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ANALYTICAL INSTRUMENTATION FOR THE 1980's

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Abstract - Several microcomputer-controlled analytical instruments are described that illustrate certain automation concepts, focus attention on some recent developments, and help us to envisage what might be introduced during the 1980's. New types of stop-flow analyzers are shown to have considerable promise for routine and investigative kinetic and equilibrium analytical/clinical methods. Throughputs of up to 500 samples/hour with 0.1 to 1% precision are practical. Various types of rotating-disc analyzers are also described. These include a multisample colorimeter, a unique multiple absorption-curve spectrophotometer, and a multitest or multisample analyzer for clinical/analytical laboratories. Complete systems are discussed, including preparation and transport of samples and reagents, the encoding of the desired chemical information as digital electronic signals, optimization and control of measurement conditions, data processing, and final display of the chemical information.

INTRODUCTION

Impressive developments during the 1970's have paved the way for an exciting new generation of automated analytical instruments for the 1980's. Microelectronics and microcomputers and other evolving technologies are having a major impact on instrument design. This, indeed, should be the decade of elegant microcomputer-controlled analyzers.

Many of the recent instrument designs now in production by several companies incorporate microprocessors to provide improved sensitivity, selectivity, precision, and accuracy for classical analytical techniques. Spectrophotometers, pH meters, titrators, gas/liquid chromatographs and many other commonly-used instruments are all benefitting from the effective control and "intelligence" introduced by inexpensive mass-produced microprocessors. The interlinking of several "intelligent" instruments by automated communication networks will lead to more and more automated laboratories and even to automated research and development.

A complete automated analytical system should, of course, start with reliable sampling and ensure positive sample identification throughout all operations. After automatically preparing the sample for measurement, all of the desired chemical information should be encoded as digital electronic signals so that the data can be readily processed and the results displayed in the best format for aiding the personnel who require the data. Every step in the automated analytical process should involve "closed loop" feedback, including calibration and checking of all devices and parameters (wavelength, photometric readings, temperature, etc.) against certified standards each day, hour, or even each series of determinations to ensure accurate results. It would also be desirable to provide automatic "trouble shooting" and maintenance of the instrumentation so as to eliminate significant "down time" and loss of critical information. Considering the present status of automation, it is reasonable to expect significant developments along these lines during the 1980's.

Perhaps, this will be the decade of super analytical robots. If so, we need to consider their impact on an already-revolutionary era of analytical chemistry. How "intelligent" and versatile will they be? Will they provide an economical work force that can efficiently handle the complex environmental and clinical bioanalytical problems? Will they work "intelligently" on both research and routine laboratory measurements? How will they affect laboratory manpower requirements? What type of training should students and present analytical chemists seek and receive so as to work effectively with them? To gain some insight into these questions, I'd first like to describe some of the microcomputer-controlled analytical systems that we've developed in our laboratories. These systems include the automated preparation and transport of samples and reagents, encoding of the desired chemical

information as digital electronic signals, optimization and control of measurement conditions, data processing, and the final display of chemical information, as illustrated in Fig. 1. With these examples, it will be possible to illustrate several important automation concepts, to focus attention on present developments and speculate on what to expect in analytical instrumentation during this decade of the 1980's.

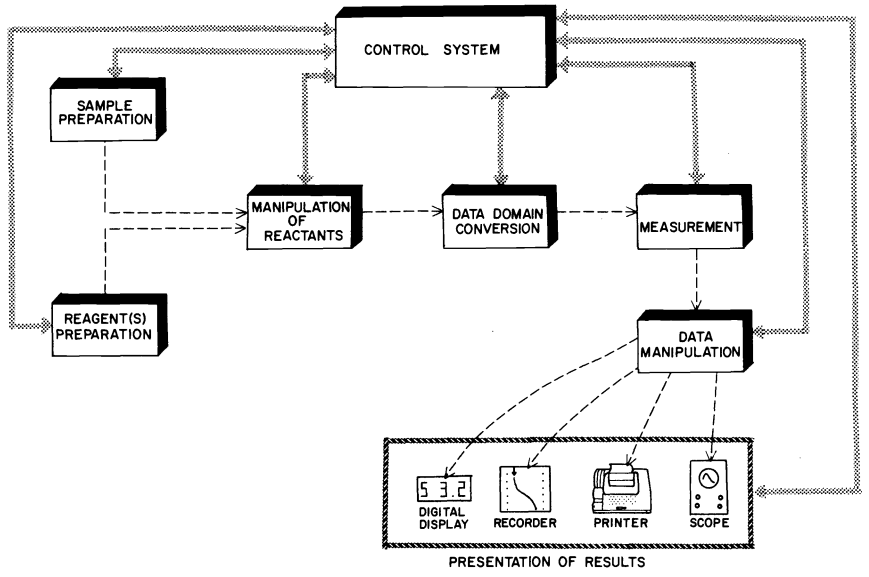

Fig. 1. General block diagram for a chemical analyzer.

MICROCOMPUTER-CONTROLLED STOPPED-FLOW ANALYZER

Sample and reagent preparation, transport, and mixing operations are often more time-consuming and costly than the encoding of the chemical information as electrical signals with subsequent data processing and display. Also, they are subject to frequent human error and bias. Therefore, a successful automated analyzer must accomplish these operations simply, economically, and reliably. An investigation of automated analyzers indicates that the greatest differences are in the methods of sample and reagent preparation, transport, mixing and cleanup.

One of the first approaches taken to automated sample and reagent handling and high throughput of measured samples was the air-segmented continuous flow analyzer (CFA) developed by Skeggs and the Technicon Corporation (1). In the past few years, the unsegmented flow injection analyzer (FIA) that was developed independently by the Ruzicka (2) and Stewart (3) groups has become increasingly popular, and its characteristics are often compared to the CFA. More than a decade ago (4,5), we developed an analytical stopped-flow analyzer (SFA) that has evolved into an increasingly useful instrument for routine or investigative high-speed analytical/clinical chemical determinations. The SFA has the high sample throughput of the CFA and FIA and has some significant advantages. The reagent and sample are precisly measured and quantitatively mixed so that precisions of 0.1% are possible with the SFA. Also, quantitative reaction-rate methods that are often more specific than the equilibrium methods can be readily used even for very fast reactions in the one second range.

Our most recent microprocessor-based SFA (6) is much simpler, inexpensive, and more compact than its hardwired or minicomputer-based relatives (7-10). The entire SFA system, shown in Fig. 2., is automated using an inexpensive Rockwell A1M65 microcomputer with self-contained keyboard, display, printer and ROMS for control of all operations, communication between modules, data acquisition and reduction, display and printout of results. The compact sample handling and photometric modules and the typewriter-size microcomputer occupy only about one-half square meter of bench space. The programs are provided for specific applications using kinetic or equilibrium quantitative analytical procedures. This system requires no operator attention during normal use.

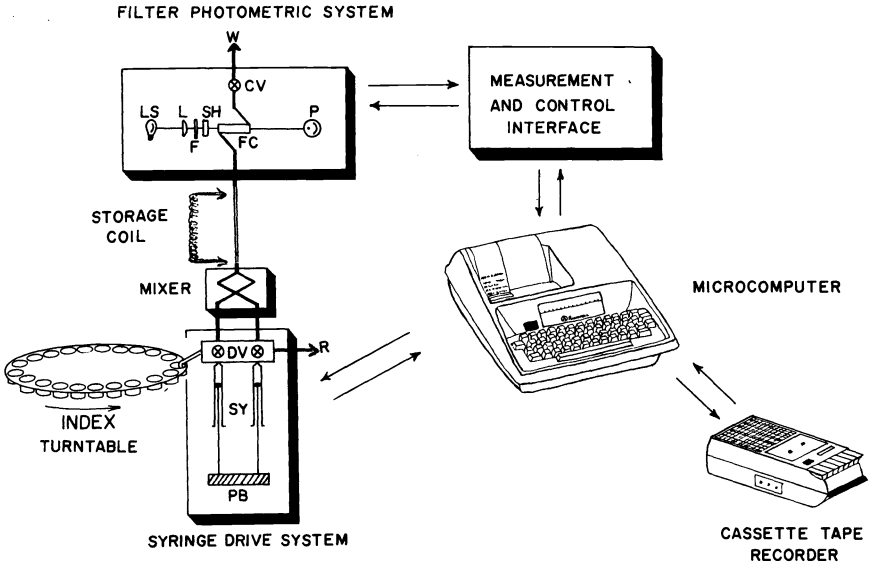

Fig. 2. Stopped-flow analyzer (SFA).

For rapid reaction-rate methods or with reactions that come to equilibrium rapidly, the SFA has a sample throughput of 400-500 samples/hour. This assumes pickup of sample from an automated turntable. However, for reactions that are slow, requiring 30 seconds or more to react, the sample throughput of the regular SFA drops to 100 or less samples/hour. To improve the throughput for the SFA with slow reactions, we have introduced a storage coil between the mixer and observation cell, as illustrated in Fig. 2. We have shown (11) that an unsegmented solution-storage technique is successful. The throughput of this new stopped-flow/unsegmented storage analyzer (SF/USA) is excellent while retaining the previous advantages of the regular SFA. Present studies indicate that the SFA with a segmented solution-storage technique (SF/SSA) has certain advantages over the SF/USA. Quantitative results with the SF/SSA compare favorably with the regular SFA.

The sampling/mixing device for the stopped-flow analyzers is illustrated in Fig. 3. It is based on an automatic dual syringe pipette/mixer that was developed in our laboratories.

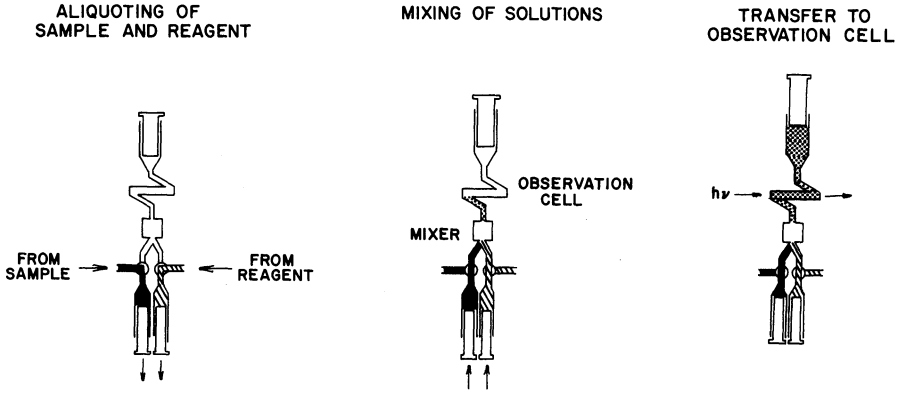

Fig. 3. Sampling-mixing system for the SFA.

The aliquoting, transporting, and mixing of solutions with a precision of 0.1% is readily accomplished. The high precision, sensitivity, excellent sample throughput, and negligible start-up time should make the SFA, SF/USA and SF/SSA very popular during this decade. Improvements in design and even more compact instruments than the one illustrated in Fig. 2. can be expected in the next few years. Plug-in programs for hundreds of specific procedures will make it possible to put these instruments into immediate use in most laboratories. Prepackaged reagents will also simplify the start-up procedure for specific methods.

Rapid sequential analyzer

The schematic diagram of a SFA that can operate in a rapid sequential mode (12) is shown in Fig. 4. The chemical methodology can be changed automatically by a simple and rapid change

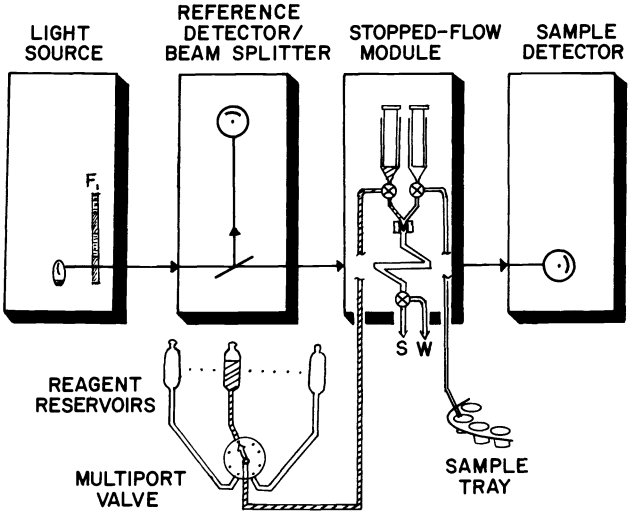

Fig. 4. Rapid sequential analyzer (S is the stopping mechanism; W is waste line; M is the mixer).

in the position of a multiport reagent valve and selection of an interference filter to isolate the desired wavelength for absorbance measurements. Analytical techniques based on kinetic, equilibrium, or enzyme activity procedures can be specified by the operator through a keyboard. A unique reagent-preparation system based on bulk solution reagents was developed (13) and used with the rapid sequential analyzer, and it is presented in the next section.

Automated solution-handling system using weights of solutions

An alternative to the automatic pipetting stations which accompany most automated discrete analyzers is a computer-controlled solution-handling system based on weights, as illustrated in Fig. 5. An electronic sensor is used to weigh accurately nominal aliquots of sample and reagent solutions that are added in small increments to a disposable beaker. Each reagent or sample is accurately weighed after addition, and the beaker is then automatically moved to a stirring station while another beaker is moved into position for weight measurements. The amounts of reagents added to the beaker can be incrementally adjusted as desired. The continuous electronic feedback of weight information allows for automation as opposed to

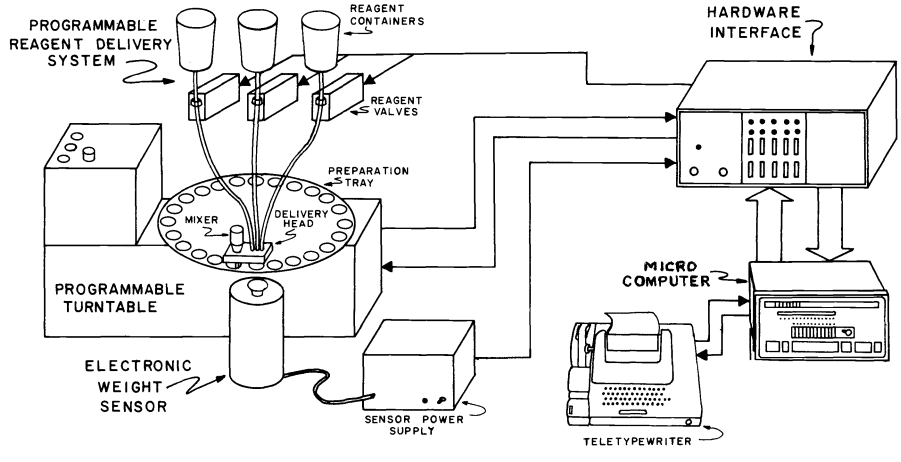

Fig. 5. Sample/reagent preparation using electronic weight sensor with microcomputer feedback.

mechanization. At present, samples equivalent to about 200 µl, must be weighed for better than 0.5% accuracy, and about 1 ml for 0.1% accuracy. For clinical samples, it would be feasible to start with one larger sample which can be measured accurately (e.g. 200 µl of blood serum) and then dilute about 10-100 times to provide a single solution from which nominal aliquots could be taken and weighed for all desired tests. The net amount of sample used for each test might be only 2-20 µl, but each weight measurement involves larger nominal aliquots (such as 200 µl or more) which can be determined more reliably. This procedure is also applicable for pipetting stations as well as electronic weighing stations and should always be considered for more accurate results when only small amounts of sample are available.

The rapid feedback of information between the weight sensor and the microcomputer allows the controller to monitor as well as control the operations (13). It is not necessary to rely on the expected delivery of a preset amount from the pumping devices. The general utility of the weight sensor system results from the ability of the microcomputer controller to quickly and without operator intervention change the solution delivery parameters, and then monitor those changes through weight sensor information. This system has considerable promise for automated mechanistic studies of chemical reactions, and for preparing samples on a routine basis for standard addition techniques. Relatively inexpensive commercial sample/reagent preparation instruments based on automatic weight, nominal digital reagent addition, and microcomputer feedback could become available in the next few years.

Automated system

The combination of the automated weight sensor and with the stopped-flow unit shown in Fig. 4. provides a completely automated system (9). Its stepwise operations are illustrated in Fig. 6. The operations are the same as for a classical spectrophotometric procedure - except each of the operations with this system is automated and rapid.

On request by the operator at the keyboard (step 1) the monochromator and electronic balance are calibrated (13,14). The operating parameters for the quantitative determination of a specific chemical constituent are automatically set (steps 2 and 3). This includes the setting of the absorption wavelength, selection of the desired composite reagent, and other parameters for optimization of each procedure.

Next, it is necessary to sequence through three procedures. One operation provides the spectrophotometric dark and 100% transmittance information for the blank solution. A second set of operations involves the standardization of the analytical method against a set of standards. A third operation is the acquisition of absorbance data for a series of unknown samples.

The spectrometer is initialized (step 4A), by delivering a measured amount of diluent into an empty cup on the turntable. This cup is now stepped to the next position (step 5), the solution is stirred (step 6), which makes the diluent(s) available to the sample channel of the SFA. Aliquots of the blank and reagent are now drawn into the syringes (step 7) and then delivered through the mixer (step 8) into the observation cell (step 9). Steps 7 through 9 are repeated the desired number of times to flush the SFA, and then the dark and 100%T data are acquired and stored (step 10).

The automated system now prepares a working curve (step 4B). An empty cup on the turntable is weighed and a nominal amount of desired stock standard solution is delivered into the cup and weighed. A nominal amount of diluent is then added and weighed to provide an accurate standard based on the weights of standard and diluent added. The turntable is then stepped to the next position where the solution is stirred and made available to be aliquoted by the sample channel of the SFA. The SFA is flushed and steps 7-10 are repeated for the desired number of standards. Thus, a working curve is automatically prepared and stored in memory.

Samples can now be analyzed by proceeding to step 4C. A nominal aliquot of sample(s) is placed in a cup on the turntable, weighed, diluent added and again weighed to give a known dilution. The turntable is then indexed and steps 6 through 10 are repeated as for the standards. The unknowns are automatically measured, and the results that are based on the stored working curve are printed out.

All of the steps described in this procedure can be performed rapidly. The selection of reagent requires less than one second, setting of parameters only about 5 secs, the preparation of four working-curve standards about 2 min. and a total time of about 3 minutes to obtain and store the working curve if the measurement time for the specific analytical procedure is only a few seconds. The throughput of samples will depend on the reaction time after mixing reactants, and will be typically 100-500 samples per hour for both kinetic and equilibrium procedures.

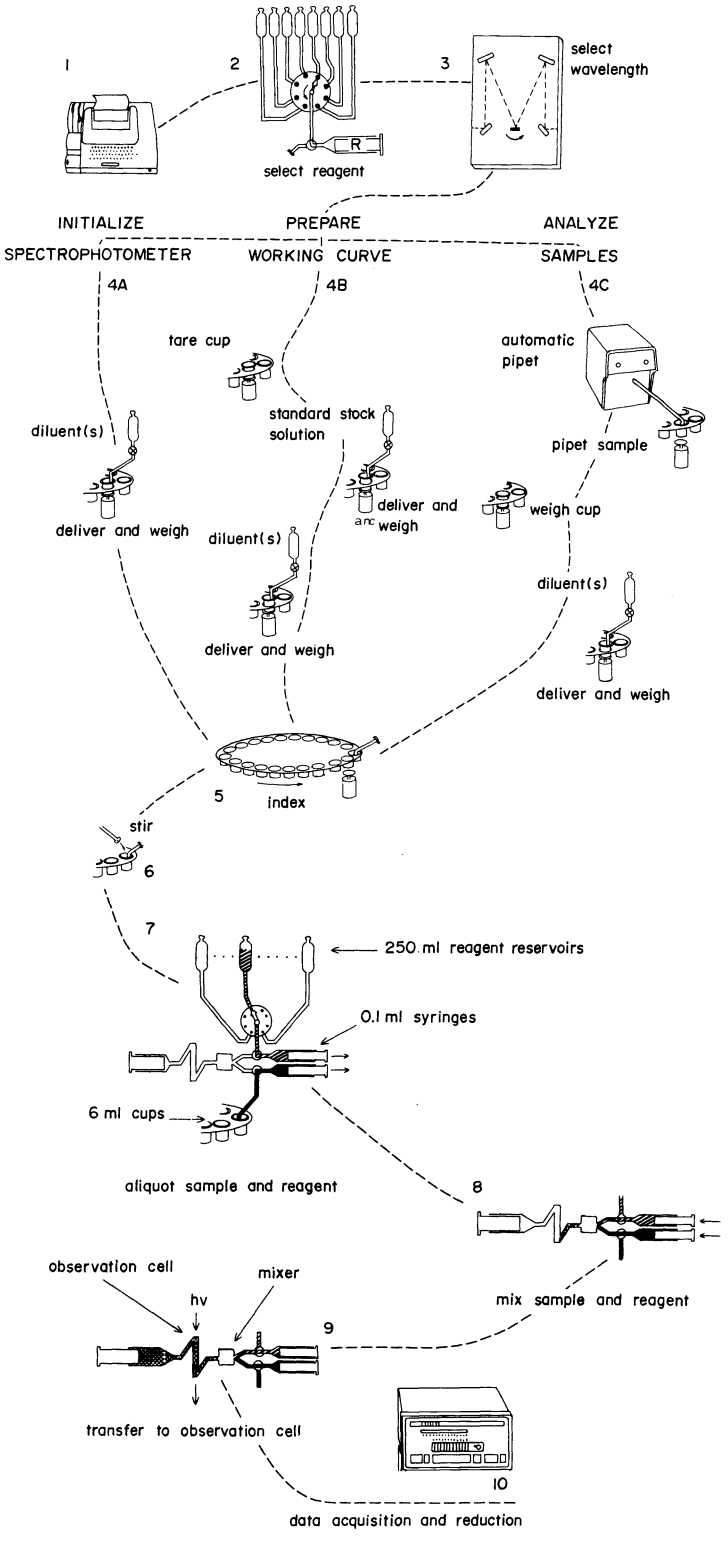

Fig. 6. Automatic system combining weight sensor, nominal incremental pipettes, and stopped-flow unit.

ROTATING DISC ANALYZERS

The novel concept of using a spinning disc for simultaneously mixing multiple samples with a reagent and determining the concentration of each by measuring the absorbance or fluorescent radiation with a single beam photometric system was originated and developed at Oak Ridge National Labs (15). The instruments introduced at Oak Ridge were known as centrifugal fast analyzers, and nearly all of the early chemical methodologies were aimed at providing clinical tests for constituents in serum. Samples and reagents are pipetted into individual holding compartments in a disc. The discs typically have about 15-30 sample compartments and one reagent compartment associated with each sample compartment. When the disc is rotated at high speed, the sample and reagent from each pair of compartments are dumped through a mixing orifice into a photometric observation cell. Each of the sample cells passes successively past a photometric measurement system as the disc spins, and usually the photometric data from several rotations of the disc are averaged for each sample. The parallel mixing of many discrete samples and standards with rapid successive measurements provides for unique procedures and high precision. The small discs and compartments on miniature centrifugal analyzers enable very small samples to be used with a significant reduction of reagent costs. At present the discrete loading of discs with sample and reagent are time-consuming when utilizing sequential loaders, but some work has been done on parallel loaders. Also, disposable discs preloaded with reagents are possible for some applications.

We have modified the centrifugal analyzers for improved precision (16) and versatility (17) for clinical analyses, but we have also utilized the rotating disc concept for applications different from the original purpose. One of these applications is as a versatile automated multisample spectrophotometer in which the desired precision and resolution can be preset at the keyboard. Another application is as a versatile multisample microcolorimeter that has several advantages compared to ordinary absorption photometers that are used for quantitative chemical determinations of specific analytes. A multichannel and multiwavelength rotating disc analyzer (RDA) has also been developed that allows multitests as well as multisamples on a single disc. Clinical profiles can be run on a single disc, and as many as 250-500 tests per hour could be performed with this system. Each of these three systems will be described because they illustrate certain concepts that should be generally applicable.

Microcomputer-controlled multisample rotating-disc colorimeter

Advantages of this RDA instrument (18) compared to ordinary colorimeters include the high precision that can be obtained, use of microsamples without the problem of micro air bubbles causing serious errors, measurement of many samples (easily 10-40) within a few seconds, optimum use of available light source energy for shorter measurement times, and automated movement of the disc into loading and measurement positions. The design features of the RDA are shown in Fig. 7.

The rotating disc unit moves into a measurement compartment as shown in Fig. 7. The light source is focused so that a sharp well-defined beam passes through the solutions in the sample cuvettes. A photomultiplier tube is used as the detector. The filter wheel has been installed on the upper side of the measurement housing in front of the PM tube. A small motor drives the filter wheel under microcomputer control, but it does have an alternative manual control.

The centrifugal head slides smoothly on two steel guide rods. Precisely-fitted linear motion bearings (bushings) ensure a friction-free movement. A threaded drive shaft connected to a reversible motor is used to drive the centrifugal head. Microswitches operate to stop the movement when the head has reached the proper position inside the colorimeter housing for absorption measurements, and outside for loading the discs.

The disc drive motor M, the mirror MR and the double convex lens L of focal length 35 mm have been installed on an aluminum base B. A metal adaptor AD is permanently fastened on the motor shaft that holds the sample disc SD and the encoding ring R. The ring R is made from plexiglass and has twelve encoding marks of black paint. The encoder and the photo-interruptor module P1 serve as the cuvet indexing pulse generator to indicate when each cuvet on the disc is in position for measurement. Another black mark on the same ring is similarly coupled with another photo-interruptor (not shown in Fig. 7) and generates the pulses for rotation indexing. The relative position of the filter FL on the filter wheel FW assembly when the centrifugal head is in the measurement position is also shown in Fig. 7.

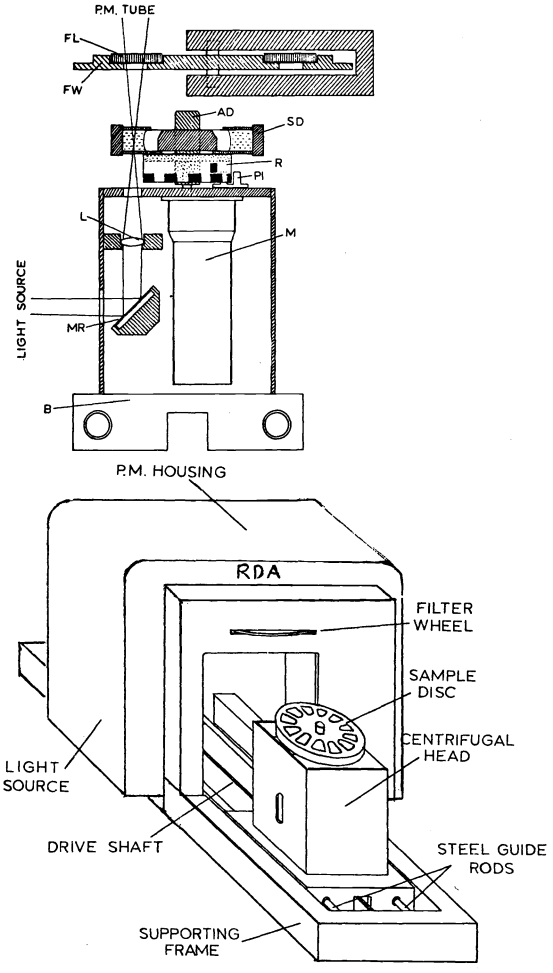

Fig. 7. Multisample rotating-disc colorimeter.

The rotating disc for this colorimeter has twelve sector-shaped observation cells with a pathlength of 1.00 cm as shown in Fig. 8. The sector shape is best for maximum collection of photon information for a given measurement period (19). The body of the disc is made from a machinable glass-ceramic material "MACOR" (Corning Co.) that combines good machining properties with a good resistivity toward most chemical reagents. The windows for the multisample disc are made from two quartz circular plates. Each plate has the necessary central hole, and the plates are cemented to the disc body with a silicone rubber adhesive.

Details of the assembled disc, one of the sample fill ports, the relative position of the solution and light beam, and the corresponding encoder are all illustrated in Fig. 8.

Measurement concepts (Ref. 18)

To obtain accurate photometric measurements over a wide absorption range two sets of correction factors should be used: The transmittance correction factors, τ_i and pathlength correction factors, p_i. The first set is used to correct for small permanent differences in the transmittance properties between the reference cuvet and each sample cuvet. These differences are mainly due to small scratches, glass defects and internal reflections, affecting the measured light intensity for each cuvet loaded even with a non-absorbing solution. The transmittance correction factor τ_i for the sample cuvet i is calculated by the Eq. 1.

$$\tau_i = \frac{T_r}{T_i} = \frac{1}{T_i} \qquad (1)$$

where T_r and T_i are measured apparent transmittance values for the reference cuvet and sample cuvet i both of them filled with a non-absorbing solution (e.g. water) in order to avoid the

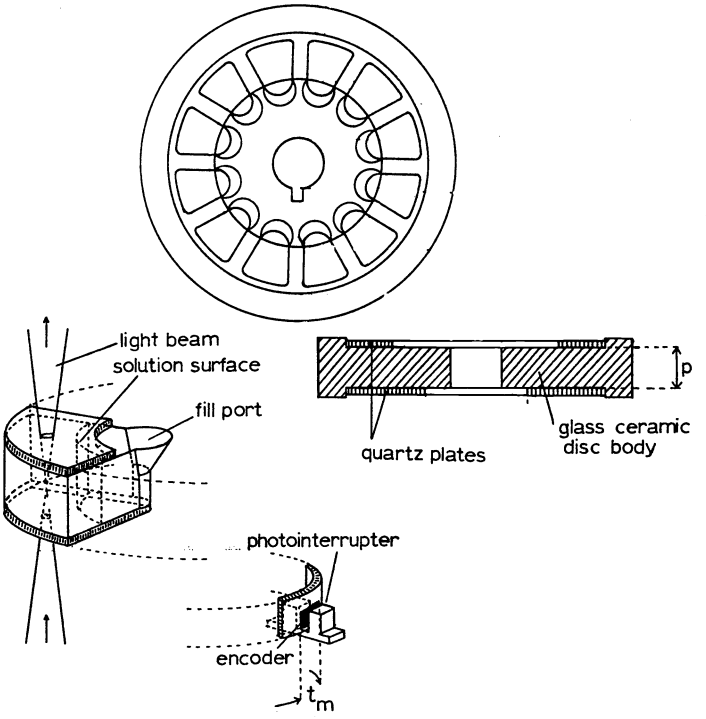

Fig. 8. Disc design for colorimeter.

effect of small differences of the pathlengths. As seen from Eq. 1. the transmittance of the reference cuvet is always equal to 1. Therefore, the corrected transmittance (T_i, cor) of the sample cuvet is given by Eq. 2:

$$T_{i,\,cor} = \tau_i \cdot T_i \tag{2}$$

Whereas Eq. 2. is valid for non-absorbing solution, when the measured absorbance becomes higher another correction should be made to compensate the small differences of the pathlengths. To compensate for the pathlength differences and match the sample cuvets between each other, one of them should be designated as the standard cuvet. The first cuvet (i=1) is considered as the standard cuvet. Therefore, the pathlength correction factor is calculated by Eq. 3:

$$p_i = A_1/A_i \tag{3}$$

where A_1 and A_i are the apparent absorbances of the cuvets 1 and i, both of them being filled with the same absorbing solution. Therefore, the absorbance when normalized for pathlength is given by

$$A_{i,\,cor} = p_i A_i \tag{4}$$

Combining Eq. 2. and Eq. 4., and using the known relation between transmittance and absorbance, the corrected absorbance is:

$$A_{i,\,cor} = -p_i \log(\tau_i\, T_i) \tag{5}$$

It is noteworthy that if the centrifugal analyzer is to be used for kinetic methods of analysis, and the measured quantity is the first derivative of absorbance with respect time, dAi/dt, the set of transmittance correction factors is not necessary. This can be shown by differentiating Eq. 5. and observing that p_i and τ_i are time independent.

A charge-to-count converter, that gives a count proportional to the number of photons observed by the photocathode over a measured period of time, has been used in this work. The apparent transmittance for the sample cuvet i can be calculated with Eq. 6:

$$T_i = \frac{(\sum_j n_i / \sum_j t_i) - (\sum_j n_b / \sum_j t_b)}{(\sum_j n_r / \sum_j t_r) - (\sum_j n_b / \sum_j t_b)} \quad (6)$$

where $\sum_j n_i$ and $\sum_j t_i$ are the total converter counts (a number proportional to the number of photons observed by the photocathode) and the total observation time, for j successive rotations. The totals $\sum_j n_r$ and $\sum_j t_r$, as well as $\sum_j n_b$ and $\sum_j t_b$ are the analogous quantities measured, respectively, during the time the beam passes through the reference cuvet and the "dark" cuvet. The use of a "dark" cuvet (a cuvet covered with black tape) allows a direct correction for any background output of the charge-counting system attributable to dark current of the PM tube and to any offset output of the charge-to-count converter.

Combining Eqs. 5. and 6., we obtain the final equation used for the calculation of the corrected absorbance values:

$$A_{i,\,cor} = -p_i \log \tau_i \frac{(\sum_j n_i / \sum_j t_i) - (\sum_j n_b / \sum_j t_b)}{(\sum_j n_r / \sum_j t_r) - (\sum_j n_b / \sum_j t_b)} \quad (7)$$

Automated multichannel spectrophotometer with rotating sample disc

By using the rotating sample disc concept, a new type of multichannel UV/visible spectrophotometer was developed (20). Simultaneous recording of UV/visible absorption spectra for several samples (10 or more with special discs) can be readily obtained with the spectrophotometer. In addition to the multichannel capability, the required sample volumes with the disc that we used are only 100 µl, and the system also provides for presetting the desired photometric precision during the spectral scans. A precision of 0.0001 to 0.1 absorbance units can be requested from the keyboard. A microcomputer can control the parameters necessary to attain the preset precision, trading longer measurement time for higher precision as required by photon statistical considerations. The block diagram of the system is shown in Fig. 9.

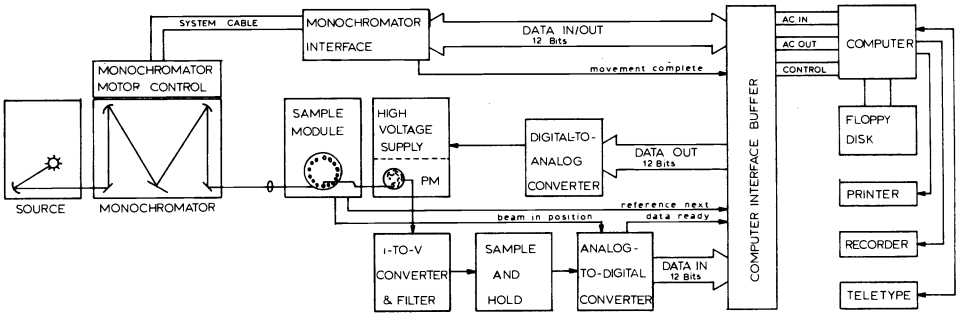

Fig. 9. Block diagram of automated multichannel spectrophotometer.

By mechanically designing the rotating sample disc system to fit on the optical axis of a modular commercial spectrophotometer, it has been possible to develop a computer-controlled ratio-recording UV/visible spectrophotometer that can simultaneously produce spectral absorption curves for many micro samples. The automated spectrophotometer allows the operator to select one of two modes of wavelength sequencing. In the scanning mode, the monochromator starts at one wavelength and obtains and stores all of the reference and sample information needed. Similar data are then acquired at preset wavelength increments (e.g., 0.01 to 10 nm steps) throughout the specified spectral range. In the discrete mode, individual wavelengths of analytical interest are selected by the operator, and the monochromator slews to each of these wavelengths sequentially. In both modes of operation, the grating is stationary during the spectrophotometric measurement so that true absorbance values can be measured when scanning across sharp peaks. The optical encoder for the wavelength drive on the monochromator used in this instrument makes it readily feasible to place the wavelength selection under computer control.

Another important feature of the spectrophotometer is the automated, real-time adjustment of instrumental conditions to obtain the level of precision desired by the operator. This type of control was originally demonstrated for photon counting systems (21). An analog output

of the photomultiplier tube (PM) detector is used in this instrument instead of counting photons, but it is found that with careful design, photon statistical errors are still the only major source of imprecision. The operator may specify the desired precision as either a coefficient of variation in absorbance, or a standard deviation in absorbance, depending upon the application, and the computer varies the measurement time at each wavelength in order to achieve the desired precision. It is believed that this feature will be included on future commercial spectrophotometers.

To implement the computer-control functions requires interfaces to the monochromator and to the photomultiplier power supply, an analog-to-digital converter system, and the software routines for photometric precision control, wavelength selection, and digital data manipulation and storage. The output information is recorded by either a chart recorder or a line printer.

Plots of precision (expressed as percent relative standard deviations, RSD's, of the measured absorbance values) versus the absorbance (19) at various numbers of averaged rotations from R = 1 to R = 1000 are shown in Fig. 10. The theoretical curves that are based on photon statistics are shown as the solid lines. They illustrate that for every 10-fold increase in the number of rotations at constant speed, there is a $\sqrt{10}$ increase in precision. It can be seen in Fig. 10 that the experimental points are quite close to the theoretical

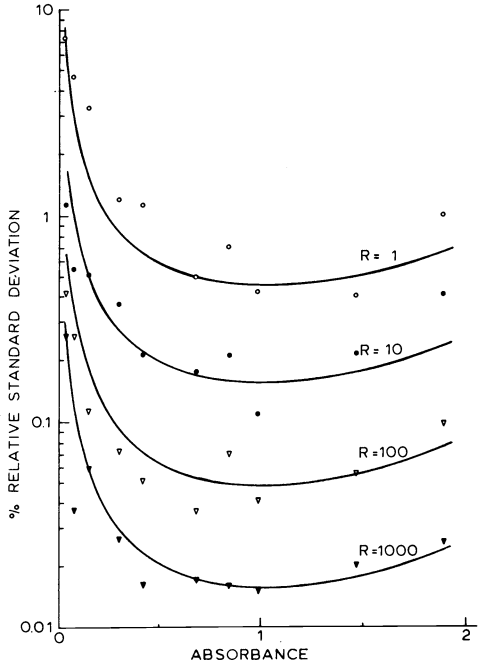

Fig. 10. Percent relative standard deviation as function of disc revolutions (at constant speed).

solid lines. This indicates that the rotating-disc system follows photon statistical considerations, at least down to % RSDs of about 0.02% for 1000 revolutions (about 30 seconds total elapsed time) but only 1-2 seconds measurement time for each cuvet). When the number of revolutions is increased to 10,000, the precision improves to about 0.01% RSD which indicates that other factors are causing variation in the absorbance measurements. It can be observed in Fig. 10 that the % RSD for any given number of revolutions does not change much from about 0.3 to 2 absorbance units, which is a point previously emphasized (16,22) but often neglected.

Spectra for five of the fifteen solutions of phenol-red indicator in buffers of varying pH that were run simultaneously on a single disc are shown in Fig. 11. Other applications include comparison of filter spectra by mounting the filters directly on the disc holder and multicomponent spectra.

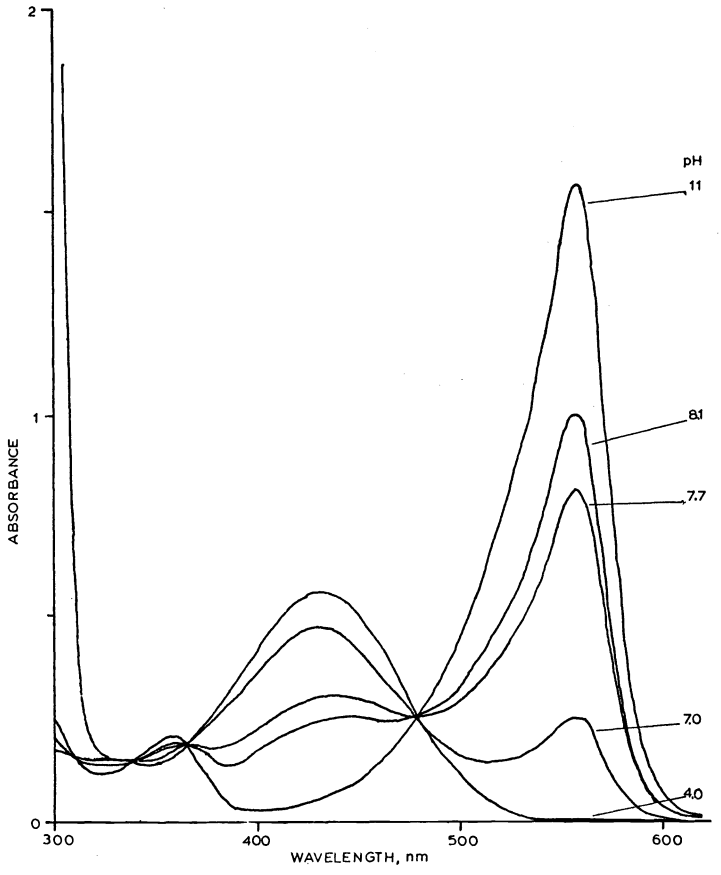

Fig. 11. Absorption spectra obtained simultaneously at 5 pH values.

Multichannel and multiwavelength RDA for multitests and multisamples.

A rotating disc instrument was designed (23) so that several different wavelengths of radiation could be observed on each revolution of the disc. The unit has six different wavelength channels, five for absorbance measurements, and one fluorescence. This provides the necessary wavelengths so that 20 of the common clinical chemistry tests can be run on each sample. Thus, stat measurements or routine profiles can be obtained on the analyzer within 15 minutes of receipt of the sample. Also, single chemistry tests can be run on multiple samples in a batch mode of operation. An 8080 microcomputer system (24) was used for all functions of the instrument.

CONCLUSIONS

Many of the classical analytical measurement techniques and chemical methodologies can be significantly improved by modern microelectronic technology. We have shown how spectrophotometers, colorimeters, stopped-flow analyzers for kinetic and equilibrium chemical methods, sample and reagent prep units, and other systems can provide better precision, accuracy, sensitivity , selectivity by redesigning with low-cost microcomputers. Although there have been dramatic improvements in the past few years, there should be even more significant developments during the 1980's, especially as more instrument designers and analytical chemists gain experience and a thorough understanding of microcomputers.

The introduction of low-cost flow injection and stopped-flow analyzers will improve the output and reliability of analytical results from many laboratories. We can expect that major improvements and applications of these analyzers will appear regularly on the market. Also, the development of hybrid systems will probably provide unique and useful analytical features.

Automated sampling and the preparation of samples and reagents for quantitative determinations should be on the threshold of major advances. Perhaps, the automated weight sensor with incremental pipette and microcomputer feedback that was described in this paper will be refined so that it will become commonplace for routine standard-addition and other analytical techniques.

In all instruments, there is a need for automated calibration and self-diagnosis of problems. The addition of these features in the new designs would improve the quality of results from many laboratories.

There will be the many surprises as breakthroughs in several areas of technology during the 1980's combined to provide powerful new automated analytical tools. It seems inevitable that nearly all analytical laboratories will become highly automated during this decade. It is certainly important that courses and conferences be provided to train and retrain chemists as they are required to work in an increasingly automated environment. The challenge to educators is very clear.

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