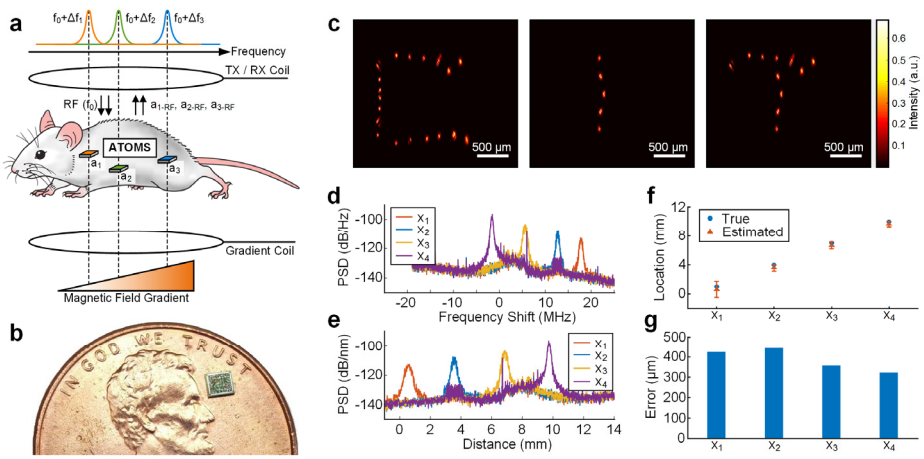

Figure 1. (**a**) ATOMS are microscale devices capable of encoding their position inside a magnetic field gradient in their oscillation frequencies. (**b**) Picture of the ATOMS chip. (**c**) *In vitro* 2-D localization results. (**d-g**) *In vivo* localization results. (**d-e**) Frequency Shift-Location mapping, showing the power spectral density of the received signal as a function of (**d**) frequency shift and (**e**) distance. (**f**) Estimated and true position, and (**g**) localization error of the experiment. N=32. Error bars represent ± s.e.m.

Conclusions: Our results establish the concept of microscale silicon devices mimicking the physical behavior of nuclear spins to enable their localization inside the body, and provide a proof of concept by localizing a device smaller than 0.7 mm^3 *in vivo* with sub-millimeter precision. The ATOMS technology combines the benefits of highly sensitive RF receivers with the simple spatial encoding offered by magnetic field gradients. The integration of ATOMS with microscale biological sensing and actuation technologies will enhance the development of a wide range of biomedical applications, from distributed localized monitoring of biologically relevant biomarkers to targeted release of therapeutic agents and tissue imaging for disease diagnosis.

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