Microfabricated MRI pH microsensors

Gary Zabow[1,2], Stephen Dodd[1], and Alan Koretsky[1]

[1]LFMI, NINDS, National Institutes of Health, Bethesda, Maryland, United States, [2]Physical Measurements Laboratory, NIST, Boulder, Colorado, United States

Introduction: Recently introduced multi-spectral, or multi-"color", contrast agents based on engineered magnetic microparticle shapes rather than on chemical molecular structures, have suggested new routes to enhanced MRI agent functionality [1, 2]. An example of such increased functionality is the prospect of transforming such micro-engineered agents into localized physiological microsensors. Since the micro-engineered agents' NMR spectral signatures, or frequency shifts, are geometrically determined, a structure that could dynamically vary its shape in response to a local physiological condition, could function as a localized sensor. Although this possibility was first suggested several years ago [1], here the first actual realization of such a microengineered NMR sensor is introduced, demonstrating, as an example, a pH-sensing agent. Preliminary NMR data is presented showing the pH microsensor agents' ability to differentiate between pH levels as well as the potential to tune the agents' sensitivity.

Methods and Results: The pH-sensing contrast agents are based on the double-disk multi-spectral agent design [1], whose induced frequency shift on water passing between the agent's pair of magnetic disks depends on, among other properties, the spacing between those disks. The double-disk agents used were produced through conventional top-down microfabrication techniques; to achieve dynamic in-situ variation of the disk spacing, however, the mechanical posts separating the magnetic disks were made from an expandable hydrogel [3]. The gel was based on a poly(ethylene glycol)dimethacrylate (PEGDMA) polymer backbone and made pH-sensitive by incorporating various fractions of methacrylic acid into the gel. In basic solutions, the incorporated acid's release of H^+ ions leads to a net charging and associated repulsive expansion of the gel; in acidic solutions, charging is reduced and the polymer gel elastically contracts. Accordingly, as the surrounding solution pH changes, the changing disk spacing modifies the magnitude of the offset magnetic field generated between the disks, yielding an NMR offset frequency shift, or agent "color", that changes proportionally to surrounding pH (see schematic in Fig. 1) in a continuous and reversible manner. Figure 2 shows a scanning electron micrograph of an array of microfabricated agents; because the microfabricated agents have dimensions on the micron to sub-micron scale with hydrogel posts diameters measuring only a few hundred nanometers, gel response times are expected to be in the millisecond regime or below, providing real-time response. To demonstrate tuning of agent sensitivity and confirm the specifically pH-dependent behaviour, two sets of pH-sensing agents were made: one with relatively low acid fraction incorporated into the hydrogel, which should lead to relatively small pH-dependent changes in NMR offset frequency shift, and one with a relatively high acid fraction, which should yield larger gel expansion and associated frequency changes. Preliminary results from arrays of such double-disk hydrogel agents are shown in Figs. 3 and 4, which show z-spectra derived from a series of magnetization-transfer pulse sequences acquired at different offset frequencies from agents submerged in water-based solutions of different pH's. The variation in the structures' offset magnetic resonance frequencies demonstrate the expected pH-sensitivity.

Conclusion: A new form of microfabricated agent, with the capacity to sense in-situ pH levels, has been introduced. Although z-spectra linewidths are presently large due to microfabrication defects, future work should narrow linewidths allowing dectection of smaller changes in structure. Since hydrogels can also be sensitized to many other physiological conditions and enzymes [3], the sensors suggest a route to increased MR functionality.
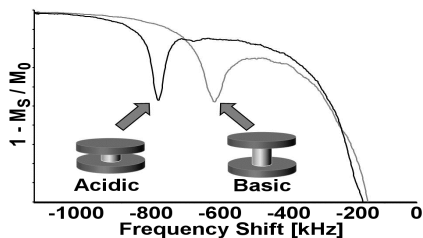

Fig 1. Schematic of sensor operation. Gel contracts at low pH increasing frequency shift and expands at high pH, reducing frequency shift. Z-spectra show offset frequency resonance through dip in normalized signal $1 - M_S/M_0$, where M_0 is original signal, and M_s the fraction saturated out by set of off-resonant $\pi/2$ pulses.
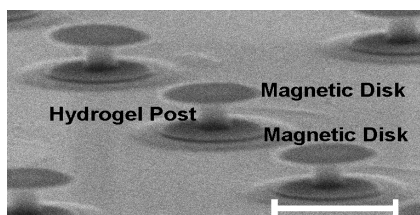

Fig. 2 SEM of array of microfabricated hydrogel-based multispectral pH sensors. Disks are 70 nm thick, with a radius of 900 nm. Scale bar is 2 μm.
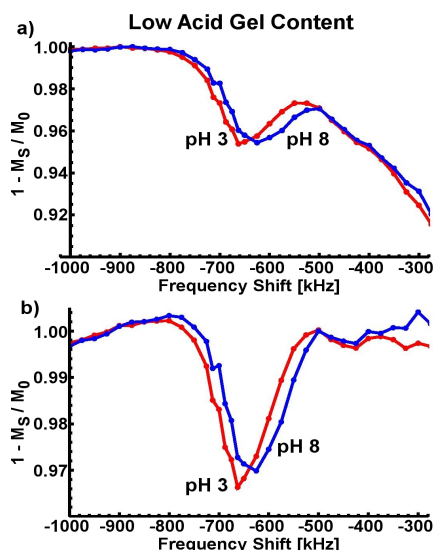

Fig 3. Low-acid-content pH sensor. a) Raw z-spectra data for array of sensors submerged in pH 3 and 8 buffers. b) To aid the eye, approximate background subtracted spectra from (a). Frequency shift changes by about 40kHz between pH 3 & 8.
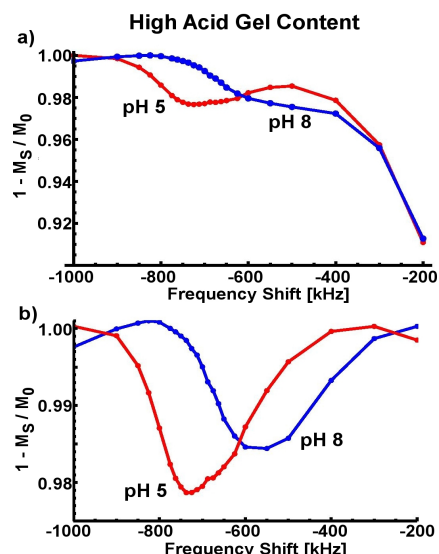

Fig 4. High-acid-content pH sensor. a) Raw z-spectra data for sensor array submerged in pH 5 and 8 buffers. b) To aid the eye, approximate background subtracted spectra from (a). Frequency shift changes by about 200kHz between pH 5 & 8.

References:
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(3) Gil E.S. & Hudson S.M. *Prog. Polym. Sci* **29**, 1173-1222 (2004)