Development of a Field-Portable Time-of-Flight Mass Spectrometer System

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APL has developed and demonstrated a miniature time-of-flight (TOF) mass spectrometer that can identify biological warfare agents. Its small size and low power consumption make the miniature TOF mass spectrometer an ideal candidate for field applications, overcoming limitations of the current generation of biodetection systems. Portable applications require additional features such as ruggedized packaging, battery-powered electronics and data acquisition, automated sample collection, and automated signal processing and control software. In this article we describe the design of a TOF mass spectrometer system that incorporates these capabilities and integrates supporting technologies under development. Design goals include short analysis times (<5 min), high sensitivity, wide agent bandwidth, portability, low power consumption, minimal use of fluids, unattended operation, and automated detection and classification.
(Keywords: Biodetection systems, Time-of-flight mass spectrometer.)

BACKGROUND

The Miniature Time-of-Flight (TOF) Mass Spectrometer Program is a 3-year Advanced Technology Demonstration jointly funded by the Defense Advanced Research Projects Agency (DARPA) and the Defense Threat Reduction Agency Chem/Bio Directorate. Two major objectives of this program are the demonstration of a TOF mass spectrometer system suitable for use on the battlefield to protect forces and rapid transition of this technology to the warfighter. Although this initial application focuses on battlefield (stationary, point detection) applications, the TOF mass spectrometer technology developed in this program provides a basis for developing systems to support counterterrorism, domestic preparedness, law enforcement, and low-cost/low-power systems for remote standoff applications. In this article we describe the development of a prototype TOF mass spectrometer system that is suitable for field applications and show its current status. Other articles in this issue describe particular aspects of the TOF mass spectrometer technology used here.

Currently deployed biodetection systems are severely limited owing to low sensitivity, limited agent bandwidth, and slow response. For example, immunoassay systems that sense the binding of an antibody with a

target agent typically require 20–30 min to identify a biological agent and are limited to detecting only those agents for which an antibody is available. The biological detector used in the Army's Biological Integrated Detection System has several limitations. First, the system is limited to the detection of only eight of the many known potential threat agents. Second, it requires the storage and replenishment of perishable reagents.

The program described in this article will demonstrate the ability to use TOF mass spectrometer technology to overcome these and other limitations. Design goals include short analysis times (<5 min), high sensitivity, wide agent bandwidth, portability, low power consumption, minimal use of fluids, extended unattended operation, and automated detection and classification.

During the first year of this program (FY97), efforts were focused on developing system requirements and concepts and selecting and evaluating technologies for further refinement. Basic technology selections included air sampling and particle capture methods, laser and optics technology, mass analyzer design, vacuum interface concepts, and signal processing. Laboratory efforts focused on identifying specific simulant mass spectral biomarkers used for evaluation. Sample preparation for mass spectral analysis traditionally involves a skilled technician and requires extensive use of fluids, making the techniques difficult to automate. As various design alternatives are considered, a high level of coordination between system design and laboratory activities is essential to ensure that the methods developed in the laboratory can be translated to the field-portable system.

The FY98 follow-on effort focused on developing and demonstrating each of the TOF mass spectrometer subsystems and testing major system interfaces such as sample vacuum interface, high-speed data acquisition, automated sample collection, sample processing, and signal processing algorithms. Key accomplishments of the FY98 systems engineering effort included the following:

- Demonstration of the "end-to-end" process of sample collection through automated identification
- Development of system requirements for the TOF mass spectrometer
- Development of a transition plan
- Completion of a conceptual design review

One of the most important aspects of the FY98 effort was the verification that laboratory sample preparation techniques could be translated into an automated fieldable technique using minimal amounts of fluids. While we are continuing to improve the efficiency of acquiring spectra from our dry collections, demonstration of the feasibility has enabled a fundamental shift in biodetection technology away from traditional techniques based on "wet chemistry."

SYSTEM OVERVIEW

Figure 1 is a conceptual diagram of the TOF mass spectrometer system under development. Air is drawn into a collector that separates particles in the range of 0.5–10.0 μm from the airflow and deposits them onto a movable tape. After collection is completed, the tape transports the sample into the TOF mass spectrometer analyzer. A microsprayer may then add small amounts of MALDI (matrix-assisted laser desorption/ionization) matrix to the sample to increase sensitivity. (The use of MALDI for biodetection is described in the article by Scholl et al. elsewhere in this issue.) A laser then ionizes the sample, and the resulting mass spectrum is analyzed for specific biomarkers that indicate the presence and identity of a biological agent. One advantage of this approach is the minute volume of fluids required for sample processing, eliminating the need for large storage reservoirs, stationary and level mounting configurations, or large power-hungry heating and cooling systems.

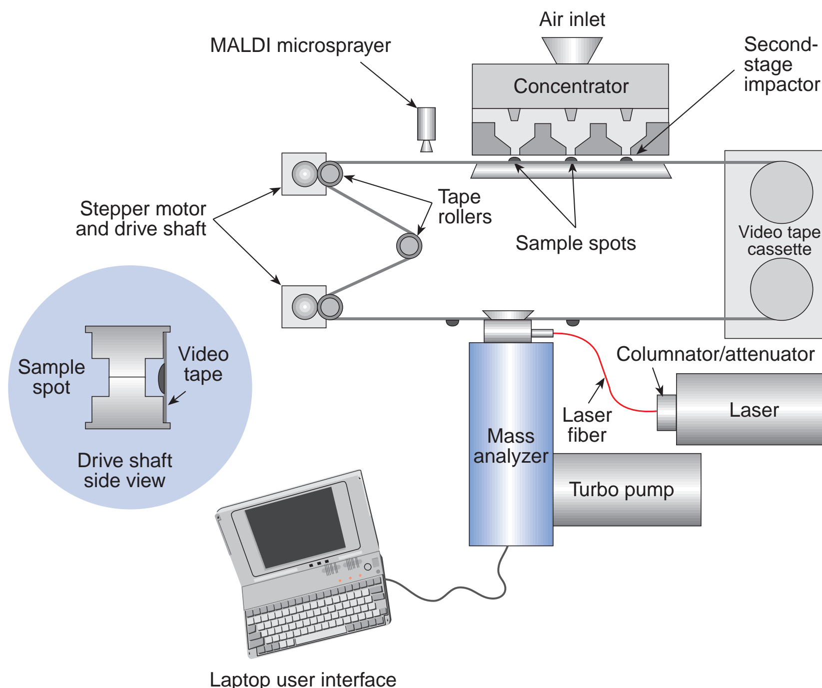

Figure 1. Fieldable time-of-flight mass spectrometer biodetection system.

Multiple samples are collected concurrently, allowing both the application of different analysis protocols and the archiving of samples for later confirmatory analysis.

Figure 2 illustrates the system configuration under development. The sample subsystem consists of a VHS tape cassette controlled by several stepper motors. The tape is positioned both inline with an array of four impaction nozzles and at the inlet to the mass spectrometer. Power, electronics, blowers for air collection, an ultraviolet laser, and data acquisition and processing electronics are located underneath. In the remainder of this article we discuss efforts to develop the tape drive, laser and optics, vacuum interface, ruggidized TOF mass spectrometer, electronics, and software components of the system.

To rapidly detect biological agents at these low concentrations, the air collection system must have high throughput and high collection efficiency to obtain a sufficient number of particles for detection. Because for some pathogens (such as *Yersinia pestis*, the causative agent of plague) inhalation of a single organism can result in infection, the system must be able to detect concentrations on the order of 10 cells or spores per liter of air. The air sampling subsystem includes an impactor to separate particles from the airflow and a tape drive to transport and position the tape (see the article by Anderson and Carlson, this issue).

TAPE DRIVE SYSTEM

A proof-of-concept design of the tape drive mechanism used commercially available VHS tape players. Current designs incorporate the basic concepts contained in commercially available units while simplifying and ruggedizing many of the components for military applications. This approach eliminates the variability between commercial models or components and simplifies field service. For example, the tape interface plate uses a simple snap-down approach to loading the tape, eliminating many of the in-and-down mechanisms and components featured in commercially available units.

The tape drive uses commercially available stepper motor drivers to position the tape. Current designs include a three-axis stepper motor driver to control three different motors independently. One motor positions the tape in the aerosol collector, the second positions a sample in the mass spectrometer vacuum interface, and the third is used to load the tape. Movement is accomplished by pinning the tape between a rubber-coated roller and a grooved drive shaft. The shaft actually drives the rubber rollers using the friction created between the two materials. The grooved shaft makes contact with the rubber roller both above and below the tape without contacting the sample location (see Fig. 1). The groove prevents any possible contamination between samples. As the drive motors turn, a motor attached to the tape interface plate provides tension to the reel while moving forward or back along the length of the tape. A single motor mounted directly below the tape cassette uses two opposing unidirectional couplings to operate both the left and right reels for tape take-up. This eliminates the need for dual motors or complex mechanisms such as those found in commercial units. Elimination of motors and actuators significantly lowers the power requirements of the system, reducing the size as well as increasing its portability.

A tape loop between two of the stepping motors permits the portion of the tape on the analyzer side of the system to be moved independently of the portion on the sample side. This provides the ability to analyze several spots on the tape without interrupting the collection process. The loop isolates the activities between the aerosol collection and spectrometry operations, preventing any potential fouling or slipping of the tape. The design has been maximized for flexibility in operation and in consideration of the transition to manufacturing. Once the system design is tested and optimized, many currently available "options" may be removed to further reduce size, power, weight, and cost.

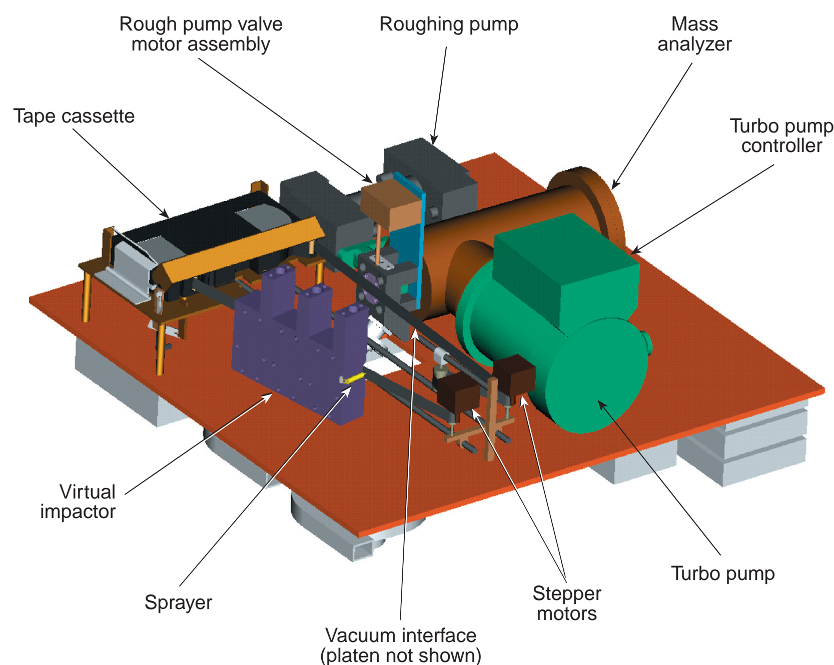

Figure 2. Current system configuration.

VACUUM INTERFACE

Introduction of a sample to the mass analyzer requires repeated breaking and restoration of a high-vacuum seal as each tape sample is repositioned over the sample port. It would take many tens of minutes to restore the mass analyzer chamber to a high vacuum if the whole chamber were exposed to the atmosphere. The vacuum interface for this system reduces the vacuum pump loading by isolating the main vacuum chamber from the sample port around the tape sample when samples are being changed, while it provides a clear passage for the ions during the measurement. The interface consists of a seal between the sample tape held by a platen and a port to the external ionization grid, shown in detail in Fig. 3. Before the tape is positioned, a closed high-vacuum ball valve isolates the large chamber containing the mass spectrometer analyzer from the small volume containing the external ionization grid. During measurements of mass, the ionization grid acts as a ground plane electrode in parallel to a high-voltage electrode located in the platen behind the sample tape. The grid consists of a screen that allows the sample to be illuminated by an ionizing laser beam. When the laser ionizes the sample, an electric field between the electrodes extracts and accelerates the ions toward the mass analyzer. The external grid assembly contains an auxiliary port that connects to a vacuum fore-pump, which evacuates most of the air trapped in the ionization grid before the main high-vacuum valve opens. Bench tests have shown that we can restore vacuum within 30 to 40 s after closing the platen, and helium leak tests of the tape seal have consistently measured less than 10^{-7} cm^3/s, well within the capability of the turbo pump to maintain microtorr vacuums.

LASER AND OPTICS

The portable mass spectrometer system uses a 300-μJ pulsed ultraviolet laser in the ionization process. The output of this laser is focused onto a circular spot between 0.5 and 1.0 mm in diameter. The energy density delivered is variable between 20 and 80 mJ/cm^2. As a result of mechanical considerations associated with a portable and rugged device, the laser power is delivered via a fiber-optic transmission channel.

The fiber-optic transmission channel consists of four main components: the output coupler, the power attenuator, the optical fiber, and the focuser. The output coupler is a series of lenses that focuses the 5 × 7 mm beam produced by the laser into the optical fiber core (see Fig. 4). Power coupling efficiency varies from 20% to 90%, depending on the lens configuration and size of the fiber core. A large-diameter multimode or specialized fiber core has a much greater ability to accept higher power than a small-diameter single-mode optical fiber core. The mass spectrometer uses a 100-μm optical fiber core, with a projected input power coupling efficiency of 80%. This selection represents a good compromise between coupling efficiency and the fiber flexibility needed for packaging.

In addition to the output coupler, the mass spectrometer incorporates a commercially available variable attenuator controlled by a stepper motor for varying the output power (Fig. 4). The attenuation range is continuously variable from 0 to 30 dB. The attenuator contains a variable position screw, which is adjusted by a stepper motor to partially block the output beam prior to the coupling optics. In the TOF mass spectrometer optics, the attenuator and laser output coupler have been combined into a single device.

The focuser consists of a variable position biconvex lens. The sample to be ionized is constrained to a fixed distance from the focuser. The magnification of the

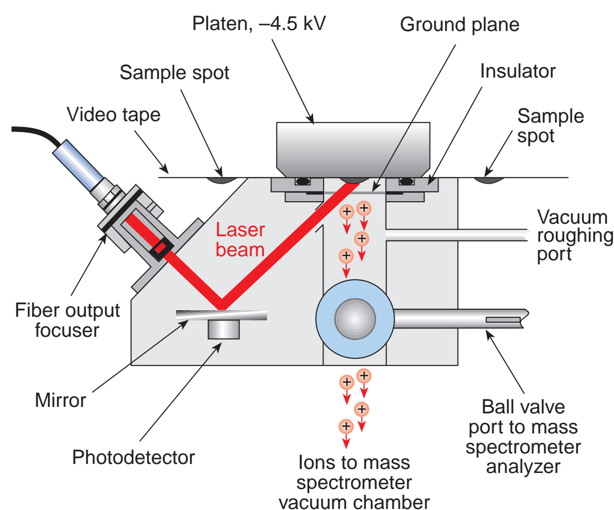

Figure 3. Ionization grid vacuum interface.

Figure 4. Laser-to-fiber delivery system.

focuser is nominally 6.5 at 76.0 mm. The output spot has a nominal diameter of 0.65 mm as a result of the size of the fiber core and the distance of the core from the focusing lens. The output spot diameter can be easily focused from 0.5 to 1.0 mm. The focuser will be customized to allow computerized focusing.

The optical fiber used for the mass spectrometer is a fused silica multimode fiber with a 100-μm core and 140-μm cladding. This optical fiber is commercially available with industry standard FC/PC-type optical connectors on both ends. Both the attenuator and focuser are also provided with FC/PC connectors. The multimode fiber was chosen to maximize the power transmission. The output beam pattern of a multimode fiber from a highly coherent light source is not Gaussian, as is the case for a single-mode fiber. The beam pattern is a time- and position-varying "speckle" pattern that depends on the number of propagating modes. The large number of propagating modes will most likely minimize any problems associated with this effect. The exact beam patterns produced will be analyzed further using a beam profiling system.

ANALYZER DESIGN

The heart of the system shown in Fig. 2 is the TOF mass spectrometer analyzer described in this issue by Cornish and Bryden. The TOF mass spectrometer has been redesigned to fit in the ruggedized vacuum housing shown in Fig. 5. The housing uses piston-type O-ring seals for the end cap and ISO-NW flanges for the access ports, thereby providing highly reliable sealing of the vacuum chamber. The external housing is made of 304 stainless steel; the internal support structure shown in Fig. 6 is made of polycarbonate. The polycarbonate serves as an insulator between charged plates found in the reflector and was selected for its excellent impact strength, ease of machining, low cost, and relatively low outgassing properties. All materials are compatible with common disinfectants such as formaldehyde. The sample exchange pump-down time is minimized by adopting a cylindrical design with as little internal volume as possible.

The reflectron is made up of 31 circular plates with a 3.3-cm-diameter hole through the center to allow ions to travel through the reflector. Slots in the rails hold these plates in place with the rails positioned 90° apart. The plates step down in equal voltage steps starting at 6000 V on the plate farthest from the reflectron detector to ground for the plate nearest the reflectron detector. Between each plate is a resistor to step down the voltage. The resistors are held in place on the top and bottom rails via resistor stocks. The rails also include cutouts that act like springs. These "springs" make contact with the inside of the vacuum chamber to ensure a snug fit over a wide temperature range. The end of the cylinder has a flange with a bolt hole pattern for connecting the end cap, which contains all the electrical feedthroughs. Five of these feedthroughs are welded in place, with four carrying high voltages (6, 8, and 10 kV). Four other feedthroughs are double-ended SMA type, which are isolated electrically from the chamber via polycarbonate inserts. The SMAs and inserts are glued in place using a low-outgassing epoxy sealant. Two SMAs are used to carry signals from each of the detector plates, and two SMAs control the ion gate.

Careful consideration was given to many aspects of the analyzer design to ensure that virtual leaks caused by gas trapped between tightly fitting components are minimized. Fusion welds are used to eliminate the introduction of outgassing materials, such as sulfur, that could be introduced from weld rods. The feedthroughs are fusion welded to the end cap for sealing and sturdy construction, and are placed to avoid arcing between

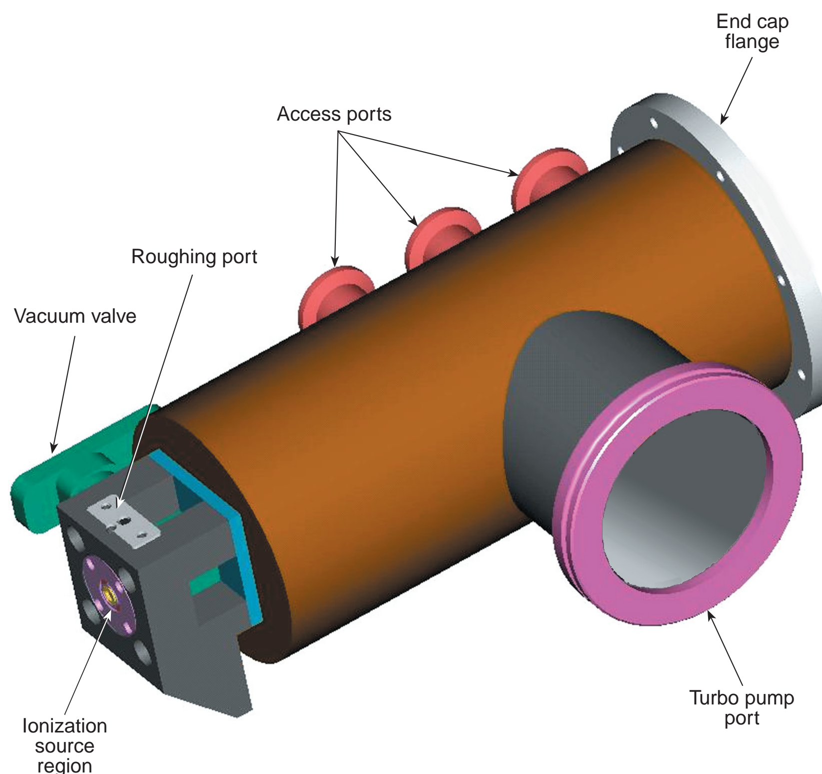

Figure 5. Grid ionization valve and vacuum chamber.

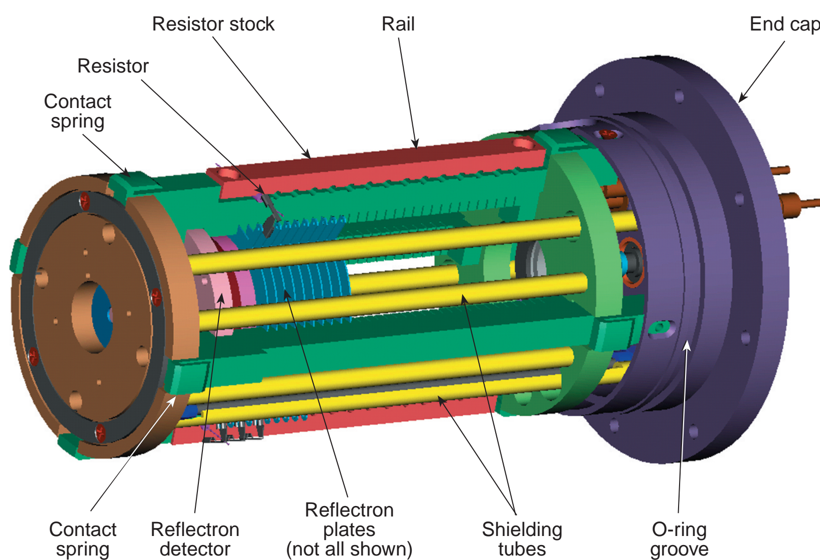

Figure 6. Internal mass analyzer configuration.

components internal and external to the vacuum. Stainless steel shielding tubes are used to prevent high-voltage feeds from affecting the ion flight paths and to reduce noise in the signal lines. Tight tolerances are maintained to prevent virtual leaks.

Because of the complexity of the design, a fused deposition model (FDM) was made of various iterations of the design to help find design flaws and to better communicate the design concept to others. The FDM machine is a cost-effective tool for building models of less than 25 cm in two of three axes. With minimal programming, the machine runs automatically, thus reducing labor. The FDM uses ABS plastic thread, available in various colors, that is laid side by side and melted together to form an approximately 0.025-cm-thick layer. The machine builds one layer at a time, melting each layer together as it builds the part vertically. Parts constructed with this process are currently being used for benchtop testing of the mass analyzer.

SOFTWARE AND SIGNAL PROCESSING

Software control of the analyzer consists of four functions: data acquisition card control, motor control, data processing, and the user interface. For initial developmental efforts, MATLAB and LABView were used for the graphical user interface and control, respectively, facilitating the rapid testing of critical system components. A switch to the C programming language was made for several reasons, including speed, cost, and robustness. C is inherently faster than MATLAB and LABView and does not have an added abstraction layer. For example, LABView under MS Windows currently has a timing resolution of 1 ms, which is unacceptable for this application. Using C code, the sampling rate is limited only by the oscillator of the computer.

The data acquisition control software operates a Gage Applied Sciences, Inc., CompuScope 8500 A/D card. This card can sample at a maximum rate of 500 MHz with an 8-bit resolution. Data acquisition is initiated by a trigger from a photodetector diode, providing a reference for the averaging of multiple spectra. The trigger pulse is also used as a reference for control of the ion gate. For low-speed data acquisition required for status monitoring (vacuum gauges, temperature, tape position, etc.), a commercially available Winsystems PC/104 data acquisition card is used.

The motor control software positions the tape for collection and analysis, and the software controls a Compumotor controller card and interfaces with the various stepper motors in the system. Compumotor provided LABView and C drivers for its card. The main requirement for this piece of software is that the tape must be repeatedly positioned within 0.1 mm to ensure that the sample is illuminated with the laser. Laboratory tests have shown that the stepper motors and controllers have sufficient accuracy to position the tape within the required margin of error.

The user interface controls almost every aspect of the instrument, from collection parameter to error condition response. This software consists of two dialog screens: the Data Acquisition System (DAS) and the Aerosol Collection System (ACS). The DAS controls how each sample spot on the tape drive is analyzed. The user selects the sample spot to analyze, the MALDI matrix to use, the ion gate settings, and the laser power levels. The DAS then discretely operates on the individual samples with the user-supplied options. Analysis protocols can be scripted and saved, eliminating the need for repetitive parameter entry. Similarly, the ACS dialog controls the aerosol collection phase of the system. The user inputs the total collection time, and the system automatically initiates collection and displays the current status in the status box.

Signal processing software provides real-time feedback to the operator about the identity of biological agents in the sample. Each sample is repeatedly pulsed with the laser, and the resulting spectra are averaged. Averaged spectra are processed using a split-window constant false alarm rate processor, which sets a variable threshold that eliminates broad elevations in the background caused by nonspecific ions. The resulting

threshold crossings are then isolated, and a cluster centroid is found. For each centroid, a list of features, including mass, peak width, and amplitude, is then passed to a discriminator. The discriminator then applies a series of rules to determine if any biomarker listed in the threat library is present, and the results are displayed to the operator.

SYSTEM TESTING

Acceptance testing for all candidate biodetection systems is performed at the U.S. Army Dugway Proving Grounds (DPG) test facility using simulants nonpathogenic to humans. These simulants include *Bacillus globigii*, a spore-forming bacterium similar to anthrax; ovalbumin, a chicken egg protein developed as a simulant for toxins such as botulinium; MS-2, a simulant for pathogenic viruses; and *Erwinia herbicola*, a simulant for a vegetative bacterium such as plague. Aerosol simulant concentration levels used in the evaluation are predetermined by DPG and are set on the basis of expectations of threat concentration levels.

Tests at DPG comprise both field and chamber tests. Field tests are designed to determine the utility of a biodetection system under simulated battlefield conditions. Simulants are released by both ground-based and airborne sprayers and simulated artillery bursts, and sensor performance is compared to ground truth monitors. Although these types of tests provide some ability to evaluate a system's performance in an operational context, sensor sensitivity cannot be accurately determined because of the difficulty of controlling and monitoring aerosol releases.

Chamber testing provides performance data on the sensitivity of the detection/identification systems. Simulants are released into a chamber at the threat concentration under controlled environmental conditions. Biodetection systems can be placed in the chamber, and detection performance can be measured. The goal particle counts per liter of air are shown in Table 1. Testing operations allow simulants to be collected over a 5-min period with the initial simulant concentrations at the levels indicated in Table 1. In preparation for the DPG chamber tests, we are performing tests using the aerosol research facilities at the Johns Hopkins School of Hygiene and Public Health.

CONCLUSIONS AND FUTURE EFFORTS

We have successfully demonstrated the functionality of all critical subsystems for the TOF mass spectrometer system and developed a design to fully integrate all components into a field-portable prototype. The fieldable system described is currently being fabricated and will be completed before the end of FY99. In early FY00, APL will demonstrate the capability of the system with chamber testing, possibly at DPG. At the end of FY00 the system will be tested at DPG in evaluated chamber and field trials, and the results will be used to determine the suitability of our system for transition to candidate acquisition programs.

Table 1. Simulant concentrations for Dugway Proving Grounds chamber testing.

Simulant	Goal for total counts per liter of air (0.47–20 μm)
Bacillus globigii	150
Erwinia herbicola	49,500
MS-2	1,500
Ovalbumin	1,650

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