μChemLab™: Hand-Portable Microanalytical Instrument for BioAnalysis

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Sandia’s interest started in biodetection with our national security mission

- **Objective:** Develop miniature, low cost chemical analysis systems for national security applications
  - First responders
  - Facilities monitoring
- **Target:** The full spectrum of CB agents
- **Requirements:**
  - Rapid detection for detect-to-warn
  - Low power for field use
  - Low false alarm rate
  - Little or no consumables
  - Adaptable to new threat agents
- **Funding start:** Internal Sandia LDRD (1996)
- **Major program sponsors:** DOE Chemical and Biological National Security Program and Dept. of Homeland Security
The µChemLab Program has seen tremendous growth over 8 years.

Start (1996)

- SNL LDRD
  - Chem-explosives Detector
- Tenix/CH2M Hill
  - Biotoxin detection in water
- DHS
  - Biotoxin & Virus Detector

Today (2005)

- DOE CBNP
  - Proof of concept device
  - Biotoxins
- NIH
  - Oral Diagnostics
- DoD
  - Modular Chem-Bio Detector
  - Bacteria
- • Second generation device
  • Viruses
Instrumentation for chemical analysis is built for the lab not the field

- Agilent Capillary Electrophoresis System
- Waters Capillary Liquid Chromatography System
- Caliper Chip-Based System
Portable biodetectors are now becoming commercially available

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<th>Example Systems</th>
<th>Detection Technology</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td><strong>RAZOR</strong> (Idaho Technologies)</td>
<td>PCR</td>
<td>- Hand-held, 6-9 lbs&lt;br&gt;- Very sensitive&lt;br&gt;- 6-12 samples/30 min&lt;br&gt;- Can detect viruses &amp; bacteria</td>
<td>- Cannot detect toxins&lt;br&gt;- Expensive reagents&lt;br&gt;- Manual sample prep (kit or cartridge)&lt;br&gt;- 30 min cycle time&lt;br&gt;- 5 runs/battery</td>
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<td><strong>Bio-Seeq</strong> (Smiths Detection)</td>
<td>Antibody</td>
<td>- Can detect toxins, viruses, bact.&lt;br&gt;- Hand-portable, 14 lbs&lt;br&gt;- Sensitive&lt;br&gt;- 10-15 min&lt;br&gt;- No sample prep</td>
<td>- Expensive reagents&lt;br&gt;- Must replace coupon after positive result or fouling&lt;br&gt;- 8 hr continuous use/battery&lt;br&gt;- 4 simultaneous assays</td>
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<tr>
<td><strong>RAPTOR</strong> (Research International)</td>
<td>Chemical Separations</td>
<td>- Can detect toxins, viruses, bact.&lt;br&gt;- Hand-held&lt;br&gt;- No expensive reagents&lt;br&gt;- Sensitivity (w/ preconcentration) comparable to Ab assay&lt;br&gt;- 10-15 min</td>
<td>- Sensitivity, specificity still unknown in real samples</td>
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**μChemLab** (SNL prototype)
Ab and PCR methods require molecular recognition event for detection

- Only see what you have primers or antibodies for
- These reagents can be expensive

Antibody-based detection (sandwich assay):

- Amplification
- No amplification
- Fluorescence threshold
- Detected
- Not Detected

PCR detection:

- Time
- Detected
- Not Detected
Chemical separations enable detection of unknowns

- Unique signatures are created from a pattern of separation times
- Signals are matched to a database
- Even if the signature isn’t in the database, may still be able to gain useful information
  - e.g., molecular weight, charge, hydrophobicity
  - What it is like
  - What it is not like
μChemLab uses a proteomics-based approach for bio agent detection

**Toxins**
- 1-10 nm
- Protein or small molecule
- May have variants

**Viruses**
- 50-200 nm
- 1-50 proteins
- May have host specific proteins

**Spores**
- 1 μm
- 50+ proteins
- Vary in copy number

**Bacteria**
- 1-3 μm
- 2000-5000 proteins
- Protein content dependent on growth conditions

**Approach:**
- Direct detection of protein toxins
- Detection of pathogens by their protein signatures
Protein detection uses two separation methods for improved detection reliability.

Separation based on charge/mass ratio:

1) CZE

Separation based on mass:

2) CGE
Microfluidic methods are much faster than traditional protein separation/detection methods.

- **Informative**
- **Time Consuming (Hrs to Days)**
- **Difficult To Reproduce**

- **Not as Informative as 2D**
- **Fast (less than 10 minutes)**
- **More Reproducible**
Microfluidic chip performs nanoliter sample analysis in 5-10 minutes
The MicroChemLab instrument has the ability to detect and distinguish toxin variants. Analyses were performed at the Defense Science and Technology Laboratory, Porton Down, UK.
Sandia’s approach: Think about the whole system

Application Space
- Solution is broadly applicable

User Requirements
- Low power
- Semi-continuous operation

MicroFluidics
- Optimized chip designs
- Fluid delivery

Control Software

High Sensitivity Detection

Miniature Power Supplies

We cover the full spectrum: from fundamental microfluidics to biochemistry to engineered solutions
μChemLab contains everything necessary to perform an analysis

We use this instrument now as flexible, reliable platforms for routine laboratory R&D

- Hand portable
- Battery operated
- On-board data analysis

- Modular packaging
- Two analysis modules

- Electrode Plate
- Reservoir Cartridge
- Liquid Manifold
- Microchip
- Fluorescence Detector

High Voltage Board

Microchip
Modular design enables straightforward component replacement & upgrades

- Sample prep module
- Separation module
- Syringe pump
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Increasing complexity
Signatures for a broad range of viruses demonstrates the ability of \( \mu \text{ChemLab} \) to identify these pathogens.

- Testing at USAMRIID and SNL
- Related pathogens exhibit distinct signatures

**Alphaviruses**
- VEE - Venezuelan equine encephalitis
- EEE - Eastern equine encephalitis
- WEE - Western equine encephalitis

**Flavivirus**
- JE - Japanese encephalitis virus

**Bunyavirus**
- VSV - Vesicular Stomatitis virus

**Other viruses**
- Vacinnia
- RSV
- Epstein-Barr
- T2, T4, T6
- MS2

*CGE data*
Viral analysis requires more sample prep than for biotoxins.
Sample Prep Breadboard Hardware

- Peristaltic pump
- Stepper drivers
- Flow-switching valve
- Syringe pump (x4)
- 50 uL syringe
- DEP chip
- SPE Cartridge
- Lyser heater
- Fused silica capillary

Approximate size: 8 inches x 12 inches
Automated, modular “front-end” sample processing system for μChemLab demonstrated

- Integrated system functions:
  - Uptake from sample vial
  - Mixing with buffer
  - Particle lysing to release proteins
  - Protein labeling w/ fluorescent dye
  - Injection into μChemLab followed by analysis and detection
  - System purging/prep for next sample

Red: Fluorescence from sample as it moves through system
Black: Fluorescence signature of detected proteins