## SESSION 6

# MASS SPECTROMETRY AND BIOSENSING RESEARCH

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Historically, there has not been complete agreement on the definition of the term "biosensor". For example, as Turner notes[1], this "…term has been used to describe a thermometer, a mass spectrometer, daphnia in pond water, electrophysiology equipment, chemical labels for imaging, and ion-selective electrodes…". However, he goes on to conclude that "…a biosensor will be defined as a compact analytical device incorporating a biological or biologically-derived sensing element either integrated within or intimately associated with a physicochemical transducer. The usual aim of a biosensor is to produce either discrete or continuous digital electronic signals which are proportional to a single analyte or a related group of analytes" [2]. Within this context, then, a mass spectrometer clearly qualifies as a biosensor. On the other hand, when one considers the desirable characteristics of a biosensor (specificity, sensitivity, stability, wide applicability, low cost and portability) there a number of respects where generally available mass spectrometry technology falls short. Most notably, it is in the areas of low cost and portability. For biosensor applications, present laboratory-based mass spectrometry provides superior performance. There are also a number of options available for so-called "field-portable" applications. Finally, and perhaps of most interest, there is considerable research directed toward the long-range goal of truly portable (or perhaps personal) mass spectrometers. Here, relevant recent advances will be reviewed, with respect to the degree that they broaden the potential for biosensor applications of mass spectrometry. Additionally, some of the factors that currently limit such mass spectrometric applications will be identified and the prospects for addressing these limitations considered.

## TECHNICAL ADVANCES

There have been a number of important developments in mass spectrometer design that are highly relevant to their possible importance as biosensors. Of course, key developments in mass spectrometer sources were the development of matrix assisted laser desorption/ionization[3, 4] and electrospray ionization[5], with the impact on bioanalytical chemistry being so important that it led to the Nobel prize for Fenn and Tanaka earlier this year[6]. From a practical standpoint, these techniques allowed extension of mass spectrometry to biomolecules with masses extending well above 100,000 Daltons. Equally important, advances in developments of mass analyzers have continued, with notable examples being Fourier transform mass spectrometry[7], quadrupole ion trap[8, 9], and new time-of-flight mass spectrometer designs[10]. As mentioned above, there has been a good deal of recent attention devoted to development of smaller mass analyzers[11]. These efforts have been driven by the recognized need for capable *in situ* mass analysis systems, which are compact and easily portable. Obviously, successful development of such mass spectrometric equipment would be of great interest for a very wide variety of applications, particularly those in the biosensor area. Cooks and Badman provided an excellent perspective on this research in a recent paper[12].

## FIELD PORTABLE MASS SPECTROMETERS

The 12th Sanibel Conference on Mass Spectrometry in early 2000 was devoted to the topics of field-portable and miniature mass spectrometry. This meeting was reviewed in some detail by Sparkman[13]. An interesting aspect of this report is the perspective of the opening speaker, J. Franzen (Bruker Daltonics, Bremen, Germany) who was reported to have said that there is little or no market for field portable mass spectrometry instrumentation. He attributed this to the fact that the limitations of the instruments were more involved with the skills required for the interpretation of the data, rather than the actual performance of the analysis. This perspective, if accurate, suggests the need for continued research into data interpretation algorithms, with the possible objective of making computer interpretation much more effective than it is at present.

## CRITICAL PARAMETERS

Virtually all types of mass analyzers have been or are under investigation for miniaturization and potential field-portable applications. Thus, small magnetic sector analyzers, linear quadrupole and quadrupole ion trap, Fourier transform, and time-of-flight mass spectrometers are being developed and evaluated, many for biosensor applications. As is seen in the publications that have resulted so far, most of the miniaturization efforts have necessarily resulted in mass spectral performance compromises, to a greater or lesser degree, depending on the type of mass analyzer involved. In a great many possible applications, these compromises may well be analytically acceptable. However, the factor currently limiting further success in miniaturization and enhanced field portability is the unavailability of correspondingly miniaturized vacuum and electronic systems. Quoting Badman and Cooks, "*Currently, the limiting factor for cost, power, size, and mass of the miniature mass spectrometer is the availability of appropriate pumping systems*"[12]. As Henry reported in her article discussing a half day symposium on miniature mass spectrometers at the 2002 Pittsburgh Conference, "One after another, the speakers reiterated that, until the ancillary parts of the system are also reduced in size, it won't do much good to continue to shrink the mass analyzer"[14].

**Table 1. – Typical Parameters for Minature Mass Analyzers[a]**

| Analyzer Type | Dimension | Mass Range | Resolution |
|---|---|---|---|
| Cooks QIT | 2.5 mm radius | 250 m/z | 100 m/÷m |
| Ramsey QIT | 0.5 mm radius | | |
| Quadrupole | 0.5 mm radius 10 mm long<br>4 x 4 array | 300 m/z | 600 m/÷m# |
| Quadrupole | 0.5 mm diam.<br>10-30 mm long | 150 m/z | 14 m/÷m |
| Cotter TOF | 7.5 cm long | 66 K m/z | 300-1200m/÷m |
| Double-focusing EB | 17 x 37x 57 cm instrument | 39-255 m/z | 131 m/÷m |

*a) examples only, parameters change often as designs are improved*

## MASS SPECTRAL INSTRUMENTATION RESEARCH NEEDED

Progress toward combining capable mass spectrometry sources with new miniaturized mass analyzer designs has been reasonable over the past few years. Research with a number of promising innovative approaches including quadrupole arrays, cylindrical ion trap arrays, curved field reflectron time-of-flight, and small permanent magnet Fourier transform mass analyzers has shown reasonable progress in the past few years. It is quite clear that development of miniaturized low power vacuum systems should be an area of the highest priority, if the promise of compact and analytically effective mass spectrometers is to be fully realized. It does not seem that there are any fundamental reasons that this would not be possible. One approach, suggested by Cotter[11], might be to develop combined mechanical and turbomolecular pump systems which could be potentially smaller and more compact than the present alternatives.

## POTENTIAL APPLICATIONS

Among the most intriguing possible applications for mass spectrometry as a biosensor tool, is the identification of biomarker signals that are expressed by viruses, bacteria, and spores, with the interpretation aided by comparison with genomic information for each organism. The successful approach will most likely involve identification of the biomarkers with high performance laboratory instruments, with subsequent routine analysis and detection by lower performance inexpensive instruments. Another possible application is the use of mass spectrometry as a tool for clinical diagnostics (e.g. protein biomarkers for cancer)[15]. Clearly, environmental analysis and emergency response applications involving chemical and biological warfare or terrorism are obvious applications of mass spectrometry, both with high performance laboratory instruments and lower performance mass spectrometers. For example, there is contemporary evidence that rapid chemical taxonomy of bacteria is possible by MALDI mass spectrometry, using detected lipid patterns and analysis of proteins detected. Such applications, in common with the previously-mentioned need for field-portable instruments, will require improved and sophisticated data analysis algorithms and software. Therefore, research in that area also should be of high priority.

## REFERENCES


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