Concerning automation of the white blood cell differential count

"Cellular Logic Computers for Pattern Recognition" (Computer, January 1983, pp. 36-47) wonderfully describes the genealogy of the hardware technology of the Cellscan/diff3 instrument for automated differential counting. I feel the need, however, to take exception to the statement in the author's biography that "he and his co-workers were the first to demonstrate the complete automation of the white blood cell differential count." In 1973, as a member of the Cellscan Product Development team, I inherited Kendall Preston's work, and that of a successor, in the pattern recognition applications area. With the benefit of hindsight, a case can be made that feasibility had not been demonstrated for this application of GLOPR technology at that point, and a full development project was in progress.

The white blood cell (WBC) differential count consists of the identification and enumeration of the six normal cell types as well as the abnormal cell types, which can number anywhere from three to perhaps a dozen or more, depending on how one groups subclasses of cell types. According to data I had documenting their work, adequate discrimination had been achieved for only three cell types (neutrophils, lymphocytes, and eosinophils), a very dissimilar set and relatively easy to differentiate. What little data I saw from work on other cell types was not particularly encouraging. In the course of the Cellscan development program, most of the cell measurements used in the discriminating function of the 1970 work had to be discarded, save for those dealing with fundamental measurements of area, perimeter, and density of the component cellular parts. The discarded measurements were replaced by ones that better discriminated the original set of three cell types and that effectively separated other cell types.

A key element in the feasibility of automation of the differential count of any image processing technique is scene segmentation from the background or environment of the desired entity to be identified. This element of the problem had been virtually unaddressed prior to the start of my work in 1973. I consider this area essential to even the feasibility of the approach and offer as evidence the following. First, discrimination of the cells appearing on Pap smears has been reported by several independent workers with excellent separation performance since at least as far back as 1975. Through the late 1970's (up to the end of my active participation in the field of medical imaging), all workers with whom I had contact acknowledged that the results were in a sense an artificial statement of feasibility. This was because the results could be achieved only on data taken from cells physically extracted from their surroundings by extraordinary preparatory means, not from the actual smears themselves. Second, I reported on this particular area of Cellscan image recognition in a poster session at the Engineering Foundation Conference on Automated Cytology, held in Pensacola, Florida, December 1976, where it received considerable attention.

So that there will be no ambiguity in the purpose of this communication, let me definitively state it here. The feasibility of the automated WBC differential count was demonstrated via the GLOPR technology by several "generations" of investigators at Perkin-Elmer Corporation, and probably cannot be claimed to have been achieved before 1974. Furthermore, the bulk of the imaging algorithms that can be considered part of the feasibility achievement were developed after 1970, primarily in 1973 and 1974. Preston's work was clearly the first step in the feasibility process, but the majority of the feasibility work aimed at the complete automation of the WBC differential count was performed by the eventual developers of the only commercially viable instrument. Exactly where feasibility ends and the solution to development problems begins is not unlike the "band/seg" problem itself, and is probably somewhat semantic as well. However, I would identify the contributors to the feasibility solution of the total problem as N.I. Adams III, D.C. DeCava, F. E. Eckstein, O. V. Greunke, A. W. McCullough, F. W. Maher, J. F. Nester, P. E. Norgren, V. V. Pirc, and F. Senk. It is regrettable that the commercialization of this technical work did not permit adequate publication of the achievement in the technical community. I hope that, in some small measure, recognition of their accomplishment is hereby given.

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Author's reply:

To summarize Fred Eckstein's letter, he contends that my group at Perkin-Elmer may not have been the first to demonstrate the automation of the white blood cell differential count. He also states that what my group did was produce a machine that automatically distinguished between only three specific classes of white blood cells: the neutrophils, lymphocytes, and eosinophils. Eckstein's information is inaccurate. I would refer him to the cover story in Scientific American (November 1970), which was the first public announcement of our preliminary accomplishments in differential counting of neutrophils, lymphocytes, and monocytes.

The Scientific American report was on progress achieved during 1969 in my laboratory in the Optical Group Research Division supported by the Department of Defense Internal Research and Development (IR&D) Program. In a subsequent Optical Group report, classified as COMPANY PRIVATE and dated April 9, 1970, an experiment is described wherein the
same system automatically differentiated lymphocytes, neutrophils, eosinophils, monocytes, stabs, and basophils in images of some 1000 cells. This was the "complete automation of the white blood cell differential count" to which my biography refers. The instrument that performed this feat was Cellscan II, an automatic three-color, high-resolution, continuously focusing, object-finding and image analyzing robot microscope. It was the successor to Cellscan I, funded by the Atomic Energy Commission in 1960 and 1961 and by the National Institutes of Health from 1964 through 1966. Subsequent to its employment for automated medical microscopy, this system was used in Department of Defense IR&D projects relating to research in automated pattern recognition for radar, sonar, infrared, and aerial reconnaissance.

The first organization to produce a commercial white blood cell differentiating microscope was Geometric Data Corporation, a privately funded company in Pennsylvania that is now part of Smith Kline Beckman. This led to the production of what is called Hematrak, of which a few hundred are now in use worldwide. Subsequently, two other privately funded companies produced such machines. They were the Corning Glass Works (North Carolina) and Cognos (Massachusetts). The Corning microscope, called LARC, was brought to commercial manufacture and sale but was then discontinued. The Cognos instrument reached limited manufacture but was not commercially sold. After that time (mid-1970's), two other privately funded groups entered the field. One was the Instrument Group of Perkin-Elmer (Connecticut), with which Eckstein was allied, and the other was Abbott Laboratories (Texas). (The instrument of Abbott Laboratories was never sold.) The Perkin-Elmer instrument, called the diff3, was a considerably different instrument from the original Cellscan II. It used two-color imaging, lower resolution, and discontinuous focus, but it was much faster in its rate of object capture and recognition. Eckstein is to be complimented on the fine work he did in the design of this instrument. The diff3 is now manufactured and sold by Coulter (Florida and Massachusetts) and, as with Hematrak, a few hundred are now in use worldwide. Subsequently, two other companies entered this field. They are Omron and Hitachi (both in Japan). Other than that, I am unaware of successful demonstrations of the automation of the white blood cell differential count using high-resolution microscopy. There is, of course, the flow-cytology differential counter of Technicon, announced in 1970 and in use in many hematology laboratories.

The fact that Eckstein is unfamiliar with these developments is not surprising, since his entry into the field occurred more than a decade after its inception. His letter does not mention the outstanding work of Geometric Data, Cognos, Corning, Coulter, Abbott Laboratories, Omron, and Hitachi. It is also not surprising that he was unaware of the contents of COMPANY PRIVATE reports prepared under the DoD IR&D program at Perkin-Elmer, Optical Group, on automated reconnaissance pattern recognition. Perhaps this letter will serve to put the entire matter in perspective.

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