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AN AUTOMATED SPECTROMETER GROWS UP

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ABSTRACT

In 1980 we reported here the development of an automated mass spectrometer for large scale batches of samples enriched in nitrogen-15 as ammonium salts. Since that time significant technical progress has been made in the instrument. Perhaps more significantly, administrative and institutional changes have permitted the entire effort to be transferred to the private sector from its original base at the Los Alamos National Laboratory. This has ensured the continuance of a needed service to the international scientific community as revealed by a development project at a national laboratory, and is an excellent example of beneficial technology transfer to private industry.

An Automated Mass Spectrometer Grows Up

A. Introduction

The application of techniques of automation to mass spectrometry is in many ways a very happy joining of scientific efforts. The data to be monitored may be highly precise as well as voluminous. Combination techniques such as gas or liquid chromatography/mass-spectrometry or the current MS/MS technique present one with a data monitoring problem which is even in principle a two dimensional matrix of data for each sample with perhaps thousands of elements in each dimension. For such applications the computer interface is mandatory. It becomes unthinkable today to perform the many repetitive calculations which were standard procedure to many of us only a few years ago. But there are still other uses for the computer interface which are typified by the application to be presented today involving the actual manipulation and preparation of samples for mass spectrometric analysis, as well as the monitoring, manipulation, and sotrage of the process data from the analytical mass spectrometer. The advantages to be gained here are those of freeing the laboratory experimentalist for other, less repetitive, tasks; of having a system which will continue working all night or weekends; which can be reliably programmed to make as intelligent a set of decisions or procedure as the programmer chooses to incorporate therein. This line of thought seems always to lead to the familiar social questions of displacement of men by machines. However, in the laboratory scene, there are several special considerations. First, the mass spectrometer analysis is not, generally speaking, a consumer product. A mass spectrometer is not a household item but is a research instrument of specialized use. The research laboratory is seldom so regimented as to create concern that automation will displace an individual. On the other hand, the frequent association of scientific research with scientific education leads to a positive benefit of experience for a student to handle samples manually rather than automatically. Also, if his funds are limited, a senior research worker may prefer to guide them to assist his students rather than to buy automatic equipment. These then are some of the pressures leading toward and resisting movements toward automation of scientific laboratory equipment.

B. The Nitrogen Isotope Analysis Problem

The stable isotope, nitrogen-15 occurs at about 0.4% in nature and is used widely as a field tracer to study details of the nitrogen cycle. Agronomic studies of the utilization of nitrogen fertilizers are of paramount interest in this case, using separated nitrogen isotopes as tracers of the element. It is a powerful research method permitting, for example, a determination from isotopic analysis of the harvested plant tissue the degree of incorporation of a particular fertilizer application made early in the growing season. Other related studies are of loss of applied fertilizers, to water or to air, or tracing the return of nitrogen to the soil from plant protein when a tree falls in the woods, or when plants die in the winter months. Such experiments will often occupy several years and involve hundreds of samples of soil, plant material, or water.

A variety of methods have been developed for processing such samples to ready them for mass spectrometric nitrogen isotope analysis. One which is widely used involves reduction of the nitrogen to ammonia using a Kjeldahl digestion, the distillation of the ammonia from the neutralized digest into a weak sulfuric acid solution, thereby reducing the sample to a slightly acidic solution of ammonium sulfate. When the sample is ready to be isotopically analyzed, the ammonia is oxidized to nitrogen gas using sodium hypobromite according to the reaction

$$(NH_4)_2\ SO_4 + 3NaOBr \rightarrow N_2 + NaBr + H_2SO_4 + 3H_2O.$$

This scheme, developed by Rittenburg nearly five decades ago, continues to be useful today.

In practice, agronomists have succeeded in accomodating their methodology to large numbers of samples in many steps of this process. The handling of many soil or plant samples, drying them, grinding them, and performing the Kjeldahl digestion has yielded to methods which process many samples simultaneously. The next step of distillation or diffusion has met with success in some hands. But the handling of many ammonium smaples which are awaiting isotopic analysis has resisted improvement until recent years.

Consider for a moment the experimental problem of automating this analysis along the classic line. The ammonium sulfate sample, either in solution or as solid salt, must have all ambient nitrogen from the air removed; the reagent solution, a strongly alkaline hypobromite solution, must be added and allowed to react briefly; the supernatent nitrogen gas should be purified and adjusted in pressure to yield a good signal for the two peaks at mass-28 and mass-29. Thus the system requires lines and automatic valves to handle highly alkaline solutions, good vacuum conditions, and very clean gases. In addition, since the amount of nitrogen sample gas which flows into the mass spectrometer is less than a microgram, a plausible design might have an inlet manifold of ten micrograms of nitrogen but with a pressure of ten torr. The required volume is then 0.6 cm^3 for a valve network, purifying trap, and a pressure transducer. We are thus considering a very small system. If you try to evacuate a 1 mm glass tubing with some liquid water in it, or try to mix two liquids which generate a gaseous product in such a small system you will soon realize some of the problems facing such a development.

Such was our situation at the Los Alamos National Laboratory five years ago when we embarked on a program to automate this analysis. Since the topic of this presentation is both the institutional interactions and the technical achievements, I should tell you that we had been engaged for several years previously in the ICONS program of the Los Alamos National Laboratory - ICONS being an acronym for Isotopes of Carbon, Oxygen, Nitrogen, and Sulfur - a program with the general objective of promoting the use of stable isotopes throughout the scientific community. A central part of this program was the production of these isotopes at our Laboratory and distributing them to the scientific community at cost. The program had been suggested and initiated by the Division of Biology and Medicine of the U.S. Atomic Energy Commission of that time, about 1960. Other facets than isotope separation were also purused, but by 1978 we came to realize that a rate limiting step - a bottleneck - in the use of nitrogen-15 was the isotope analysis of the samples from field experiments. Our funding agency, the Office of Health and Environmental Research of the Department of Energy approved of the development program for automated instrumentation. The general argument was that a laboratory of high technology such as Los Alamos might have special expertise for such a development even though the need - the place where the samples were generated - was at agricultrual colleges and universitites or at regional agricultural laboratories of the U.S. Department of Agriculture. An institution of particular help to us was the Tennessee Valley Authority's National Fertilizer Development Center at Muscle Shoals, Alabama which had previously taken a similarly broad view of the needs of the country and of the world-wide scientific community for fertilizer research.

It required about two years to have some success in this program. The automatic data taking, processing, and storage was easiest of all. A particularly knotty problem was that of an automatic micro-valve which did not leak. We had to design our own pneumatically operated valve using O-ring seals and seat, with an intermediate region separating the actuating gas and the process sample gas which was continually pumped, so that the sample gas might leak and be pumped away, but it would not be contaminated by the actuating gas. The problem of liquid eruption under vacuum which was referred to earlier was solved by purging the air from above the sample in the reaction vessel with dichloro-difluoro methane gas and permitting the oxidative reaction to take place in te atmosphere of this Freon gas. The evolved nitrogen was then carried to a chilled U-tube tape at -200°C and of small dimensions using the Freon as a condensible carrier gas. A serious and recurring problem was that of internal cleanliness of the system. The alkaline reagent seems able to migrate throughout the whole system contaminating the small capillary lines and eventually plugging them with solids. Periodic washing water was necessary every few days or oftener. The Freon purge gas proved to have some nitrogen contaminant and a small purifying column to remove the nitrogen was designed and built. But by 1980 the equipment seemed to be working satisfactorily and the design and performance was reported here in Milan at a Mass Spectrometer symposium.

Subsequent to that report some technical progress was made in the equipment. Especially exciting was the use of disposable plastic trays with 96 wells for loading and anaylsing the samples, where previously small individual vials were used and cleaned for re-use. The trays were moved about under a fixed head which would lower onto a desired well, would process that sample, and then move on to the next well. Trays were moved by a modified flat-bed plotter under computer control. In addition, a mechanism was developed which would dump a tray when it was finished and proceed to pick up a new tray, so that the machne could continue to analyse samples overnight or over a weekend, unattended. Several hundred samples per day could be analysed. The sample portions in each well could be 10 μg N and it proved perfectly practical to analyse all samples with duplicate aliquots for added confidence in the results.

As part of the testing program for this machine we informally told a few interested users of nitrogen-15 that we would be glad to analyse any samples they or their colleagues might have. The word spread throughout the agronomy community and into related scientific areas that Los Alamos was doing nitrogen isotope analyses at no cost. By a year later about fifty university and government laboratories, one industrial laboratory, some German and one New Zealand worker had submitted nearly 20,000 samples. Several hundred would arrive daily. We had no idea there were so many samples in the U.S. At first we assumed that these must be accumulated backlogs, but the flow kept increasing, although still less than our estimated capacity of 60,000 samples per year. And gradually our attention turned from the original technical problems of how to build an automated mass spectrometer to problems of how to handle financially and institutionally the problem of thousands of samples which continued to flow to us.

For consider our dilemma: no longer could we claim that this was instrument development. The funding agency, although impressed and sympathetic, could not really continue to underwrite the cost of doing other peoples samples. The Los Alamos National Laboratory could not ignore such a clearly expressed need of the scientific community for this service and was most reluctant to terminate it outright, yet it was unclear how to fund its contiuation. But even if the comparatively small cost could be managed in order to continue the service, the general R & D mission of the Laboratory was incompatible with a sustained program of service work, however financed. Efforts were made to transfer the responsibilities to another government agency, but unsuccessfully.

The final solution of this matter lay in transferring the entire technology to a private company established by the first two authors of this paper under the name of Isotope Services. To treat this subject with some detail I will spend a few minutes in describing some policies and procedures of technology transfer from Los Alamos National Laboratory, as well as programs at other federal laboratories in the U.S. and more general impresions of such acitivies in Europe and Japan. These remarks were prepared by Dr. E. E. Stark who is the Industrial and International Initiatives Officer at Los Alamos.

C. Technology Transfer

Motivation and Policy

There has been a growing concern in the U.S. about the international competitiveness of all sectors of its industry since the mid-1970's. This concern has been manifested in numerous initiatives by both liberal and conservative political leaders having many specific objectives, generally including: promotion of greater R & D performance by and for industry; identification of common technology needs by specific sectors of industry (e.g. instrumentation needs of the steel industry) and research in those areas; strengthening of assistance to small businsses and individual entre-entrepreneurs, who together have historically accounted for a major portion of industrial innovations; changing of taxation regulations to encourge risk-taking in both investments and research. A special class of objectives has been the promotion of new relationships between universities and industry and between the federal laboratories and industry. The latter objective has been an informal aim of many federal laboratories for some years, but a 1983 report on the federal laboratories by a subcommittee of the White House Science Council recommended specifically that there be stronger relationships for technology transfer between industry and laboratories.

The wide-ranging aims and recommendations outlined above can be summarized in these key points:

- The federal laboratories in the U.S. employ ~15% of the nation's research and development personnel and perform approximately half of all the basic research in the U.S.
- There is significant need and opportunity for the technology developed in these laboratories to be made practically available to U.S. industry, both to strengthen existing industrial sectors and to create new ones.
- National policy strongly supports more fruitful interactions between industry and laboratories.
- It is therefore a fundamental responsibility of the federal laboratories to make their technology pragmatically available.

Methods

Because the transfer of technology is normally a person-to-person process, the methods can vary widely, but all depend on interpersonal interactions and individual initiative. The specific methods outlined below are in place at Los Alamos National Laboratory, but most are found at other U.S. laboratories.

- Technical Collaboration - Most technologies, as they exist in federal laboratories, are not at a commercial stage; this is to be expected because any laboratory technology, whether a small tool or a major new energy source, is necessarily at a research or prototype stage owing to the fundamental research missions of the laboratories. Commercial-stage development, engineering, testing and market research are not assigned to tese laboratories. A major component of technology transfer, as a result, is technical collaboration between the laboratory research group possessing the technology and the industrial group seeking to carry this technology to commercial application. Specific methods for this collaboration include:

Industrial Staff Member Program. Industry professionals, fully supported by their companies, may spend 1-2 years at the Laboratory both contributing to the Laboratory's programs and receiving directly the in-depth know-how of specific technologies of interest to his company. Companies such as Westinghouse, Grumman, Kodak and Armco Steel have participated.

Staff Exchange Program. This program expands the Industrial Staff Member program to a two-way staff exchange. The government has developed a fully reciprocal approach to ownership of intellectual property (e.g. patents) resulting from these exchanges. The first exchange partner in this relatively new program is Tektronix, Inc.

Informal Collaboration. As with more frequent collaboration between Laboratory staff and researchers in other public institutions, informal collaboration in areas of mutual interest can transfer basic knowledge and research approaches as well as technologies.

- Individual Entrepreneurship. The Los Alamos National Laboratory encourages its staff to consider founding new business ventures based upon unclassified technology arising directly and indirectly from Laboratory programs. This approach is motivated in part by a general need for greater economic activity and diversification in Northern New Mexico. Another important reason for emphasis is the role of the entrepreneur in American industry, that of driving force and major agent of change and innovation. Successful examples in Los Aamos include: Hot Hole Instruments, using instrumentation developed in the Hot Rock Geothermal Energy Program for applications in the petroleum industry; Pulse Systems, applying in low-cost laser amplifier arising from the Inertial Fusion Program to a variety of industrial making applications, and Isotope Services, which is the commercial subject of the other sections of this presentation.

- Patent Licensing. Until recently, inventions developed at the Los Alamos National Laboratory were generally held by the U.S. Department of Energy, which is subject to onerous regulations on the granting of exclusive patent licenses. This situation hindered the transfers of some technologies in which a significant further R & D investment would be required to reach commercial applications; the unavailability of an exclusive license would prevent protection of this risky investment. Beginning in the past two years, there has been a significant change in policy emphasis, which has led to the University of California, operator of the Laboratory, receiving ownership of some Laboratory patents. The University's active licensing program now makes these licenses pragmatically available. The first instance of such a transfer occured in May, 1984, when the University licensed two patents on a medical instrument to a new firm, Radtech.
- Industry-Sponsored Research. The Laboratory is permitted to accept sponsored programs for industry if there is a technical benefit to the Laboratory and it is not competing with private or university research capabilities. This work has typically involved the extension of Laboratory technologies to a specific industrial application. Several firms have sponsored work in areas such as laser development, electronics, life sciences, applications of explosives, heat-pipe design and petroleum reservoir modelling.
- Market Development. In certain cases, the Laboratory both develops a technology and represents a market for that technology. In these areas, the developers seek industrial interest by demonstrating the market for this technology in the Laboratory and elsewhere. Technologies transferred in this manner include several radiation-detection devices, lasers and optical elements, high-voltage capacitors and cables and high-speed electronic instrumentation.
- Staff Consulting. Laboratory employees are encouraged to consult privately for industry, avoiding conflict-of-interest situations. In this way, both technology and personal expertise developed at the Laboratory become available to industry.
- Users' Facilities. Several unique or rare facilities at the Laboratory are available to outside users as users' facilities. These make state--of-the-art research equipment available to industry and universities. These facilities include, for example, a laser spectroscopy laboratory, a rock mechanics facilty and other rare facilities.

Other U.S. Laboratories

Although the details of their methods may vary, the other national laboratories in the U.S. encourage several of these methods. These laboratories, operated for the Department of Energy by contractors, have been directed to become more agressive in technology transfer.

The National Aeronautics and Space Administration has the best known record of technology transfer from government programs. It uses a variety of methods to identify innovations, to determine their potential applications and uers and ultimately to transfer the results of space program technology. Numerous important innovations in materials, electronics, medical instrumentation safety and other areas have resulted.

The National Bureau of Standards has a program under which researchers representing industrial trade associations use its facilities to develop and test technologies important to their industries in such varied areas as dentistry, flame-retardant clothing, and materials standards.

The laboratories of the Department of Defense routinely transfer their results to the defense industries in the U.S., but also undertake special efforts to provide technical assistance to state and local governments and to prive industry.

The Department of Agriculture, through its Cooperative Education Service and technology transfer programs of the Forest Service, has made a revolutionary impact on the productivity of agriculture and forestry in the U.S. for 70 years.

Because of the diversity and location of the U.S. Federal Laboratories, it can be difficult to establish the necessary person-to-person contacts for technology transfer. For this reason, ~300 of the larger laboratories and research centers have joined the Federal Laboratory Consortium for Technology Transfer. Through this Consortium, there is a network of transfer representatives who help establish this contact even between individuals in different parts of the U.S. It also assists in developing new methods for technology transfer and in transferring these methods to the laboratories.

Programs In Other Nations

Our understanding of the methods used in Europe and Japan is superficial, but several observations may be made. In the UK, a deliverate government policy in the early 1970s forced its government laboratories to seek industry-sponsored research and technical services to maintain the size of their professional staffs. Laboratories in the Federal Republic of Germany have come under increasing government pressure to demonstrate effective technology transfer. Industry researchers participate in the programs of the Max Planck Institute, which also commercialize some of their technologies through a related institution, Garching Instruments. The applied research laboratories, such as those at Karlsruhe and Julich, emphasize patent licensing and industrially-sponsored research, respectively, and also encourage individual entrepreneurship, though with few successes. The technology (versus research) emphasis of many Japanese laboratories, coupled with strong involvement of industry and university personnel, appears to create an institutional continuum between technology development and industry which bypasses much of the transfer problem.

d. Transfer of the Mass Spectrometer Technology

Besides these considerations of transfer of technology between a national laboratory and private enterprise, the institutional interactions of this scientific experience also included those of customer needs. These largely stemmed from university research and government agricultural research laboratory needs, with a small component of private industrial research requirments. These led to an increasingly urgent desire for a solution to the mounting problem represented by the continuing flow of smaples.

During its development at the National Laboratory, no patents were granted for the automated mass spectometer, which probably made the transition easier. In order to hasten the transition process, we attempted unsuccessfully to use temporarily the existing mass spectrometer equipment in an industrial capacity either where it was or elsewhere. Instead, an interim arrangement was developed whereby the Laboratory charged a fee for services and continued to perform analyses while Isotope Services was purchasing and constructing its own equipment, which occupied about six months.

Although the two machines were of similar design, several improvements were incorporated into the new machine. A water wash cycle was included which was automatically operable. The liquid nitrogen chilling for sample gas purification now consists of lowering a loop of tubing into a cup of liquid nitrogen rather than causing a small stream of liquid to flow over the tubing. This conserves the cryogenic fluid better. By using a viscous inlet leak as wide open as possible without producing fractionation of the flow, we are able to achieve good reproducible signals from less than one torr inlet pressure. This is a ten-fold improvement over the Los Alamos National Laboratory instrument.

We have been operating for about a year. Meanwhile, we are considering automation of other isotopic analyses at the Laboratory. If we succeed we shall be very thoughtful when we say, does anyone have any samples for us to run?