BEAMS Lab at MIT: Status report

Rosa G. Liberman*, Paul L. Skipper, and Steven R. Tannenbaum
BEAMS Lab, Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Abstract
The Biological Engineering Accelerator Mass Spectrometry (BEAMS) Lab at the Massachusetts Institute of Technology is a facility dedicated to incorporating AMS into life sciences research. As such, it is focused exclusively on radiocarbon and tritium AMS and makes use of a particularly compact instrument of a size compatible with most laboratory space. Recent developments at the BEAMS Lab were aimed to improve different stages of the measurement process, such as the carbon sample injection interface, the simultaneous detection of tritium and hydrogen and finally, the overall operation of the system. Upgrades and results of those efforts are presented here.

Keywords
tritium AMS; bouncing Wien filter electric field; high throughput laser-induced combustion interface; control system; biomedical research; carbon-14; tritium; gas-accepting ion source; GC-MS-AMS; transients; control system performance

Introduction
It has been almost nine years since the Biological Engineering Accelerator Mass Spectrometry (BEAMS) Lab at the Massachusetts Institute of Technology was established. The AMS instrument that is at the core of the laboratory is based on a 1 MV tandem accelerator and was designed as a dual-isotope instrument with a gas-fed ion source. Research goals of the laboratory are centered around the application of carbon and tritium AMS to life sciences research. The nature of the samples involved in this kind of research and the need of making sample processing easier, less expensive and with higher throughput has driven the development of novel ways of sample introduction into the ion source of the accelerator. The omnipresent aim of those developments has been to use the AMS instrument as an online detector, allowing the introduction of samples in their original matrices or subsequent to resolution through separation techniques such as liquid or gas chromatography.

Volatile samples are amenable to high resolution separation by gas chromatography and the gas chromatograph can be coupled with a gas-accepting AMS ion source relatively easily. We recently described one such configuration for analysis of $^{14}$C-labeled compounds which incorporates simultaneous mass spectrometric analysis to improve compound identification...
Non-volatile samples present a greater challenge. We continue to pursue technologies for coupling liquid chromatography with AMS analysis but focus in this paper on analysis of non-volatile carbon samples such as plasma, urine, HPLC (high performance liquid chromatography) fractions, tissues and cell cultures, and sub-cellular fractions. These types of samples are processed using a laser-induced combustion interface described previously [2,3], with further improvements presented here. We also describe a method for increasing sensitivity in the analysis of large volume samples in which the radiocarbon concentration is relatively low.

The BEAMS Lab instrument was originally intended for dual isotope operation [4]. For carbon, the design allows the possibility of simultaneously measuring one of the stable isotopes $^{12}\text{C}$ or $^{13}\text{C}$ in a Faraday cup before the accelerator, while the system is tuned for $^{14}\text{C}$ on the beam line. This enables either determination of isotope ratios or use of the stable isotope current as a parameter to normalize $^{14}\text{C}$-only measurements for variation in cathode efficiency. Given the characteristics of the instrument and the inherent ion optical conditions, measuring $^1\text{H}$ in the carbon Faraday cups requires a change of multiple operating parameters, including the injector magnet, relative to the settings for detecting tritium, making the measurement of hydrogen current in real time unrealistic. To overcome this problem a change in the optics and the control of the operation of the whole system was required and is reported here.

**Laser-induced combustion interface upgrade; low $^{14}\text{C}$ concentration samples protocol**

Liquid-phase carbon samples such as HPLC eluents, urine, and plasma are processed by means of the laser-induced combustion interface that directs CO$_2$ produced from the samples into the gas-fed ion source. The conversion to graphite normally used for radiocarbon measurements is not performed. One improvement to the interface involves the CuO support, which was initially in the form of a narrow trough for continuous operation. This had been changed to a multi-well format (circle of 16), with the CuO being placed in porous alumina cup-shaped holders [2]. The benefits of this change were greatly reduced cross contamination and more effective transfer of CO$_2$ into the ion source. However, the alumina from which the CuO holders were made captured a significant fraction of CO$_2$ as a result of its adsorptive affinity for the gas. Therefore alumina holders were replaced by ones made from press-formed stainless steel screen which could readily be mounted in Swagelok ferrules for simple assembly. While preserving the more recent configuration of the interface with its facile design and operation (single-axis motion control and one-step sample changing), it was upgraded to a 32-well format and operation was put under computer control. Throughput of this latest version is 128–160 samples/day.

A major issue for the laser-induced combustion interface has been the dependence of the limit of quantitation on $^{14}\text{C}$ volumetric concentration because the small mass of CuO required by the design of the apparatus can be loaded with only a small volume of sample, typically 1–2 µL. For samples of 0.3 dpm/mL or greater, adequate counting statistics can be achieved with 1.5 µL of sample. For reference, it may be noted that 1.5 µL of a 0.3 dpm/mL solution contains just 3.2 amol of radiocarbon, which, in this instrument will produce about 2000 counts. Certain types of samples, especially HPLC eluents, can easily be well below 0.3 dpm/mL. Therefore, a protocol for increasing the volume of the sample deposited onto CuO through repetitive application was developed. To facilitate repetitive loading, a flow of warm argon gas was directed over the CuO to accelerate drying successive 1.5 µL aliquots after each was delivered. Figure 1 shows a schematic diagram of the apparatus used for this method. Gas flow rate and temperature were empirically obtained in order to dry the liquid as quickly as possible (about 20 to 30 seconds) without disrupting the CuO bed. Proportionality between number of aliquots applied and total isotope detected is revealed by the data shown in Figure 2a. Adjusting sample...
concentration to be inversely proportional to number of aliquots applied resulted in a constant number of detector counts as shown in Figure 2b. These results indicate that the best achievable concentration limit of quantitation may be considerably lower than when only a single aliquot of sample is analyzed.

**Modification of the instrument for simultaneous detection of hydrogen and tritium**

As noted in the introduction the BEAMS Lab instrument was designed to be used for tritium AMS as well as radiocarbon AMS; however, no provision was made for measurement of mass-1 stable isotope current simultaneously—or nearly so—with tritium particle counting. A major difficulty for us to overcome was that ions with \( m/z \ 1 \) and \( m/z \ 3 \) take vastly different trajectories through the injector magnet at the same field. Because of geometrical constraints we did not even consider the possibility of appropriately positioning a Faraday cup to collect \(^1\text{H}\) ion current deflected by the injector magnet when set to transmit tritium ions. It was also not considered realistic to switch the energy of the ions entering the magnet in order to use the existing Faraday cups. The approach that was adopted is not unlike that taken at LLNL for their BioAMS spectrometer [5], which has a magnetic sector ahead of the injection magnet that apparently can cleanly resolve hydrogen and tritium ions without changing settings. In our instrument, the corresponding magnetic sector is present in a Wien filter. Detailed analysis indicated that with selection of an appropriate pair of permanent magnets for the Wien filter, space available in the vacuum system would permit installation of a Faraday cup to collect \(^1\text{H}\) ion current ahead of the injection magnet. It is recognized that this configuration, in which the hydrogen ion current is measured before the accelerator will exhibit less precision than one in which both isotopes are accelerated, but such a system is expected to have more than adequate precision for bio-AMS, as suggested in [5].

There are two Wien filters in this instrument, located immediately after the Einzel lens on the ion source and a substantial distance ahead of the injection magnet as shown in Figure 3. Each is comprised of a pair of permanent magnets (5.1 cm×2.5 cm) and a pair of electrodes (5.1 cm × 1.9 cm), 2.5 cm apart, so as to apply a permanent magnetic field and a variable electric field to the ion beam for bi-directional steering. “Vertical” and “horizontal” refer to the steering direction at the stripper. The original design incorporated magnets of about 300 Gauss (at the midpoint between them), while the electric field varied in a range from 300–400 V/cm). At 300 Gauss, the magnetic field is insufficient to achieve a separation between mass 1 and mass 3 at the greatest available distance from the Wien filter that would be sufficiently large to permit collection of the one ion current with a Faraday cup of even minimal geometry while fully transmitting the other ion beam. In contrast, at magnetic fields in the range of 1000–1500 Gauss, still achievable through the use of NdFeB magnets, the two ion beams would be separated by a distance on the order of 2–3 cm. If the beam size at this location were sufficiently small, it was considered possible to design a Faraday cup that could be positioned where it would not interfere with transmission of tritium.

The Wien filters were thus reconstructed with new magnets and new electrical components appropriate for the higher voltages required. The physical constraints of the chamber where the Faraday cup could be located dictated that only the vertical Wien filter could be used for increasing beam deflection so this unit was fitted with stronger magnets that produced a measured field of about 1300 G at their midpoint. The horizontal Wien filter was also reconstructed even though no change in field was required because the two together form an integral unit. With the instrument tuned for maximizing tritium at the detector (E ~1200 V/cm), the center of the hydrogen beam was found to be 2 cm off from the beam line as revealed by placement of a physical target at the intended location of the Faraday cup. Placement of variable size apertures at the same location revealed that the beam diameter was substantially
greater than 0.64 cm but not detectably greater than 1.3 cm. Based on these results, a Faraday cup with 1.3 cm aperture was constructed following the design of M. Friedrich in [6].

The foregoing indicated that it would not be possible to locate a Faraday cup where static electric field conditions dictated. The anticipated alternative approach was to move the cup further off axis and bounce the electric field. With the field off, the calculated location for the cup is approximately 5 cm off axis. To avoid the need for two bouncing power supplies—since the electrostatic deflectors are biased with equal positive and negative voltages—a compromise has been selected: fixed bias on one plate and bouncing the other between 0 and the opposite, fixed voltage. This results in a calculated position for the cup at about 3.5 cm off axis, where it is sufficiently distant from the beam line.

The mechanical design, which includes provision for 2-axis positional adjustment of the cup within a short range of its calculated position, is finished, and the necessary components have been fabricated and installed. In testing, the cup has produced hydrogen ion currents of 3–4 µA from titanium cathodes in the absence of sample H₂, and a peak response over 20 µA when 0.5 µL of hydrogen was injected (by means of a Rheodyne 7520 injector installed in the He carrier line). These measurements were made with the Einzel lens and horizontal Wien filter set for tritium transmission and the electric field of the vertical Wien filter set at 500 V/cm to create the effect of switching off the bias on one plate when this Wien filter is also set for tritium transmission. The current configuration incorporates a Trek amplifier with a slew rate of > 500 V/µsec to bounce the electric field, which permits switching between hydrogen and tritium data acquisition at the rate of 10 Hz while maintaining a corresponding dwell time ratio of 1:20. These relatively demanding parameters permit tracking the rapid changes in sample concentration that typically occur during chromatographic separations while resulting in only a 5% loss of particle detector acquisition time.

**Control system upgrade**

A completely new control system has replaced the original system that was based on Group3 technology. Hardware and custom software was provided by Pyramid Technical Consultants, Inc. [7]. The technical approach is based on distributed control modules for the various power supplies and diagnostic elements, such as pressure gauges, valves, etc. Each digital/analog input/output control module is located as close as possible to a controlled unit and linked fiber-optically in loops to a loop controller which, in turn, is Ethernet-connected to the main computer. The proximity of each unit to the corresponding power supply and the fiber optic and Ethernet connection have proven very effective in reducing the impact of noise and transients on overall system stability. The upgrade also was necessary in order to implement the changes described above for making hydrogen/tritium measurements.

**Conclusions**

The latest modifications to the laser-induced combustion interface as well as a new protocol for increasing usable sample volume reported here expand the range of non-volatile carbon samples that can be analyzed in their original matrixes. They also provide the groundwork for development of a laser-induced combustion interface based on industry standard well-plate formats. The modifications for measuring ¹H near-simultaneously with tritium particle counting are not quite complete but are expected to be fully operational in the near future. Last, but not least, the control system upgrade has already proven to be considerably more resistant to the effects of electrical transients and other disturbances on instrument stability and performance.
Acknowledgments

This work was partially supported by GlaxoSmithKline, grants from the NIH, P30-ES02109 for the MIT Center for Environmental Health Sciences and R42-CA084688, and made possible by UL1 RR 025005 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at www.ncrr.nih.gov. Information on Re-engineering the Clinical Research Enterprise can be obtained from http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp.

References

Figure 1.
Cross-sectional view of apparatus for drying samples during application of multiple aliquots. The configuration replicates that used in the combustion of samples with gas flow direction reversed.
Figure 2.
(a) Effect of keeping $^{14}$C concentration constant and varying aliquot number. The total $^{14}$C detected is, as expected, proportional to the number of aliquots. (b) Effect of maintaining constant $^{14}$C deposition through simultaneous variation of $^{14}$C volumetric concentration and volume (i.e., number of aliquots). Slope of the regression line is not different from zero indicating that constant sample deposition was achieved. In both (a) and (b) the error bar represents the SD of three measurements; statistical error of $^{14}$C counting is not included.
Figure 3.
Schematic of the injector on the BEAMS Lab instrument showing the position of the new Faraday cup for mass-1 current measurements. Wien filter V, the one modified, steers vertically at the stripper, therefore from left to right in the plane of the figure. Wien filter H steers horizontally at the stripper, therefore perpendicular to the plane of the figure.