In Situ Magnetic Relaxation Localization and Hydrogel Coating of a Nanomaterial Biosensor Device for Continuous Biochemical Surveillance

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Statement of Purpose: Implantable diagnostics hold the promise of continuous sentineling of chemical data in patients. While sensing modalities have been proposed in the optical, magnetic, and electrochemical regimes, the challenges of *in situ* localization, robust data storage, on-demand signal transfer/access, and long-term compatibility with the local tissue environment remain to be solved. Our advances in nanomaterial medical devices have validated a functional, dosimetric implant for the measurement of biomarkers using a magnetic particle assay platform[1,2]. Exposure to target induces a switch from a dispersed to an assembled state with a corresponding change in magnetic relaxation properties allowing for contrast. In our current applications within chronic cardiac disease, we sought to characterize the permeability of biomaterial stealth coatings designed to improve the interaction with subcutaneous tissue. We also sought to develop and compare novel localization algorithms for transferring sensor data from implanted devices encased in a heterogeneous, challenging environment. This study forms the foundation of the *in vitro* validation necessary to achieve multi-month implantation *in vivo*.

Methods: Polyclonal anti-Myoglobin antibodies were conjugated to aminated cross-linked dextran superparamagnetic iron oxide nanoparticles (20 nm) by maleimide-thiol chemistry (Figure 1a). Proton Magnetic Relaxation measurements (T_2) were acquired on a custom, single-sided, single-voxel inhomogeneous field relaxometer (0.43 Tesla, 25°C, NMR MOUSE) with a programmable robotic scanning stage[3]. Sensor depots (center pocket) and fiduciary end-caps were filled with aqueous colloidal particle suspensions and sealed with 30 nm pore semi-permeable membranes and Delrin sheets (0.076mm), respectively. Device dimensions ranged from 24.6x8.6mm down to 12.1x6.1mm (Figure 1b,c). Kinetics of sensor functionality with varying agarose or alginate hydrogel layers were used to derive permeability values for coated devices. Device localization methods by T_2 NMR (in phantoms of varying heterogeneity) with custom MATLAB analysis routines (2 parameter-1 exponential average fitting, fixed parameter T_2 pinning, and regularized inverse laplace transform T_2 spectra) were compared for reproducibility, speed, and accuracy.

Results: Fiduciary marker end-caps enhanced localization of sensor material by maintaining a constant T_2 value substantially lower than surrounding proton populations. Fiduciary marker location and centered sensor T_2 values were successfully extracted in the presence of a 2%v/v Agarose phantom (Figure 1d). 2 parameter-1 exponential average fitting proved to be the fastest yet least robust localization method for heterogeneous

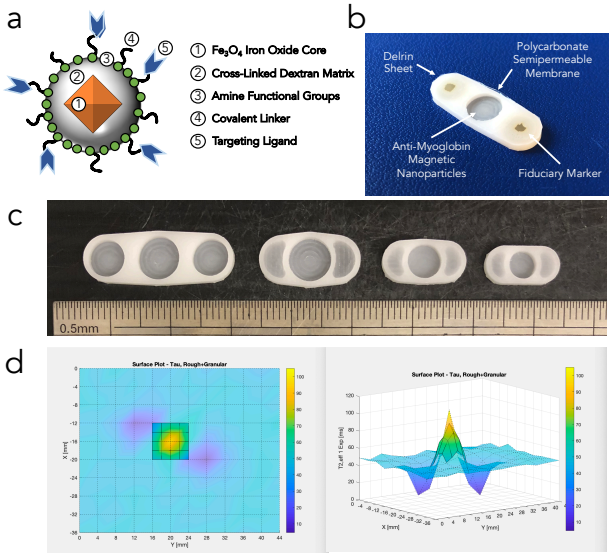

Figure 1: (a) Structure of layered 20 nm iron oxide-dextran particles with anti-Myoglobin binding ligand; (b) Nanomaterial sensor design with fiduciary end caps; (c) Varying device size allows for custom applications and sensitivity levels; (d) T_2 NMR localization of device embedded within 2%v/v Agarose phantom. Granular, centered scan (4x4 box) overlaid on quick device localization scan (background) using fiduciaries to find device within 36x44 mm area.

environments. Regularized inverse laplace was limited by SNR constraints of the NMR sensor as well as the dependence on a smoothing parameter. Fixed parameter T_2 pinning balanced robust sensor data access with scanning speed. Scan algorithm optimization resulted in localization within a 24x24mm area in <4 minutes. Permeability results of agarose and alginate hydrogel coatings showed that the biocompatible coatings did not significantly affect sensor device performance.

Conclusions: *In situ* diagnostics offer continuous tracking of critical biomarkers, providing a deeper understanding of local biology in dynamic, heterogeneous systems. The development of a custom NMR search algorithms has the potential to broaden implantable diagnostics in personalized medicine by addressing the hurdle of localization in complex environments. Prior to this study, the main methods to extract T_2 sensor data from implanted dosimetric devices were expensive MR imaging or large sensor depots in precisely-known, superficial implant locations. This work advances the use of implanted biosensor devices in environments they are designed to sentinel, coated with materials intended to bridge the medical device-tissue interface.

References: [1] Daniel KD, Biosens Bioelectron. 2009; 24:3252-3257. [2] Ling Y, Nat Biotechnol. 2011; 29:273-277. [3] Blumich B, Magn Reson Imaging. 1998; 16:479-484.