Design of Novel Synthetic Antiferromagnets for Nano-RF reporters for Single Cell Tracking

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Purpose: The current generation of gadolinium based MRI contrast agents used for enhanced T1 contrast and superparamagnetic agents used for T2 contrast, suffer from several problems. Gd contrast has decreased relaxivity at increasing field strengths and has toxicity issues. T2 agents have negative contrast and, even with their relatively large relaxivities, require many agents for visibility. Better positive contrast agents are needed to give large enhancements with a small number contrast agent (or a single agent) at clinical fields for applications such as tracking single cells (i.e. cancer or stem cells). Here we present the development of novel T1 contrast agents nanofabricated with lithographic techniques which are engineered to have large-moment fluctuation modes that correspond to proton resonances at clinical field values.

Theory: The goal is to design nanoresonators with frequencies that match the proton resonance. Here, we use patterned magnetic thin film stacks that are antiferromagnetically coupled by nonmagnetic interlayers. These particles are referred to as nano synthetic antiferromagnets (nano-SAFs). While ferromagnetic resonances are typically at high frequencies ($\gamma_e = 28$ GHz/T), some of the antiferromagnetic resonances can be at low frequencies when the exchange fields compensate the applied fields. The magnetic response and mode structure of a two-layer nano SAF, calculated using the stochastic Landau-Liftshitz-Gilbert equation, are shown in Fig. 1. The particles have no moment at zero field and become aligned at a saturation field, whose value is determined by the strength of the exchange coupling. At the saturation field, the optic or scissoring mode goes to zero frequency and has a large spectral weight at MRI frequencies. At resonance, these nanofabricated agents will have large moment fluctuations, leading to large field fluctuations around the particle and, we anticipate, a strong T1 relaxation. This mechanism can then be tuned to match any clinical field strength. These nanoagents can operate in two modes: 1) utilizing thermal fluctuations to drive the resonant modes, which requires small nanoagents (<50 nm) or 2) RF driven relaxation where off-resonance pulses are utilized to excite the nanoagent resonance.

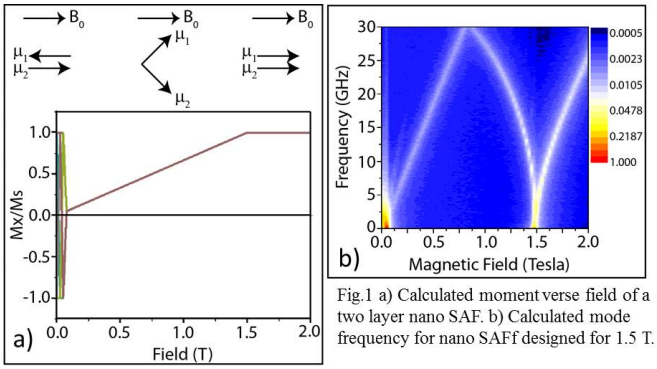


Fig.1 a) Calculated moment verse field of a two layer nano SAF. b) Calculated mode frequency for nano SAFf designed for 1.5 T.

Methods: The nanoagent design, shown Fig. 2a, consists of a sputter deposited stack of cobalt/iron ($Co_{0.9}Fe_{0.1}$) and ruthenium (Ru) bilayers that are repeated up to 20 times on an oxide-coated 400 μm thick silicon wafer. The Ru layer creates a strong antiferromagnetic coupling between the CoFe layers causing them to anti-align at zero field. The layer thicknesses were adjusted to provide a range of interlayer coupling strengths and saturation fields to match the desired scanner field. The magnetic response and resonance structure were studied with magnetometry and ferromagnetic resonance, which provided feedback to fine-tune the nano-SAF properties. Thin film stacks were then patterned by photolithography and ion beam etching, as shown in Fig. 2b. The particles were placed on a 2 μm square grid with 25 x 10^4 particles per mm^2. 10 mm x 20 mm dies were cut: half covered with nano-SAFs and half left blank.

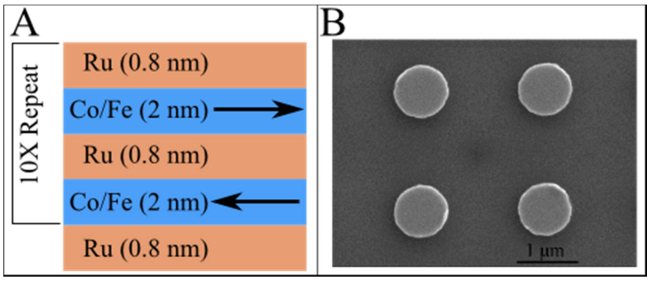
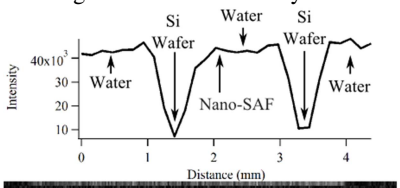


Fig. 2 a) nano-SAF layer structure optimized to obtain a saturation field of 1.5T. b) Patterned nano-SAFs with 830 nm diameter.



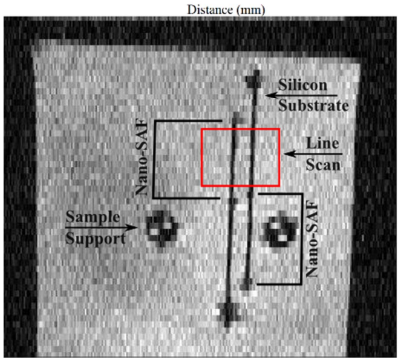


Fig. 3 GRE image of two silicon dies. There are nano-SAFs on the facing surfaces with the opposite surface left blank. The line scan shows the signal through a rectangular ROI shown in red.

Results: Two nano-SAF dies were imaged (Fig. 3) on a preclinical scanner at 1.5 T (the scanner can be operated at variable fields from 0.5 to 7 T) with a GRE sequence with TE= 5.6 ms, TR=25.5 ms, 256 averages. The voxel size was 625 x 156 μm with the smaller dimension along the direction perpendicular to the wafer plane. The ends of the nano-SAF arrays show a dark feature due to T2 contrast. There is little T2 contrast above the array since the magnetic field is channeled through the array and only diverges at the edges. The sequence was chosen to saturate long T1 components, and only give signal from the short T1 components. No additional signal was observed on the silicon faces with the nano-SAFs, indicating that strong T1 relaxation was not present.

Discussion: Initial nano-SAF agents were fabricated with 830 nm diameter. The fluctuations scale inversely with the volume of the magnetic material, and we conclude that the current nanoagents are too large to provide the requisite fluctuations for enhanced T1 contrast. While it is possible to differentiate the areas of patterned media from bare silicon wafer, the desired effects have yet to be observed. New generations are in production with smaller diameters and with asymmetric structures to allow RF excitation. In conclusion, a new class of contrast agents is being developed with dynamic properties specifically tuned to give enhanced T_1 relaxivity at desired magnetic field strengths. Further development of the agents is progressing to realize their potential as a T1 based single cell tracking agent.