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Computer assisted automated drug analysis

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THE NATIONAL CENTER for Drug Analysis was established in 1967 as a division of the Office of Pharmaceutical Research and Testing, Bureau of Drugs, Food and Drug Administration. Programs assigned to the Center called for the analysis of large numbers of pharmaceutical products. We decided to use automated analytical equipment as a means of handling the large volumes of assays required by these programs.

A typical automated system has four major subsystems: 1) sampling, 2) analytical, 3) electronic detection, and 4) read-out or reporting. A typical system in use at the Center employs a liquid sampler, a miniature wet chemical analytical system, a colorimeter, a spectrophotometer or a photofluorometer, and an analog strip-chart recorder. Such a sys- tem operates as follows:
An equilibrium condition is established by pumping washing solvent through the system with the recorder running. The recorder pen traces a straight line (baseline). Once equilibrium is established, the liquid sampler is started, and a prearranged group of samples and standards is pumped through the system at timed intervals. Quantitative values for all solutions pumped through the system are traced by the analog recorder. The usual run amounts to a combination of 60 assays and 12 standards flanked by baselines. (Each assay represents one individual dosage unit of some drug.) The usual rate of analysis for a run is 20 or 30 assays/hr.

We soon found that these automated systems could generate data much faster than we could process them by visually reading the charts, doing the calculations on a desk-top calculator, and manually recording the results. The acquisition of digital concentration read-out units was the first step toward speeding up calculations. This phase was followed by programmable calculators, which were a great improvement. Since we still needed greater throughput of calculating and reporting, however, we obtained a small digital computer for use in the laboratory.
The initial objective was to have the computer collect analytical data directly from laboratory instruments, perform the necessary calculations, and produce a print-out of the results. We soon realized that it would also be very desirable to have the computer keep track of our sample inventory and produce periodic summary reports. Thus, our revised goal for computerization became the development of a direct (on-line) data collection and reporting system, and an information system. Together, these systems would afford the Center a highly efficient means of performing tens of thousands of assays on a variety of pharmaceutical preparations, statistically analyzing these results, reporting these results to the proper decision makers, and collecting the necessary historical data for the planning of future programs.

A Hewlett-Packard model 2116C minicomputer was selected because of the advantages of the total hardware system and the multiprogramming capabilities of the real-time executive software operating system. Peripheral input options include analog-to-digital conversion, punched cards, and punched paper tape. Output options include paper tape, a line printer, and digitalto-analog conversion. Input/output devices include Teletypes, a cathode ray terminal, and magnetic tape and disk mass storage units. We now have 24,000 words of core memory.

The previously mentioned software system provides from one to four distinct areas of core storage for use by the programmer. This division of core memory into separate areas allows simultaneous residence of multiple programs in the computer. The program priority, system, the interrupt system, and a program swapping feature work together to allow simultaneous execution of several programs (commonly referred to as multiprogramming). All input/output requests are controlled by the system, and the necessary drivers for the computer I/O cards are supplied with the system. The system accepts user programs written in FORTRAN or the vendor's assembly language.

The project of providing the electronic hardware necessary to make the automated analytical instruments compatible with the computer was undertaken by NCDA staff. The original basic design employed conditioned operational amplifier circuits that converted the output of a spectrophotometer, a photofluorometer, or a recorder slidewire (when using colorimeters) to a range of + 10 to -10 v. A recent design for use with colorimeters employs only a retransmitting potentiometer attached to the recorder slidewire to produce voltages in the range of + 10 to -10 v. The output from the instrument interface module is transmitted to a multiplexed analog-to-digital converter over shielded, twisted pair cabling. (The converter multiplexes 16 analog channels.)

The programs that comprise the data collection and reporting system have been given the name AUTO1, a system of 15 FORTRAN programs working together to provide simultaneous, direct collection of data from 1 to 16 automated systems, each starting and stopping independently of the others. For each channel, the computer detects and stores values for a leading baseline, all peaks encountered, and a trailing baseline (end-of-run condition).

Upon detection of end-of-run condition for any channel, a flag is set to notify a processor program to attempt calculations. At this point the processor module attempts to extract data from a file supplied by the chemist and entered into the computer via punched paper tape. If the file is present, and the number of peaks observed matches the number of peaks expected, the assay values are calculated and statistically analyzed by the computer. The results of the chemical and the statistical analyses are ultimately printed on a line printer
by the report-writer subsystem. Upon completion of a report, the report writer calls back the processor module. The processor checks a list of work-to-be-done to see if another channel is ready for processing. If so, either the cycle of processing, analyzing, and reporting is repeated, or the processor program halts until again executed because of the occurrence of an end-of-run condition.

In addition to the ability to process data immediately at the end of the run, the system can reprocess the data by an off-line program module. This same module can be used to process data collected by visually reading analog charts.

We have also had some success with the information system portion of our goal. Again using FORTRAN programs, we have developed a computerized system for the control of sample inventory and for producing periodic summary reports.

In summary, the National Center for Drug Analysis is a Food and Drug Administration laboratory having the responsibility of analyzing large volumes of varied pharmaceutical preparations. These preparations are now being processed chiefly by means of computer-assisted automated drug analysis. We have been successful in interfacing automated systems that use a variety of detection devices. The present hardware and software will support up to 16 independent systems. Our chemists and technicians have shown excellent acceptance of AUTO1, and have cooperated in the establishment of an interactive feedback loop with the computer group, whose members include Raymond C. Grant, Wade Noxon, Clyde E. Wells, Edward O. Gotway (Consultant), and Eugene Bosley (Supervisor).