REVIEW & OUTLOOK

Automatic Instrumentation for Hematology

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A customary definition of automation is the replacement of human hands by machines in repetitive and usually fairly simple industrial procedures. Early attempts to introduce industrial automation in the mid-nineteenth century not surprisingly led to strikes and civil disorder because workers believed that the machines were taking away their jobs. Although redundancy of human effort was one of the consequences of automation, the principle motive of the inventors of automatic processes was to achieve increased productivity and more uniform product quality. To contemporary eyes, the introduction of automated industrial processes must have seemed a major threat to society; but now, with the wisdom of hindsight, we know that this did more than any other economic event to generate equitable distribution of wealth and raise living standards.

Apparently, automation in hematology has different roots. It began with the realization that better diagnosis of all varieties of anemia could be achieved if the accuracy and precision of the red cell count were improved. The diagnostic value of Mean Cell Volume (MCV) and Mean Cell Hemoglobin (MCH) was severely limited by the poor precision of the hemacytometer red cell count. Although it was well known that precision would improve as a function of the square root of the number of cells counted, it was thought to be impracticable and uneconomic to do this. It would have meant increasing the number of technicians tenfold to improve the precision of the count little more than three times.

At this time, significant advances in optical and electronic technology became available as a result of the wartime development of nuclear weapons, radar, and radio communications. This combination of perceived need and availability of new techniques produced a spattering of automated blood counting machines, most of which relied on optical detection of the cells in a mechanized version of the chamber count. Generally, these machines were not commercially exploited and were specially developed in response to local needs at a few major academic centers. Much of the pioneering theoretical work for optical scanning systems had been done by Lagercrantz at Uppsala. McFarlane at Oxford University and myself at Harvard simultaneously developed mechanical scanning counters using Wolff's raster edge com-
taught the feasibility of using a flying spot scanning method, and this technique was also used by Brown and Beattie at Duke University to give the accurate red cell counts needed for cell survival studies. RCA described a prototype cell counter in which the counting chamber was scanned by a television camera and Emerson at Boston University worked on a mechanical scanning system similar to the one described by Lagercrantz.

The effort that was made in those days to increase the precision and accuracy of the red count was quite intensive. Nevertheless, none of the mechanical or electronic scanning machines achieved any commercial success. They failed to find a marketplace for several reasons. Firstly, apart from a few teaching institutions, not enough clinical laboratories perceived a real need to improve the precision and accuracy of their red cell counts. Secondly, the machines themselves were unreliable and not yet brought to the stage of development where they were fully capable of replacing the human operator. Thirdly, the hoped-for statistical improvement was limited by the relatively slow speed and restricted counting volume inherent in the chamber scanning method. Finally, none of these instruments were able to measure red cell volume directly. In my own laboratory, some progress was made in measuring cell diameters, but the conversion of this information to cell volume appeared to be out of reach.

It is therefore not surprising that the first commercially successful automated blood cell counter was the flow-through aperture impedance system invented by Wallace Coulter. This new counter offered two important advantages over all previous designs. The first was the very large number of cells counted. Because of this the coefficient of variation of the red cell count was brought down to less than half percent giving, for the first time, substantial clinical utility to MCH measurement and an equal improvement in MCV. Secondly, the Coulter System possessed the ability to make precise measurements of cell volume and cell volume distribution. The evaluation report by Mattern and Brackett left no doubt as to the scientific validity of the method. Now, for the first time, some of the true purposes of automation had been achieved. In addition to the basic industrial purpose of improving productivity and standardization of product quality, it was now possible to make measurements that had not, hitherto, been feasible. This new factor in hematology automation was cell size discrimination. Today’s descendants of the original Model A COULTER COUNTER® use cell size discrimination to identify white cells, red cells, and platelets as clearly defined and well separated classes and also to provide, within each class, size distribution information and cell-subset identification.

Although aperture impedance cell counters occupy a dominant position in today’s hematology laboratory, instruments using optical sensing also play an important role in meeting other diagnostic needs and in providing measurement of cell function and antigenic structure. Among the pioneers of flow-through optical sensing were Kamentsky who developed the Cytofluorograph, an instrument that evolved into Ortho’s Spectrum series of flow cytometers, Herzenberg at Stanford University who fathered the Becton-Dickinson FACS series of analyzer and Fulwyler,5 directing a Coulter Subsidiary in Los Alamos Scientific Laboratory who devised a combination cell analyzer and cell separator that was the progenitor of the Coulter EPICS® and Profile family of instruments.

Although some of the analyses performed by optical flow cytometers can, in principle, be made with a visible-light
or ultraviolet microscope, the automated machines offer major improvements in analytic precision, provide cell-by-cell quantification of fluorescent response at several wavelengths, cell-by-cell absorption photometry, and characterization of cell size by forward light scattering measurement.

The most recent analytical tool for automated cell analysis is the radio frequency opacity probe. This is one of the measurement methods used in the Coulter® VCS automated differential counter.10

Looking back over the past 30 years, it is clear that one of the goals of automated hematology instrument design has been to expand the range of parameters along with continuing improvements in productivity, cost-effectiveness, and reliability. Automation has made the standard hematologic measurements more widely used than could be possible if only manual methods were available, has encouraged both research and commercialization of new parameters and has made it possible for their clinical utility to be evaluated on a wide scale.

The commercial failure of automated blood counting systems that merely replaced the human operator with mechanical and electronic analogs should have provided a valuable lesson in how not to automate hematology methods. The experience was apparently unheeded by another section of the Medical Device Industry that, in the late 60s and early 70s, began to apply new computer technology to the design of pattern-recognition automated differential counters. In these machines, the technician’s hands were replaced by stepping motors that drove the stage and focussed the microscope. The technician’s eyes were replaced by a television camera and the technician’s brain was replaced by a computer.7 Of the five major corporations that entered this commercial arena, only one, Geometric Data, survived for a significant period of time. The capital losses suffered by industry in this misguided attempt to automate differential counting must have been well over $50,000,000. Although the technology and engineering of these pattern recognition differential counters was very advanced, they conferred little advantage in productivity, accuracy, precision or additional information.

It is tempting to see pattern recognition differential counting instruments as the dinosaurs of automated hematology. However, future hematologic paleontologists, on looking back at this technology, might very well conclude that the essential ingredient in the commercial failure of these machines was not their size, cost, or relatively low productivity but the fact that they reflected the uneasy marriage of highly sophisticated opto-electronic technology to traditional Romanowsky staining methods. It would seem logical to have used more specific and definitive stains in order to improve accuracy and to increase processing speed.13

Another reason why pattern recognition differential counters did not evolve into successful commercial products might have been that automated differential counters were placed in Regulatory Class III by the U.S. Food and Drug Administration. This classification, made contrary to the representations of both industry and the medical profession, undoubtedly had a chilling effect on innovation. In particular, the law specifically restrained manufacturers from claiming positive recognition of neoplastic cells without these claims first having been approved through the Pre-Market Approval (PMA) process. This is a time-consuming and costly procedure that would have overburdened the price-structure of these products. In spite of industry’s prolonged, and ultimately successful, attempts to ameliorate this regulatory burden, a “window of opportu-
nity” for pattern recognition systems was lost and the field is now completely dominated by flow-through machines based on aperture impedance technology, optical technology, or some combination of these.

Trends in automated hematology measurement are, I think, driven by both economic and regulatory forces. On the one hand, economic forces, epitomized by the Byzantine pronouncements of the Health Care Finance Administration (HCFA) and the reimbursement policies of private sector insurance companies, are creating a growing demand for automated hematology instruments in physicians’ offices and increasing the need for high-productivity automation in hospital laboratories. The design goals for physicians’ office machines include the need for them to be “people proof”. This need for simplicity of operation and extreme ruggedness may result in a reduction in the number of parameters these machines are able to report. In the hospital laboratory there are shrinking budgets and an increasing need to make better use of technologists’ skills. There, emphasis will be on total automation in the industrial sense so that test results can be produced at minimum cost and with minimum human intervention.

A second major factor in determining design trends in automated hematology instruments is the regulatory climate. It is inevitable that there will be increasing federal surveillance of clinical laboratory performance to match the increasing provision of tax-funded health care. This could lead to the development of instruments that are capable of automatically providing proof that they have produced accurate diagnostic information. We have made some progress in this direction by giving our instruments built-in computing power for analyzing conventional quality control results. A future goal is to provide an instantaneous peer comparison analysis by two-way communication between many remote machines and a central computer. This is not as costly or complicated as one might think.

A prototype that reflects both the joys and sorrows of attempting to do this is the system we have developed for the National Institutes of Health, Health and Nutrition Examination Survey Program (HANES). This program, the fourth in a series, has the purpose of establishing reference values for many physiological parameters over a wide range of racial and socio-economic groups in a variety of geographic areas. HANES plans to test 40,000 subjects over a period of four years, performing the work in mobile testing centers. When moving from location the equipment will be subject to harsh environmental conditions. Thus, instruments might be damaged and the data may lose accuracy. The need for high standards of accuracy is paramount since there is no possibility of revisiting test sites to investigate apparent disparities of data.

Our present program requires that each mobile unit daily transmits its quality control and calibration data over a phone link to our central computer. The central computer verifies that the instrument precision is within a stipulated range, corrects any calibration bias and transmits this information to the HANES central computing facility in North Carolina. The telephone link is fully automatic, directing the operator to enter information through the touch-tone pad by robotic voice instructions. If the computer detects inconsistencies in the transmitted data set it will automatically switch the remote operator to a technologist in our central reference laboratory to resolve the problem.

In its present form, this performance verification method is too cumbersome for the physician’s office or even for a moderate size institution. However, we think that the principle has been proven and with modest improvements in tech-
nique we have confidence that the next few years will see several thousand institutions enjoying on-line real-time proof of performance of their automated hematology analyzers.

Another significant trend in automation stems from the increasing availability of monoclonal antibodies for performing immunophenotyping. The rapid growth of this technology is linked to wider availability of optical flow cytometers. These instruments, which a few years ago were only to be found in research institutions, are now beginning to find a place in routine hematology laboratories.

In addition to gaining clinical acceptance, the promising combination of optical flow analysis and hybridoma technology must also prove itself in the regulatory arena. When the Medical Device Amendment to the Food, Drug and Cosmetic Act was passed in 1976, our legislators, in their eagerness to protect the public against medical device quackery, placed strict proof-of-performance burdens on newly invented devices. Diagnostic monoclonal antibodies, having been invented since 1976, have been caught in a regulatory trap. Very few of the wide range of available antibodies have been “approved” by the FDA for diagnostic use. Most are in need of proof of diagnostic utility while some, having been accorded clinical value, must now be subjected to the exhaustive investigational process that is necessary for the FDA to approve their use as in-vitro diagnostic products. The next level of automation in hematology, namely, the routine integration of the traditional “CBC,” the automated differential count and the use of monoclonal antibodies for the characterization of cell function and maturity, may well depend less on developments in engineering and biotechnology than upon an easing of regulatory restraints on innovation.

The next predictable phase of automation in hematology is already within our grasp as far as technology is concerned, but it is a year or two away from wide commercial availability.

In 1982 I gave a talk with the title, “What the Medical Device Industry is not Doing for Hematology.” In casting about for a theme, I discovered that, starting with Leuvenhook’s invention of the microscope, reported by Schierbeek, and his observation of blood cells with it in the 17th century, the cumulative sum of hematologic cellular parameters expressed as a function of the time intervals of their introduction was very nearly logarithmic. I was skeptical of this relationship because it said that we would be reporting at least 10 more cellular parameters in 1988 than at the time I made the prediction. The truth of this forecast has been proved by the increasing acceptance of immunophenotyping as an adjunct to the diagnosis of leukemias and lymphomas.

I foresaw that one of the consequences of adding an increasing number of parameters to the output of automated hematology instruments would be an over burdening of our ability to interpret the information. I think we have already arrived at this condition and we are suffering from what I would like to call a “comprehension gap.” This means that, under the usual conditions of medical practice, very few of us (and I include myself) are capable of grasping the total significance of the information that is generated by automated comprehensive cell analysis methods. Many of us (and I include myself) try daily to absorb this information piece-meal and end up admitting our inability to see all the interrelationships of the separate measurements. It is possible that we overlook significant interactions by not appreciating, for example, the meaning of one parameter approaching the lower
limit of its reference range while another is moderately elevated but still within normal limits. Bessman has suggested that microcytosis associated with a "normal" cell size dispersion index (RDW) is strongly suggestive of Beta Thalassemia. This diagnostic lead may, however, be overlooked if moderate iron deficiency has distorted the cell size distribution pattern. In a case like this the instrument provides us with information, but because of haste or lack of insight we may be unable to read the message.

This is a simple but typical example of the comprehension gap, and I believe it can be bridged by delegating to computers the initial stages of interpretation of the data given by automated hematology analyzers. In the case I have just cited, analysis of the cell size distribution curve by the Expectation Maximization Algorithm would possibly have pointed the diagnostician's thoughts in the direction of appropriate additional investigations.

I predict that on-line computer programs will shortly offer real-time analysis of all available hematologic parameters, provide a tentative differential diagnosis and will suggest additional tests that would sharpen the diagnostic focus.

This is a safe prediction because two software packages are already available that provide sophisticated analysis of hematologic information entered through the keyboard of a computer. One of these, described by Bates & Bessman and published by Lea & Febiger is available now in the United States. The other, published in France by Coulter, is designed by Claude Sultan of the Hopital Henri Mondor in Paris, has similar features, and can be used as an aid to diagnosis or for teaching.

Both these programs rely on "if-then" logic in combination with Bayesian statistics for estimating of the likelihood of the differential diagnosis. Both programs require information about the patient over and above that which is furnished by the automated hematology analyzer and, thus, we are faced with an intriguing consequence.

For the interpretive software to operate efficiently, it must be given clinical information that is normally not provided to the hematology laboratory. This makes it mandatory for the clinician to become interactive with the hematology analyzer, leading one to wonder whether computers will bring the laboratory closer to the bedside or the clinician closer to the laboratory. Perhaps we are standing on the edge of a new era in medicine in which the wheel has turned a full circle and the physician, liberated by the computer from struggling with complex parametric interrelationships, will again become dedicated to the solution of humanistic problems.

References


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