

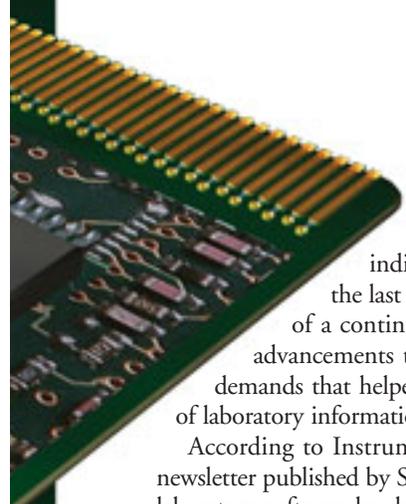
ILLUSTRATION: TONY FERNANDEZ

# LIMS

## From Chromatograms to Computers

Laboratory information management systems  
were born of the needs of  
researchers and regulators alike.

*James F. Ryan*



**I**t is amazing to witness the way in which computers and laboratory software have changed how an individual chemist works in the lab over the last 50 years. This dramatic change is part of a continuing evolution, fueled by technology advancements to be sure, but also by the regulatory demands that helped launch the rapidly developing field of laboratory information management systems, or LIMS.

According to Instrument Business Outlook, a bimonthly newsletter published by Strategic Directions International, Inc., laboratory software has become a world-class enterprise in and of itself. According to SDI, computer systems for chemical laboratory applications are a \$2.5 billion market made up of six key sectors. These include proprietary software for such lab staples as pH meters, balances, and similar equipment; chromatography and spectroscopy software for automating the identification and quantification procedures of laboratory analytes; LIMS to track laboratory sample and affiliated data; informatics subscriptions to proprietary databases; and the newest category—laboratory data management systems—which allow data from disparate data sources to be stored and accessed securely.

Today, lab data are handled by vast computer warehouses of servers and processors, all connected to extensive networks of data highways coming from various laboratory instruments or

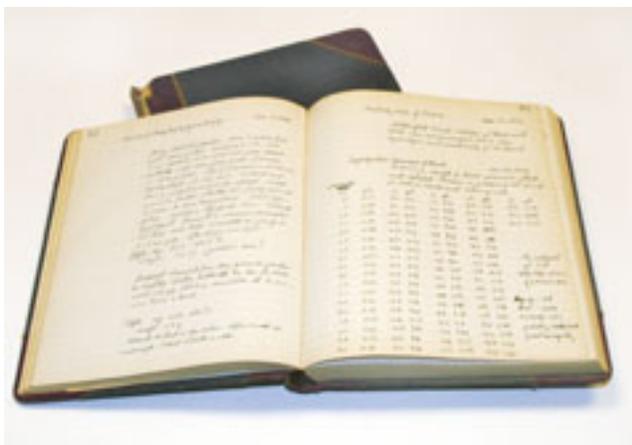
sample warehouses. These warehouses track every facet of a lab operation, from who did an analysis to how it was quantified, and even when and by whom the data were accessed. But it was not always this way.

Figure 1 shows how lab data looked in 1945—handwritten notebooks that had pen-stroke descriptors of experimental design, sample source, sample location, and analytical data. Such notebooks offered security as well, because each page was signed by the practicing chemist and could be photographed and reduced to microfiche as a means of archiving data and intellectual property. In many instances, original notebooks could be locked in vaults to ensure the ultimate integrity of original data.

### Chromatography

Laboratory data can consist of any measurement. Tare weight, pH, solution composition . . . any of these numbers can be recorded in a lab notebook or a modern computer. A preponderance—some would say in pharmaceutical research, most—of our laboratory data comes from some type of chromatographic process.

Chromatography, arguably the technology that helps to make chemistry the central science, was conceived in the 18th century and named in the 19th by Mikhail Tswett, a Russian botanist. While studying chlorophyll and other pigmented constituents of plant materials, he poured a petroleum extract down a glass column filled with precipitated chalk. As he contin-



**Figure 1.** Laboratory notebooks from 1945.

ued to pour more solvent onto the column, the mixture migrated down the column, separating into colored bands. He named this process from the Latin for “color writing”, chromatography.

Modern chromatography was the progeny of A. J. P. Martin, then working for the Wool Industries Research Institute in the United Kingdom in the early 1940s, who found he could separate amino acids on a column of silica gel if the latter material had been coated with water. Water, when bound to silica gel, served as a stationary phase while the amino acid mixture, dissolved in chloroform, moved over and around the stationary water beads. As the amino acid mixture traveled down the column, each component partitioned and separated from the others.

Martin noted that as long as one could volatilize the constituents of a mixture, a gas could be substituted for chloroform as the chromatographic mobile phase. For these discoveries and this insight, a cornerstone in the work of laboratories around the world today, Martin received the 1952 Nobel Prize in Chemistry.

There are numerous applications for the many types of chromatography. Among the most widely used in today’s laboratory are gas and high-pressure liquid chromatography. In the former, helium or nitrogen acts as the mobile phase. HPLC has come to be used extensively in the pharmaceutical world, where analytes can be very complex and subject to temperature degradation in the gaseous state.

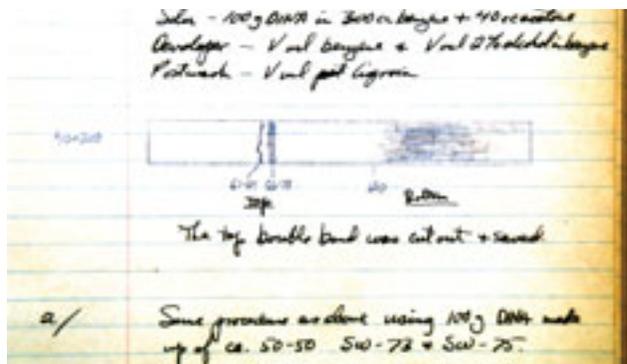
Figure 2 shows a chromatography experiment from 1945 in which DINA, a nitroamide explosive, was separated from a complex mixture on silica gel. Note the double band that was isolated for further study and characterization in a process similar to what Tswett used 42 years earlier. This is a very physical chromatographic separation, easy to visualize and understand. Separated material could even be weighed to determine its percentage of the original mixture.

In the early 1950s, chromatography, especially gas chromatography, developed into a laboratory experimental process that was not nearly so literal. Red strip-chart recordings on printed graph paper were data repositories, with postchromatographic algebraic quantitative calculations dependent on techniques that ranged from counting graph paper squares under each GC peak to laboriously cutting peaks out and weighing them in a laboratory balance.

## The Integration Era

In what now appears to be the first movement toward laboratory automation, instrument companies in the late 1950s began to develop electronic integrating devices to automate chromatographic identification and postrun quantitative calculations. Figure 3 shows two integrators from those days. The first used nixi tubes that counted up peak areas. The second is an HP 3350 integrator, which was the first that could print both a chromatogram similar to the earlier red-pen strip-chart recorder as well as the peak area of each analyte and standard and the postrun calculation of analyte concentrations. These devices were very popular in the petroleum refining industry and environmental monitoring labs of the time.

But in the 1980s, the world of single-method integrators was augmented, if not supplanted, with the rise of the chromatography minicomputer. Hewlett-Packard’s 3350 LAS Lab Automation System and Perkin-Elmer’s LIMS 2000 CLAS chromatography laboratory automation system began to be widely used in research and quality control centers associated with pharmaceutical companies, forensic labs, and the like. These systems handled data acquisition and postrun calculations from 16, 32, or even more chromatographs simultaneously and probably represent the high point in terms of cost of computers devoted exclusively to a laboratory function. In contrast to the “big iron” of minicomputers, the 1980s were also the years when chromatography, among other laboratory data acquisition functionality, came to the personal computer.



**Figure 2.** Chromatography experiment from 1945.

At first, the Apple II was used for data acquisition, but it was with the development of the IBM PC and its clones that the era of laboratory instruments, especially chromatographs, being individually connected to a computer began. Nelson Analytical introduced its 2600 chromatography data acquisition in 1984 (see Figure 4), and laboratory computing has never been the same.

## Fighting Fraud

We have moved from the era of notebooks to strip-chart recorders to integrators to minicomputers to PCs to the integrated and networked lab world of today, and the rationale is in part the need for analytical efficiency. Cutting out peaks from a red strip-chart trace or even bands from a chromatographic column is time-consuming. But other rationales for laboratory computer omnipresence also exist, one of the more important being the



**Figure 3.** Early digital integrators.

need for organizations that provide data for government review to document every facet of their laboratory operations.

In a 2001 *TCAW* article (<http://pubs.acs.org/subscribe/journals/tcaw/10/i11/html/11regs.html>), Roger Novak showed that laboratory fraud, specifically a case involving a company named Industrial Bio-Test of Northbrook, IL, resulted in the imposition of Good Laboratory Practices (GLP) regulations on commercial laboratories. It may be hard to imagine today, but in 1977, Industrial Bio-Test was performing 40% of all toxicology studies in the United States. Unfortunately for those who contracted with IBT, record-keeping could be described at best as slipshod. The numbers of animals in different toxicology studies were miscounted and, in some cases, if too many animals died during a study, new animals were substituted. According to a story in the *Washington Post*, "Some animals died more than once and others disappeared and reappeared." This of course became known as the Lazarus rat phenomenon.

### Tweaking and Spiking

There have been other cases of lab fraud that involved fraudulent manipulation of chromatographic data. As reported in the *Dallas Morning News* in 1992, the president and 14 employees of Craven Labs in Texas were convicted of "fabricating tests by skillfully tweaking knobs on lab machines, spiking test samples, and other methods." In still another case, 13 employees of a company called Intertek Testing Services in Austin, TX, were indicted for failing to follow adequate environmental quality control procedures in the analysis of samples from over 1700 sites. In a six-week trial in 2001 with over 60 witnesses and 1000 exhibits, the defendants were acquitted when the government failed to show that the manual manipulation of laboratory data resulted in compromising the quality of the submitted data. The government argued that "accuracy of results" was immate-

rial and what was prosecutable was Intertek's failure to follow the laboratory's standard operating procedures.

Among the hoaxes recounted in these cases were offenses such as time traveling, where computer time stamps on sample receipt or data collection times were changed; peak shaving, where the area of chromatographic peaks was adjusted to meet quality control specifications; and overspiking of standards to show acceptable chromatographic limits of detection. There were even cases in which companies kept double sets of sample log books, and in one memorable case, analysts were shown to have used the zero control knob on a strip-chart recorder to dial in a peak where none existed.

### Running with Regs

The IBT case in particular resulted in 1976 federal regulations requiring laboratories that submit data in support of environmental or pharmaceutical applications to adopt and follow GLP guidelines. These regulations require that there be verifiable standard operating procedures in every lab and adequate quality control procedures that are audited by sources outside normal laboratory staff. Over the years, GLP regulations have been extended to where they are now required for the collection of data for all Food and Drug Administration submissions, as well as for pesticide toxicology studies and registration applications. A similar set of Good Manufacturing Practices regulations, analogous to those affecting labs, has been extended to those who



**Figure 4.** Nelson Analytical advertisement, 1984.

manufacture or process drugs, medical devices, and similar products.

In the latest round of laboratory computer procedures, in 1997 the federal government promulgated regulations on data security, data integrity, and data traceability. Known as 21 *CFR* Part 11 for the location of these specific regulations in the panoply of government documents, these regulations require laboratories, pharmaceutical manufacturers, and similar organizations to carefully control and monitor access to electronic records, and that data integrity be ensured by preventing unwarranted changes to research data. Further, electronic signatures can be used, but only if they are linked back to an authorized individual and include

the date and time of their application. In addition, there are extensive requirements for audit trails and data storage.

The 21 *CFR* regulations were revised as an absolute standard in February 2003, becoming more a federal guidance policy than a regulatory necessity. This allowed older record-keeping systems that may have depended on paper audit trails and physical signatures to remain in what might be called a state of FDA grace, and any movement by pharmaceutical manufacturers toward full electronic systems to be done at a more measured pace. This view was echoed by Soheil Saadat, president and CEO of Scientific Software, a large supplier of electronic tools for chromatography data systems, content management, and data acquisition software. Saadat said, "Withdrawal of the mandatory requirement for 21 *CFR* regulations allows companies with enormous amounts of legacy systems to be more flexible in their process of change."

As companies implement LIMS technology ever further, these systems will undoubtedly become more integrated with organizations' enterprise resource plan systems and their document management electronic structures. According to Jo Webber, CEO of Innaphase Corp., "The successful integration of LIMS with a customer's overall IT infrastructure is critical to that organization's profitability strategies and regulatory compliance. This allows companies to fully monitor and control all the resources in their



organization, from laboratory to final product."

If you look at today's laboratory data world integrated throughout an organization, it's almost like a set of Russian dolls. Each electronic system opens to reveal a smaller one inside. There are terabytes of laboratory data based on sample location and data integrity, much of it tied to a chromatography data system that answers questions on retention time and analyte quantity.

Over the last 50 years, computers have become so much a part of the laboratory that we sometimes fail to realize that their coming arose from the need to change pen-and-ink recorded data and cut-out chromatography peaks into a manageable form. Nevertheless, if you look deeply enough at a modern LIMS chromatography system, there will ultimately be a chemist trying to separate one chemical from another.

#### Suggested Reading

Gibbon, G. A. Brief History of LIMS. In *Laboratory Automation and Information Management*; Elsevier: 1995.

*Chromatography: Creating a Central Science*; American Chemical Society: Washington, DC, 2001. ♦

**KEY TERMS:** biotech, data handling, environmental, GC, LC, MS, pharmaceutical, sample prep, separation science, spectroscopy, synthesis