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Trends in Analytical Instrumentation

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Summary. Methods for deriving chemical information from a variety of systems and environments have changed dramatically in the last decade. Unique principles from physics, chemistry, and biology are the basis for sophisticated instruments that incorporate computers for data acquisition, reduction, and interpretation. Such analytical systems have shown orders-of-magnitude improvements in sensitivity, specificity, and speed, yet with greater simplicity and lower price. The increasing importance of analytical instrumentation requires reexamination of its coverage in educational curricula and of the role of the analytical chemist in its further development and application.

Sophisticated instrumentation integrated with powerful computers has created an analytical revolution of broad scope (see box) in the last two decades (*1, 2*). Applications of these systems in such varied areas as basic research, industrial control, environmental monitoring, and health continue to expand faster than anticipated by all but the most optimistic predictions. Analytical instruments, broadly defined, are now essential tools for most chemists ("Chemistry Without Test Tubes;" see cover) (*3*) and for a broad spectrum of physical and biological scientists. Appropriately, fundamental discoveries across these areas have provided the bases for these new methods, as well as a growing challenge to the breadth and flexibility of analytical chemists. Detailed examples of instrumentation leading this revolution are provided by articles in this issue.

Analysis of an atomic or molecular species involves deriving measurable signals which are characteristic of the identity and/or amount of the species. The "wet" analytical chemistry of yesteryear derived these signals by condensed-phase reactions such as acid-base neutralizations for volumetric analysis and precipitations for gravimetric analysis. An analysis requiring many minutes by a trained analyst produced a single value such as milliliters of titrant or grams of precipitate. Thus specificity was dependent on the reaction chemistry, sensitivity on this and the volumetric or gravimetric measurement, and speed on the skill of the analyst. In contrast, computerized instrumental methods can provide much more and better data in much less time, in the most favorable cases even showing a selective "real-time" response for a single atom or molecule and minimizing the requirements of a trained analyst for operation and interpretation.

The capabilities required of the analytical chemist have increased at least as dramatically. Chemistry was critical to the success of wet analytical methods, so these were largely developed by chemists; fortunately, chemists needing a method in their work were often those best qualified in the requisite chemistry. Modern instrumental methods, however, have originated from a wide variety of disciplines, often in combination, including spectroscopy, nuclear and ion physics, electronics, computer science, and biology. Development of such analytical instrumentation thus usually requires competence in other relevant disciplines without diminishing the requirements in chemistry. Similarly, a key factor in the best modern research in chemistry and other sciences is often the capability to develop and/or utilize such instrumentation.

Analytical chemistry comprises both characterization and measurement of chemical systems—qualitative and quantitative analysis. The accuracy and overall value of a method to its user depend on its sensitivity, specificity, and speed, as well as its simplicity and cost (see box) (*4*). Sampling can also be of critical importance to the applicability of a method. Each of these aspects will be examined here to define and illustrate the magnitude of this analytical revolution.

Sensitivity

A part per million was considered an impressive sensitivity a generation ago. Now a part per trillion ($1/10^{12}$) sensitivity is achieved for some routine analyses such as that of the notorious dioxin (*5*), while a special tandem-accelerator mass spectrometer can detect three atoms of ^{14}C in the presence of 10^{16} atoms of ^{12}C (*6*), corresponding to a radiocarbon age of 70,000 years. A pinhead would occupy a part per trillion of the area of a road from New York to California (*2*). As infinitesimal as this appears, 10^{12} molecules of molecular weight 600 weigh only 10^{-9} g.

Sensitivity depends on the efficiency of converting the analyte to a measurable species, and on the ability to measure this species. In addition, the actual detection limit (signal-to-noise ratio) is also affected by the response of interfering species present (that is, specificity, discussed below). These measurable species include the photons whose absorption or emission is the basis of a wide variety of spectroscopic methods (x-ray,

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ultraviolet, infrared, nuclear magnetic resonance, Raman, Mössbauer, and so on), and the charged species which are the bases of electron and mass spectrometry and of detectors (electrochemical, flame ionization, and so on) for chromatography. The efficiency of converting the analyte to photons (and even electrons and ions) has been dramatically improved with intense energy sources such as lasers, synchrotron radiation, and plasmas. Efficiencies approaching 100 percent have been reported for resonance-enhanced multiphoton ionization of atomic (*7*) and molecular (*8*) species. Multiplier detectors can respond to the arrival of a single photon or ion, so that these methods can actually detect a single cesium atom (*7*) or naphthalene molecule (*8*). The sensitivity obtainable from multidimensional techniques is also dependent on their specificity and speed, as discussed below.

Specificity

The amount and utility of the information from an analytical method are key determinants of the resulting selectivity for the atom or molecule sought; a completely "universal" detector would have to produce an infinite amount of information. The total information obtained depends on the number of dimensions and on the amount of data per dimension. Measurement of refractive index or optical rotation, for example, provides only one value indicating displacement in one dimension. Most instrumental methods are multidimensional, resulting in an exponential increase in information. Common spectroscopic techniques have two dimensions, for example, plotting absorbance against wavelength for infrared spectroscopy or ion abundance against mass-to-charge ratio for mass spectrometry.

The amount of data possible in the X dimension of a spectrum depends on the number of peaks and the number of distinguishable locations (resolution increments) possible for each peak. Reducing the number of peaks in a spectrum to one essentially makes it unidimensional; here specificity is determined by the peak width relative to the response position of other components. Specificity can still be high, such as for chemical reactions of wet methods; with modern autoanalyzers these account for hundreds of millions of routine analyses yearly. Radioimmunoassay (*9*) measures the amount of unknown antigen by the response to a specific antibody, of which

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there could be 10^7 to 10^9 giving distinguishable responses. Iron-57 Mössbauer spectra (*10*) cover an energy range of only $\sim 2 \times 10^{-11}$ of the source energy, but absorption values can be measured at ~20 distinguishable energy values because of the incredible resolution of $\sim 1/10^{12}$ (a peak width of 5×10^{-8} eV compared to a source energy of 1.4×10^4 eV). Dramatic increases in resolution, and thus information content, have been achieved in many techniques. In the ultraviolet region the molecular absorption spectrum of a compound in solution is a "band" electronic spectrum, with possibly a dozen resolution increments. An orders-of-magnitude increase can result from gas-phase cooling by supersonic expansion to resolve the vibrational and even rotational "line" spectra for measurement by a tunable laser. Gas chromatography with capillary columns (*11*) makes possible $\sim 10^5$ resolution increments, a substantial improvement over that with packed columns. The potential utility of high-resolution ($\sim 1/10^5$) mass spectrometry of high mass (<10,000 daltons) compounds (*12*) is reflected in the $\sim 10^6$ possible resolution increments (*13*). The number of possible resolution increments for the single value in a spectrum's Y axis (for instance, absorbance or ion abundance) depends on the measurement accuracy as well as the dynamic range; 10 to 10^3 increments are common for spectroscopic methods.

Techniques of even higher information dimensionality are among the most exciting new ways to obtain "needle-in-a-haystack" specificity (*4*). Such combined techniques can be classified as "cloned" or "hybrid." A prime example of the former is two-dimensional nuclear magnetic resonance (*14*), which provides information on the spatial relationship of the ^1H, ^{13}C, . . . atoms of a molecule in addition to the information on the type and number of atoms provided by the normal nuclear magnetic resonance spectrum. Tandem mass spectrometry (*4, 15*) (see cover), which has shown amazing recent growth, can similarly provide an extra dimension of structure information for pure samples, and can also serve as a fast ($<10^{-3}$ second) separator interfaced to a highly specific detector or identifier.

The hybrid multidimensional technique combining gas chromatography with mass spectrometry (GC-MS) is a classic example of analytical instrumentation development, having grown in 20 years from a research curiosity to worldwide sales exceeding those of most types of spectroscopic (noncombined) instruments. GC-MS provides powerful and convenient abilities for separation, identification, and quantitation of complex mixture components which have proved ideal for insect pheromones, environmental pollutants, forensic problems, process control, and so on. The counterpart GC-infrared (GC-IR) (*16*) and liquid chromatograph-MS systems (*17*) have advantages in terms of isomer specificity and have applicability to less volatile mixtures.

Multidimensional spatial analysis is important for inhomogeneous samples. Special "microprobe" and "microscope" techniques employ electrons, ions (*18*), or laser photons as both probes and sensors to map the concentration of a selected element or molecule in two (or even three) dimensions of the sample. Such improved methods for surface analysis have been a key factor in elucidating basic mechanisms of heterogeneous catalysis (*1*), while nuclear magnetic resonance imaging (*14*) is revolutionizing medical diagnosis.

Speed, Simplicity

Many analytical problems in research, process control, and toxicant monitoring have critical time requirements. Further, the rate and ease of producing useful information are often key factors in justifying the high purchase and maintenance expenses of modern analytical instruments; the "cost per analysis" must be minimized. Progress in increasing speed has been particularly impressive recently. Although in selected cases this is due to specific instrumentation, such as picosecond lasers (*8*), the nearly universal application of the dedicated computer to analytical instrumentation in the last decade has given dramatic improvements in speed as well as in accuracy,

control, and dependability. The information rate for multidimensional instruments such as GC-MS and two-dimensional nuclear magnetic resonance is so great in most applications that the computer is required for data acquisition and reduction.

Fourier transform techniques have greatly increased both speed and sensitivity (the latter by orders of magnitude) for infrared (*16*), nuclear magnetic resonance (*14*), and mass (*19*) spectroscopy. With these techniques, in contrast to a scanning spectrometer with slits, the collective frequencies representing a spectrum are simultaneously recorded as a function of time, from which the Fourier transform produces the frequency-domain spectrum. Dedicated, reasonably priced array processors can perform several transforms per second. This is particularly valuable for techniques like GC-IR (*16*), allowing several infrared spectra to be recorded across each GC peak.

Relatively complex calculations represent key steps in other methods such as pyrolysis-MS (*20*) and process control (*21*). Although a dedicated computer improves speed, the improvements in simplicity and reliability can be equally important. Computer interpretation of results, such as GC-MS on-line matching of the spectra of eluted components (*22*), increases the productivity of professional personnel.

Sampling

Many analytical problems require special arrangements to make the sample available to the instrument, or vice versa. Elegant examples of the latter were the orbiter and lander instruments on the Viking mission to Mars (*23*). Remote sensing, particularly of thermal or laser-induced emission spectra (*8*), is used routinely for analysis of smokestack effluents or stratospheric components. "Chemical profiling" of a large area for toxic or other critical compounds can be done expeditiously (at 35 miles per hour) by using a van-mounted MS-MS instrument with atmospheric pressure ionization and high-speed cryogenic pumping (*24*).

The Education of Chemists and the Future of Analytical Chemistry

This revolution in analytical instrumentation promises high future productivity in chemical research and manufacturing. The rapid progress in so many areas undergirding these instrumental advances brings new challenges, however, for proper education and training of both student and experienced chemists. In many schools the undergraduate curriculum is undergoing constant updating for this, including experience with relatively sophisticated analytical instrumentation as well as electronics, computers, vacuum systems, and so forth. The continuing education of experienced chemists would appear to be a greater problem. This is much like the computer familiarity of grade school and high school students compared to that of their parents.

As an analytical chemist, I see even more serious problems for us in defining our role in the development and application of such analytical instrumentation. Its promise for all areas of chemistry is much too great for other chemists to wait for us in this matter; note that fewer than half of the articles in this issue are authored by card-carrying analytical chemists. Understanding the chemistry is still central to the success of an analytical method, such as the interplay of species in the solution analyzed, the interaction of molecules with an electrode surface or a chromatographic support, the unimolecular dissociation of organic ions in mass spectrometry, or the folding of polypeptide chains in immunoassay. To the extent that we attain real leadership as chemists in research and applications of such computerized instrumentation, analytical chemistry will be even more exciting and deserving of the respect of other chemists and scientists.

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