Micro-NMR and Nanoparticle Amplification for Bio-Agent Detection

LABORATORY DIRECTED RESEARCH & DEVELOPMENT

Sandia National Laboratories

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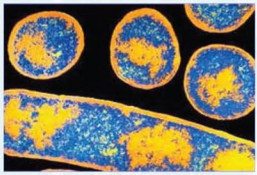
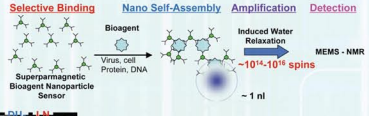
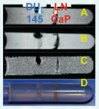
Problem - Goal

- Development of micro-NMR with nanoparticle amplification for non-optical bio-agent sensor.
- Develop and test different micro-NMR detection coils for performance and ease of fabrication.
- Optimize and miniaturize detection platform to produce portable and rugged sensor system.
- Botulism present target involving Botulinum neurotoxins (BoNT).
- Rare but serious paralytic disease that can lead to respiratory failure and death.
- BoNT's easily produced with high lethality, one of the most toxic substances known.
- Dispersion an issue as witnessed by the Japanese cult Aum Shinrikyo attempted spraying of aerosols three times without success.
- Recent Botulism events.



Technical Approach – Nanoparticle Amplification

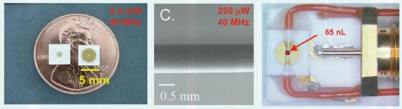




Prostate Cell Antigen Tag

- Spin relaxation basis used in MRI.
- Targeted contrast agents – antibody specific.
- Direct detection towards miniature NMR system.
- Optimized detection volume (~ 100 nl).
- Generalized detection scheme, <3 hour analysis.
- Bio-selectivity through antibody/nanoparticle complex

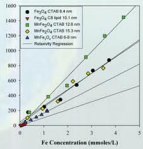
Micro-NMR Coil Development

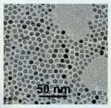


- Testing and optimization of two detection platforms. Flat micro-coil based on conventional LIGA technology (with through via connects) and a horizontal micro-coil etched directly on metal coated capillary using FIB.
- S/N performance similar, while horizontal coil gave superior excitation profile.
- Flat coil design pursued based on ease of fabrication, and future integration with micro-fluidics.
- Frequencies and power levels for both systems very low and at 40 MHz. Cell phone technology: easily allows further miniaturization and commercialization.

Results – SPION Synthesis

SPION – Superparamagnetic Iron Oxide Nanoparticles

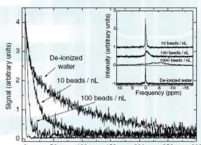


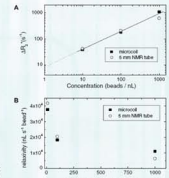


Polymer + Streptavidin

- NMR relaxation linear with concentration.
- R_1 (= $1/T_1$) and R_2 (= $1/T_2$) will be dependent on particle size and composition.
- R_1 and R_2 have different responses as a function of size, frequency and temperature. 40 MHz (1T) optimal range for T_2* effects.
- Non-specific! Need something to assure bio-agent identification.

Micro-NMR Coil SPION Detection

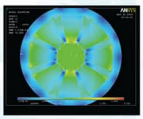


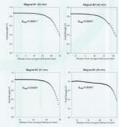


Sillerud *et al.* "1H NMR Detection of Super Paramagnetic Nanoparticles at 1T Using a Microcoil and Novel Tuning Circuit", Journal Of Magnetic Resonance (2006) *181*, 181-190.

- Initial demonstrated the ability to detect 10 SPIONs per nl, has been extended to 1 SPION in 7 nl!
- These relaxation changes were observed both for the Micro-NMR (1T) and larger sample coils.
- Limiting factor is the observed line width – field inhomogeneity on magnets with10- 60 mm gap.
- Need to improve field by a factor of 10 to observe the 1 SPION per nl.

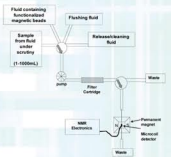
Approach – Micro-NMR Magnet Development

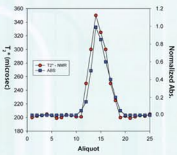




- Sandia recently designed and fabricated a 1 Tesla Octapole Halbach magnet based on NdFeB permanent magnets.
- Active volume is ~500 microns.
- Magnet is 47 mm tall, weights about 0.5 kG.
- Field mapping in progress. Homogeneity still undetermined.
- Targets the goal to reduce micro-NMR instrument size (magnet is a major component of total size) below the "coffee cup" size.
- Portable device!

Initial Column Integration





- Separation and preconcentration of bio-agent based on attachment to antibody modified column.
- These agents are then tagged with antibody/SPION complex, followed by release into micro-NMR system.
- BoNT A testing underway. Release from column distinctly identified by dramatic change in T_2.

Significance

- Have demonstrated fabrication of micro-NMR device with ~ 65 nL detection volume. Single scan S/N ~ 200:1.
- Have demonstrated that a single SPION particle (in 7 nL) can be detected via nano-particle amplification of water NMR relaxation.
- Have demonstrated that specific bio-agents can be detected using antibody modified SPIONs.
- Non-optical detection platform usable in opaque and high scattering media (milk, blood, effluent)
- System could be coupled to other detection systems.
- Easily combined with existing micro-fluidic platforms.
- A portable system – magnet weight is – 0.5 kG, cell phone technology.
- Generalized detection scheme for a variety of bioagents.
- Botulism testing presently in progress (UNM – BLIII).
- Miniaturized NMR could have other application in industrial process monitoring, including in-line chemical and solution analysis.

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