CERN - DATA HANDLING DIVISION
DD/73/27
P.W. Neurath*
J.F. Brenner*
W.D. Selles *
E.S. Gelsema
B.W. Powell
G. Gallus**
E. Vastola***
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COMPUTER IDENTIFICATION OF WHITE BLOOD CELLS

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(* Tufts University, New England Medical Center Hospital, Boston, Mass.)
(** Istituto di Biometria e Statistica Medica, Milan, Italy)
(*** State University of New York, Brooklyn, New York)

COMPUTER IDENTIFICATION OF WHITE BLOOD CELLS

P.W. Neurath, J.F. Brenner, W.D. Selles
Tufts University, New England Medical Center Hospital, Boston, Mass.

E.S. Gelsema, B.W. Powell
European Center for Nuclear Research, Geneva, Switzerland

G. Gallus
Istituto di Biometria e Statistica Medica, Milan, Italy

E. Vastola
State University of New York, Brooklyn, New York

The hardware and software problems for an effective image processing system are described, with a real time high speed system solution as the goal. The discriminating power of the algorithms has been tested in a simulation made on the PIQUANT film scanner and is between 67 and 92% depending on the definition of accuracy. The results are expected to be of value to firms designing and building commercial equipment and to prospective purchasers of it.

To construct a system which will automatically perform pattern recognition requires both hardware and software to accomplish a large number of separate tasks. An intelligent person is taught or learns by himself to optimise the performance of each of these tasks. Equipment has over the years been invented and built to help him with each. The resulting people-oriented optimal solutions may well not be optimal for an automatic system and a great deal of research into each separate task will need to be done before a machine will be working efficiently. Until then ad hoc solutions which copy the operator will be the rule, particularly when it is possible to make a machine mimic a person's actions.

It is therefore of interest to review several of these tasks involved in performing a white cell differential count, and indicate the present status of available solutions for an automatic system, including our own. Results of a simulation experiment using PIQUANT (Neurath[5]) will be presented.

(1) Most samples for differential white blood cell counts in a typical U.S. hospital are obtained as part of one or two 10 cc vacutainers of blood drawn by a special team of technicians for all kinds of blood tests. An order to draw blood must initiate the process, it must be scheduled, and the sample with the patient's name and number and the doctor who ordered it must be identified. The sample is then stored for a shorter or longer time at a temperature which is uncontrolled. Possibilities exist for coordinating the scheduling, paperwork and labelling by the use of a computer system linked to the cell scanning system.

(2) Using a drop of blood from this sample, after suitable agitation a so-called "smear" is made in the laboratory. It is necessary to produce a single layer of "undistorted" cells on a microscope slide. The shape of red cells and of white cells can be used to check on the success of this process. A "smear" can be made by hand, in which case not all areas of the slide will meet the above criteria. A person can, however, select "good" areas and employ sampling strategies to minimize the chances that the good areas will have an unrepresentative differential count. A slide "spinner" machine, using centrifugal forces produced by rotating the slide at a given angular velocity for a given time under suction, represents a considerable improvement over the reproducibility of the hand process. The cells which first touch the stationary slide when the drop of blood settles on its central ≈2 cm diameter circle tend to stick; the remaining cells are spun off with just enough force so as to (i) remove them all from that area and (ii) keep the monolayer of "sticking" cells from being distorted. Because of the differences in the number of cells/cc and of the different surface properties of blood samples, automatic feedback during the spinning process, so as to change its time or velocity, is required to meet these criteria. Alternatively, several preparations under different spinning parameters may be made, until one satisfactory by visual inspection is produced. The LARC system of Corning Glass Co. [1] has used the first approach with a special spinner, while our hospital uses the second method with a Platt machine. A machine recognition system works best if no red cells touch white cells, because otherwise additional processing time is needed for isolation. A person has no such problem. The best trade-off between obtaining the proper cell spacing on the slide by preparation, vs. separating touching cells through suitable image analysis, remains to be explored. The spinning machines do not space all cells properly.

(3) Staining of the cells helps to make them more easily visible in the transmission light microscope and the resulting color differences are very useful for cell identification. A person can calibrate his use of colors by the appearance of easily recognized cells and adapt to large differences in stains. He also adapts to differences in light intensity. A machine is more easily programmed if color and intensity values are either absolute or at least have a constant, linear relationship to a single reference value. To meet this requirement staining should be controlled and a special machine using special chemicals such as the one proposed for the LARC system [1] may be necessary. Performance differences for either people or machines using conventional vs. such controlled staining have not been reported. Our laboratory has used the Ames machine, and we have found that for satisfactory machine results it will need to be kept cleaner than is customary in routine visual work.

(4) The stained dried slide must be identified with a code referring to the patient. Ideally the machine should be able to read that code. It must then be inserted in a microscope. In spite of the intense competition between many major microscope manufacturers who produce new models every few years - square shaped ones are "in" presently - not one of them offers an automatic slide changer and coder, not even a stage which holds and indexes the slide by its front surface which could help keep it in better focus and would at least eliminate the need for refocussing because of differences in slide thicknesses. Our hardware is designed to meet these problems partway, with a slide changer in mind, designed on paper, but not yet built.

(5) The slide must be moved to find the cells. There is approximately one 15μ diameter cell in each 200 x 200 μ area and it needs to be located approximately within 4μ. This means scanning twenty five to fifty 8μ strips of 200μ length per cell. If one cell is to be found in 1/5 second, an 8μ wide strip of 25,000μ length must be scanned per second. This can be done by moving the slide at that rate or by performing several (n) 8μ scans optically or electronically, while the slide moves at 1/n the rate. Young [2] uses a television camera which stores a 100μ x 100μ image at one scan. LARC uses a rotating mirror. Data to decide between such options are not available. Our own system was designed to perform the single strip high speed option with a servo motor driven, light weight slide holder. As yet it is only performing stably up to 1/2 the design speed. Commercial stepping-motor driven stages have a great deal of inertia and take a good part of a second to stop. However, if the cell detector scans ahead and stops the slide gradually, this limitation can be overcome. This means steering it so that the cell will be in the center of the final scanning area when the slide stops.

(6) Next, one must find the position of the white cells. This is relatively easily accomplished, because in yellow light the cell nuclei are almost the only dark objects which are several microns in diameter. A coarse threshold detector is adequate although its performance is improved if the average light intensity of the slide area is used as a reference.

We are using a photo diode and hard-wired circuitry independent of the computer to detect the white cells and stop. Repeated stops on the same cell after adjacent scans must be prevented. It is not essential that every cell be detected, but in that case there must be no preferential skipping of certain types of cells. Focussing is not too critical for cell detection. Whether a small central square or a narrow long strip should be scanned depends on the method of preparation and needs to be investigated. The main problem with cell finding is the accuracy of centering of the cell because this determines the area which must be scanned in the end.

(7) Before scanning the cell itself, it must be focussed. Several schemes to focus an image exist, but over a limited area of the slide it may be possible to eliminate refocussing on the basis of the image by checking the focus in the corners of the scan area and driving the focus axis linearly, proportional to ΔX and ΔY from one corner. We still have to test this approach. The criticality of the focus depends on the resolution desired in the final scan. The focus tolerance is of the same order of magnitude as the distance to be resolved.

(8) At this point, having a well-stained focussed cell in the center of the microscope field, one is ready to capture the information in its image and to transfer all or part of it to the computer for analysis. A number of different scanning schemes exist. A CRT or other flying spot scanner is one option [3]. It operates close to being photon limited for signal to noise ratio, if the point scanned is small and if 10^6 points or more per second must be examined. Take for example, 32,000 points spaced 0.25μ apart, which would make up a 180 x 180 raster about 45μ on a side. If these 32,000 points are to be scanned in 1/30 of a second, it presents a serious challenge to existing technology. If the raster size is increased to 0.5μ and therefore the number of points is decreased by a factor of 4, the time per point and its size can be increased proportionately, and this signal-noise problem can be reduced. An alternative which eliminates this photon noise limit is to use an integrating scanner. A TV camera is an example of such an integrator. It adds up the light received on its faceplate for a time equal to the scan time of all points, thus gaining a factor of about 10^4. Its disadvantages are lag (requiring at least 2 scans per frame), shading, high band width (making it susceptible to external electrical noise), and faceplate imperfections. Linear arrays appear to offer an attractive

alternative, but at the moment TV systems, perhaps because of their availability, are more popular. Because color is important for WBC differentiation, scanning must be done in several colors. This requires the use of 2 or more color filters. Either narrow band interference filters (as used by I. Young[2] at MIT) or wider band Wratten filters may be used. For high speed data acquisition with a TV system, where each frame scan time counts, the filter should be in focus and moved across the image in synchronism with the scan motion. The focus of the microscope objective must also be adjusted for the different wave lengths. Visually at least, microscope optics are notably not achromatic.

(9) To digitize the image and load the computer memory with the resulting data can present a problem when standard TV rates are used. One half of 525 lines are usually scanned in 1/60 of a second. If the central 180 lines of the 262 lines are used to give 32,000 points equally spaced in X and Y, the rate per point is 60 x $(262)^2$ or almost 4 megahertz. A to D conversion at this rate with sufficient accuracy and memory access at half this rate, assuming packing 2 points to a computer word, are possible, but only marginally. The A to D converter must digitize to 10 bits accuracy if histograms of the image at 64 levels (6 bits) are not to give spurious minima or maxima of more than about $\pm$3% (one bit in 5). Solutions are to decrease the resolution or to slow the TV scan rate. We have chosen the second, providing up to 256 x 256 raster points (84,000), but extending the scan time to 1/15 second, while digitizing to 6 bits and including an optional log conversion of the intensity values. The price is a degree of flicker in the monitor, and the TV system modifications which are required to slow it down. Use of scan converters would offer a convenient alternative if their limited grey scale resolution could be improved. With them any standard TV system could be used. Consideration of a monitor enters into these decisions, particularly if the system is to be flexible for research purposes and a light pen may be desired - or if a high quality TV picture must be presented to the operator. A second camera could be provided for this purpose, which would, however, introduce a problem of alignment and of cost.

All TV systems suffer from non-uniform response across the face plate. To reduce this to 1/64 of the maximum signal requires considerable hardware effort, as in the IMANCO "Quantimet" [4] or a time and memory consuming software correction of every point. It may of course not be necessary to make this correction if only relatively local contrast in the image must be measured accurately for purposes of cell recognition. A really informed choice cannot be made until the relationship between the desired accuracy and the spatial, grey scale and color resolution needed to meet it have been thoroughly tested.

(10) The computer selection is largely influenced by the economics of the problem. With 32k, 16 bit machines now selling for less than $10,000 on a single order and going down in price, it probably makes no sense to use anything smaller. Beyond that it should perhaps be pointed out that where fine scale texture is important, computations will be more demanding.

The LARC system uses a PDP-8E. Our research system interfaces the microscope and scanner to a Data General NOVA 840 with 128K of memory, disks and a 9 track tape. With that size machine we can investigate almost all aspects of the image processing algorithms without resorting to machine language programming. If eventually it turns out that for some purpose very lengthy algorithms are absolutely necessary, hardware preprocessing, possibly using holographic techniques, might eventually be an inexpensive alternative to digital computations in routine use. Computers too are still on an increasing performance/price ratio curve so that future systems may well be most economical with a large computer and fewer other special components.

(11) Finally any such system requires operator interaction. The arrangement of switches, keyboards, alphanumeric displays, and hard copy output, video monitors, microscope controls, etc. can greatly influence the usefulness of any system. In our own system we have so far been concerned less with convenience than with having available a variety of controls and options: X, Y and Z stage controls, a TV monitor, a CRT with light pen, function buttons, a keyboard and CRT computer terminal and a fast line printer for hard copy output and as a means of recording tonal images of the cells. These options allow us to try any scheme. In the hematology laboratory in which a Coulter counter is used, a printer using the same card to record the differential might be a convenient first step. A color TV, if it were really stable and true to color, would make observation easier. Keys and buttons should eventually be reduced to a minimum. The computer classification should probably be displayed on the cell monitor screen with the cell.

(12) Isolation. Once the picture has been digitized the cell must be isolated from the background and a nucleus must be found within the cell. The usual way to do this is to construct a histogram of the density values (Prewitt[7]), which ideally has three peaks, corresponding to points in the background, cytoplasm and nucleus, respectively. The density values corresponding to the two minima in such a histogram can then be used as threshold values to separate the cytoplasm from the background and from the nucleus. In using this procedure we have become aware of a few inherent shortcomings in the isolation of the cell (cytoplasm from background) as well as in the isolation of the

nucleus.

A. Isolation of the cell. In a standard peripheral blood smear there are many instances where one or more red cells touch the white cell under consideration. The boundary as detected by the method referred to above will include the touching red cells. This may be corrected by either detecting points of maximum concavity in the boundary and then replacing the segment between suitable pairs of such concavities by straight lines, or by making use of the difference in color between the red cell and white cell cytoplasm.

Tests have been done on a geometrical cell isolation approach, consisting of fitting an ellipse (E1) through a number of boundary points, detected as points of maximum gradient along a radius vector. The ellipse E2 defined by the five boundary points closest to E1 is then taken as the cell boundary. This procedure has been tested on a few cases with touching red cells and the results look promising. An attractive feature of this method in contrast to the edge following procedure is that the closure of the boundary requires no special programs.

In a smear of peripheral blood instances of two white cells touching each other will be rare and a simple test on the shape of the area enclosed by the boundary will detect such cases which can then be rejected.

An additional problem that may arise with the automatic cell detecting instrument is that the cell may not be centered in the digitized frame so that part of it may disappear beyond the frame edges.

B. Isolation of the nucleus. It is our belief that the detection of the nuclear boundary is the most difficult, yet the most critical part of the software. Using density histograms and boundary following techniques, the isolation of the nucleus is straightforward in most cases. Sometimes, however, the minimum corresponding to the nuclear boundary is ill defined and there are cases where the high density peak in the histogram even when it is separated by a well does not correspond to the morphological nucleus. As a result, the distributions of all parameters extracted from the cytoplasm and from the nucleus will be broadened for many cell types, resulting in a high confusion rate.

An additional method used to help isolate the nucleus is that of an edge follower, which correlates the boundary with points of maximum gradient in the density distribution, or similarly, the use of a Laplacian (see Gallus [8]). In some cell types, e.g. in basophils, the morphological nucleus is often completely masked by the presence of heavy granules.

A way to overcome this difficulty is to combine logical decisions and statistical decisions in one classification scheme. Before nuclear detection is attempted one should differentiate such cells as basophils on the basis of their heavy granularity. Only the remaining cells would then proceed to the stage of nuclear isolation.

After the boundaries have thus been defined and traced, they are stored in a convenient way, usually in the form of a segment list (see Rutovitz [9]). In this way the different parts of the cell (i.e. cytoplasm and nucleus) are easily accessible for the parameter extraction.

(13) Parameter extraction. The parameters extracted from the image after preprocessing as described above may be subdivided in four categories (Neurath [6]):

i) optical density parameters
ii) geometrical parameters
iii) color parameters
iv) texture parameters

i. Examples of parameters in this class are average and integrated optical densities of the cell constituents as seen through a particular filter. Also included are parameters describing contrast between the cell constitutents. These parameters can be estimated from the histograms but they are more accurately determined after boundary tracing has been completed.

ii. The geometrical parameters describe e.g. the shape of the nucleus, the area of the nucleus, the area of the whole cell, the ratio of these last two, etc. They are easily obtainable using a segment list description of the cell constituents.

iii. For the extraction of the color parameters one relates the densities of points in one color image to the densities of the corresponding points in the second color image.

One can either derive parameters from a comparison of the histograms of the images as seen through two color filters or from a two-dimensional plot, mapping all points in the original image onto a scatter diagram displaying one filter density versus the other.

If one had three color images available one could go a step further and compute average chromaticity coordinates of the cell constituents, as first described by Young[2]. Our experience indicates, however, that with two suitably chosen filters (Wratten 44 and 22) a third filter does not contribute significantly to the determination of the colors arising in this application (Gelsema [10]). It may be emphasized here that parameters of color (especially the color of the cytoplasm) are amongst the most important in terms of discriminating power.

iv. Texture describes the fine structure of the density pattern in the image. Texture parameters may be extracted in a global way, e.g. by studying the standard deviations of the density histogram peaks, corresponding to the cell constituents under consideration. This, however, does not lead to a knowledge of how the different density values are distributed topologically in the image. Moreover, it is often not possible to correlate these peaks with the cell constituents.

Procedures to evaluate texture in a more precise way tend to be very time consuming. On the other hand, granularity is often the discriminating feature in the separation of certain cell types. Although the texture parameters used by us (see Vastola [12] and Gelsema [11] so far rank low in discriminating power, it is felt that this could be improved upon. In particular a hybrid scheme combining logical and statistical decisions may give texture parameters the greater importance which they have in the judgement of hematologists. Once such parameters are well defined, their lengthy computation could be eliminated by constructing specific texture analysis hardware. Texture is one of the areas of feature extraction where the scope for experimentation and improvements is largest.

Summarizing these comments about parameters, we want to emphasize once more that all parameters relating to the cell constituents depend heavily on the way in which the boundaries between these constituents have been drawn. This makes the nuclear boundary tracing algorithm a necessary and worthwhile object for further study.

(14) Classification. Before classification can be attempted, the best discriminating parameters must be selected. This is done with a stepwise procedure which, using a pooled covariance matrix, provides us with a ranking of the parameters according to their linear discriminatory power. This ranking is in general dependent on the cell types under consideration, which is one of the major weaknesses of this classification scheme. If for instance one wants to separate promyelocytes from myelocytes effectively, one should not attempt to do so using the set of parameters that separate all 17 classes most effectively.

This is another reason why a hybrid decision scheme combining logic and statistics seems most attractive. Easily recognisable types should be separated at an earlier stage, leaving the more subtle differences to be decided upon by a statistical procedure, using selected parameters that best reflect these differences. The best 20 out of a total of 70 parameters have been used in a discriminant analysis. In contrast to previous work, using a quadratic classifier assuming multivariate normal probability distributions (Gelsema [11]) we now use a linearized version of this classifier, which further assumes equal covariance matrices for each class.

Our experience indicates that on the average the two classifiers give comparable results. We find, however, that the linear classifier is more stable.

Testing and training may be done on the same sample or one may use different samples for the two phases. Using the same sample is likely to lead to misleading results, especially when the sample sizes of different cell types are small. The results shown in the next section have all been obtained by training and testing on different cell samples, each sample containing half of the total number of cells available for each type.

RESULTS

The results presented in this section have been obtained in a simulation experiment, using PIQUANT (Neurath[6]). Prior to doing the analysis the reconstructed cell images were judged in terms of the quality of the cellular and nuclear boundaries and the cases showing serious disagreement with the real boundaries were eliminated from both the training set and the testing set. In this way 98 of a total of 1494 cells were removed. The computed classification of the remaining cells in the testing set were compared with the hematologist's classification and the global results are given in the following tables.

In each case the computer classification was obtained using the 20 best discriminating parameters. The best five of these are: cytoplasm color, cell area, a measure of high density red material in the cell, ratio of nuclear to cell area, nucleus color. The first parameter involving texture is ranked eighth.

As mentioned previously, all quoted figures were obtained using a linear discriminant analysis. Overall classification results using a quadratic discriminant function differed from the linear results by no more than 2% in any case. The confusion matrix in table 1 shows the result obtained when classifying the 5 normal cell types plus bands. The testing set contains 247 cells. The overall rate of correct classification is 91.5%.

Table 1

	COMPUTED CLASSIFICATION						
	BAS	EOS	LYM	MON	NEU	BAN	%
BASophils	48	0	0	1	1	0	96
EOSinophils	0	38	0	0	0	0	100
LYMphocytes	0	0	39	3	0	0	93
MONocytes	0	0	0	38	0	0	100
NEUtrophils	1	0	0	0	26	8	74
BANds	1	0	0	0	6	37	84
%	96	100	100	90	73	82	

Table 2
COMPUTED CLASSIFICATION

HEMATOLOGIST CLASSIFICATION	BAS	EOS	LYM	MON	NEU	BAN	MET	MYC	PRO	MYB	LYB	LYA	LYI	NRA	NRB	NRC	PLA	%
BASophils	40	0	1	0	1	0	1	2	0	0	5	0	0	0	0	0	0	80
EOSinophils	0	38	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	100
LYMphocytes	1	0	31	4	0	0	0	0	0	0	0	6	0	0	0	0	0	74
MONocytes	0	0	0	29	0	0	2	3	0	0	1	3	0	0	0	0	0	76
NEUtrophils	0	0	0	0	25	8	2	0	0	0	0	0	0	0	0	0	0	71
BANds	0	0	0	0	6	32	2	0	0	0	0	0	0	3	0	1	0	73
METamyelo	0	0	0	6	0	0	18	7	0	0	0	0	0	1	0	0	0	56
MYeloCytes	5	0	0	1	0	0	11	16	0	0	5	1	0	0	0	0	0	41
PROmyelo	0	0	0	1	0	0	2	5	6	8	2	1	1	0	0	0	2	21
MYeloBlasts	0	0	0	7	0	0	0	0	1	25	3	5	3	0	0	0	1	56
LYmphoBlasts	4	0	1	0	0	0	0	1	1	2	23	1	2	1	0	0	0	64
LYmph (Atyp)	0	0	1	3	0	0	0	0	0	1	3	22	1	0	0	1	7	56
LYmph (Immuno)	0	0	0	1	0	0	0	0	1	2	1	3	10	0	0	0	3	48
Nucl.Reds (A)	0	0	0	0	1	1	2	0	0	1	5	2	0	20	5	0	1	53
Nucl.Reds (B)	0	0	0	0	1	1	0	0	0	0	1	1	1	4	25	3	0	68
Nucl.Reds (C)	0	0	1	0	0	0	0	0	0	0	0	0	0	0	5	49	0	89
PLAsmas	0	0	0	2	0	0	0	0	0	0	0	0	2	0	0	0	27	87
%	80	100	89	54	74	76	45	47	67	64	47	49	50	69	71	91	66	

Relating these results to those expected on a smear of "normal" composition (65% neutrophils, 27% lymphocytes, 5% monocytes, 2% eosinophils, 1% basophils), and ignoring the neutrophil-band confusion, it can be seen that only in the case of basophils are the errors in the computed classification outside the statistical errors (square root of the number of cells of each type expected in a sample of 100 cells).

Table 2 shows the result of the classification of immature as well as normal cells into 17 cell types. The testing set contains a total of 648 cells. The overall correct classification rate is 67.3%. It is interesting to note that if one accepts the cells in the extended diagonal drawn in table 2 as correct classifications, i.e. if two subsequent stages in the evolution of a given cell type are considered as indistinguishable, the rate of correct classification rises to 77.3%. Thus, 30% of the misclassified cells are found within the extended diagonal.

Table 3

COMPUTED CLASSIFICATION

	BAS	EOS	LYM	MON	NEU	BAN	IMM	%
BASophils	40	0	1	0	1	0	8	80
EOSinophils	0	38	0	0	0	0	0	100
LYMphocytes	1	0	31	4	0	0	6	74
MONocytes	0	0	0	29	0	0	9	76
NEUtrophils	0	0	0	0	25	8	2	71
BANds	0	0	0	0	6	32	6	73
IMMatures	9	0	3	21	2	2	364	91
%	80	100	89	54	73	76	92	

Generalizing even more, if one collects all immature cell types (except bands) in table 2 in one single category, the confusion matrix reduces to the one shown in table 3. The rate of correct classification as obtained from this table is 86.3%. The rate of false negatives (immature cells classifying as normal cells) is 8.7% and the false positive rate (normal cells classifying as immature ones) is 12.5%.

As a reference, according to the Poisson distribution, the probabilities of not detecting an event with a frequency of occurrence of 0.02 and 0.03 in a sample of 100 are 0.14 and 0.05, respectively. Therefore, if one analyzes a sample of 100 cells, the false negative rate of 8.7% is comparable to the Poisson errors, if between 2 and 3 abnormal cells are present.

The false positive rate of 12.5% in the sample studied here drops to 9.1% if related to a normal sample.

CONCLUSIONS

In our view, a practical differential white cell counting machine must, at least, reliably distinguish the five normal cell types and flag abnormals to be reviewed by an operator in an interactive system.

From the results of our simulation experiment we can draw the following conclusions:
i. The performance of a system based on our methods would be adequate for distinguishing normal cell types.
ii. If one includes abnormal cells such a system would be capable of recognizing them as such. However, the false positive rate of 12.5% would be too high for an interactive system. Even working on a sample consisting largely of "normal" smears, too much time would be spent in reviewing normal cells.

Since even a minimal system must handle abnormal cells in the manner indicated above, we must

aim to reduce the false positive rate to the order of a few percent.

An ideal system should classify the different types of abnormal cells as reliably as normals, and thus the discrimination among the abnormal types must be improved.

We feel that significant improvements will result from: 1) increased accuracy in nuclear isolation, 2) introduction of hierarchical classification schemes, 3) introduction of more specific parameters to separate pairs of classes for which differences are often subtle.

Our experience indicates that the consistency of human classification in defining the training set must be carefully checked, as Bacus [13] has also shown. For example, we have found significant disagreements between hematologists in distinguishing monocytes and metamyelocyltes, and this is directly related to the false positive rate.

The entrance of commercial companies into the differential white blood cell counter field makes it look as if the moment has come in which an almost 15 year effort in biomedical computer pattern recognition is coming to fruition. It can be expected that the introduction of machines for image analysis in the biomedical field will save time and costs, and equal human performance, particularly as computer hardware suited to such tasks is further developed. It should also lead to a more systematic examination of the results and their significance. For instance, the statistical meaning of a differential which differs from certain norms could be calculated routinely as part of the machine's program. Finally, new cell classes may well come to be defined by quantitative criteria not used by people. Such cell typing could increase the diagnostic usefulness of the differential white blood cell count.

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