Bead-based Multiplexed, Orthogonal BW/ID (BioWarfare/Infectious Disease) Detection Microsystem and Technologies

LDRD
LABORATORY DIRECTED RESEARCH & DEVELOPMENT

Sandia National Laboratories

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Problem and Introduction

Rapid CBN-Isotope Identification
in Raw Samples Using with a Portable Detection Platform

Sandia has been developing a concept for a detector system promising ultra high sensitivity chemical detection, biological, nuclear (e.g. Pu, U) and isotope discrimination in a portable, modular package. Utilizing quantum-dot embedded, magnetic-core beads as a concentrator for multiplexed detection. Combining chemical sandwich assays, nucleic acid hybridization assays, as well as Purex/Urex chemistry (in collaboration with Argonne National Labs) for actinide, lanthanide, and fission product identification, we can obtain high sensitivity and specificity for CBN threats. Concentrated samples can then be injected into mass analyzers for isotopic measurements.

Key Questions

- Benefit to the user?
- How does this affect day in life of first responder or WMD locator employee?
- How long to detect?
- How sensitive?
- How specific?
- What is the technology?
- ROC curve (receiver operating characteristic)?
- What are critical issues?
- What might it look like?
- How long until deployment?

System Level Concepts

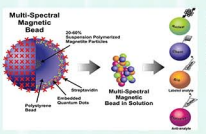
Potential Concepts of Operation

Benefits

- Multiplexed
- Integrated Sample Handling and Preparation
- Sample Preservation
- Chemical and Isotope ID
- Fast
- Portable
- Sensitive
- Adaptable to many sample types
  - Airborne (particles)
  - Liquid
  - Swipe

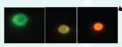
Approach and Basic principles of the technology:

- A magnetic core-quantum dot bead
- A concentrator
- A sandwich assay and optical chemical detector platform
- And mass analyzer (e.g. RGA, IMS)

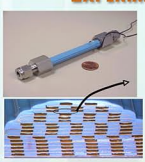


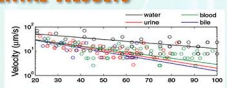
The bead is a capture and carry chaperone -- it is used as a "handle" to grab and move targets (which are small and hard to manipulate and visualize) to various locations (preconcentrator, detector, etc.)

Quantum dots embedded in beads (means of barcoding)



Experimental Results





Demonstrating trapping for capture of beads in various media.

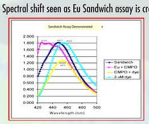
Top picture: Concentrator (Magnetic Trap)

Bottom Picture: Velocity at input vs distance to capture. close up of channels inside trap

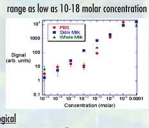
Proof-of-Concepts and Preliminary Data

Sensitivity

Spectral shift seen as Eu Sandwich assay is creat4eed in solution



Linear response over wide concentration range as low as 10-18 molar concentration



Chemical and Biological

Double-Blind Study w/ Botulinum surrogate in Raw Milk

- No false Positives
- approximately 87% sensitivity and 100% specificity

Experimental Results cont.

Nuclear

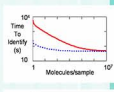
- Eu sandwich assay observed in solution
- Two stage detection: Positive/negative result for analyte presence
- Experience suggests actinide, lanthanide, fission products can be specifically, sensitively detected

current ptototype

Limitations - Modeling

Predicting System Performance

Variation in system performance for small molecules (e.g. Botulinum or Plutonium) with respect to the sample size. 1ml (blue) and 1 L sample (red) using 2x104 beads. This figure represents system performance envelopes expected in water/urine samples



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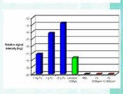
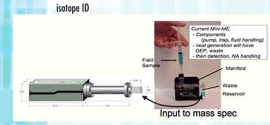


Isotope Identification

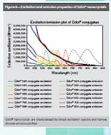
Integrating the bead platform to a commercial mass analyzer (e.g. residual mass analyzer, MS, or IMS) for isotope ID



Multiplexing Limits

$(3^1)\text{-}1 + (4^1)\text{-}1 = 6560 + 65535 = 72,095$ combinations if we get 8 bits dynamic range

$(3^1)\text{-}1 + (4^4)\text{-}1 = 728 + 4095 = 4823$ combinations if you play it conservative (There's a lot of detection details that goes into whether you can realize 8 bit dynamic range -- we just don't have enough information yet to tell)



Time Budget

30min assay today

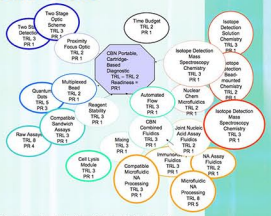
10min/assay October

Automated<10min

Components and Risks

Component	Maturity	Risk
Beads	2	Fab/multiplexing
Assays	8	Common fluidic platform adaptation; building off huge prior investments
Mixing	5	Development
Automation	5	Development
System	3	Development
Size	4	tbd
Countrate	5	Modeled
Power	4	tbd
Optics	5	development
Nucleic Acid Handling	4	Others do it.
Cell lysis	5	Many ways
Stability Air Coil	5	Not begun; WESP has 30 year history

Technology Readiness Level (TRL) Estimates, Product Readiness(PR) Level Assessments for the Portable CBN Module [no isotope, no environmental]
(color codes are roughly meant to represent disciplines
Line thickness roughly correlates to technology maturity for this application)



- Example of how final product readiness is influenced by both an assessment of product readiness (PR scale) and inclusion of technologies with immature technology readiness assessments (TR scale)
- The product is at the lab demo stage, so is its product readiness is PR1 by definition
- The inclusion of multispectral magnetic bead technology, which is at the research stage, also limits the product readiness to a PR1 level.

Significance: Technology meets multiple near-term national security needs

Many approaches are being developed to detect and identify chemical/biological agents. However, they all fall short of meeting first responders' needs because they are slow and only identify one potential threat at a time. The audacious goal of this project is to develop the technologies necessary to create a detector capable of simultaneously identifying from a single sample a vast number of different agents: chemical, biological (bacterial proteins and viral DNA/RNA), and radionuclides. The potential impact on first responders is clearly revolutionary.

There have been two patent applications and 15 Technical Advances filed to-date. There has been one paper accepted for publication in a prestigious journal and two more are in preparation. There have been numerous conference presentations and invited talks, including one to the OSTP subcommittee on CB WMD.

The project has already attracted supporting funding to advance beyond the scope of LDRD funding. A small amount of funding from the Dairy Milk Institute and UC Davis supported successful field testing in Tulare. In FY 2007 DTRA funded the continued development of the radionuclide assay and more support will come in FY 2008. At least five contacts from industry have been received inquiring about commercializing the technology.

Sandia is a multiprogram laboratory operated by Sandia Corporation, a Lockheed Martin Company, for the United States Department of Energy's National Nuclear Security Administration under contract DE-AC04-94AL85000. SAND2007-5994C CreativeArts 98429.LWB.07

NNSA National Nuclear Security Administration

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