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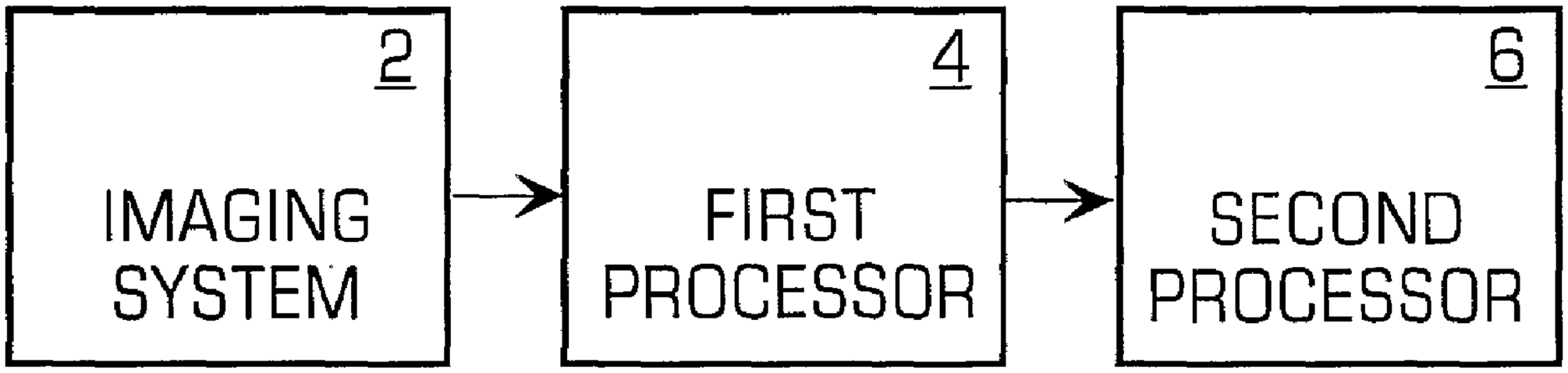

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A multi-neural net imaging apparatus (2) and method for classification of image elements, such as biological particles. The multi-net structure utilizes subgroups of particle features to partition the decision space by an attribute or physical characteristic of the particle and/or by individual and group particle classification that includes an unknown category. Preprocessing (6) classifies particles as artifacts based on certain physical characteristics. Post processing (6) enables the use of contextual information either available from other sources or gleaned from the actual decision making process to further process the probability factors and enhance the decisions.

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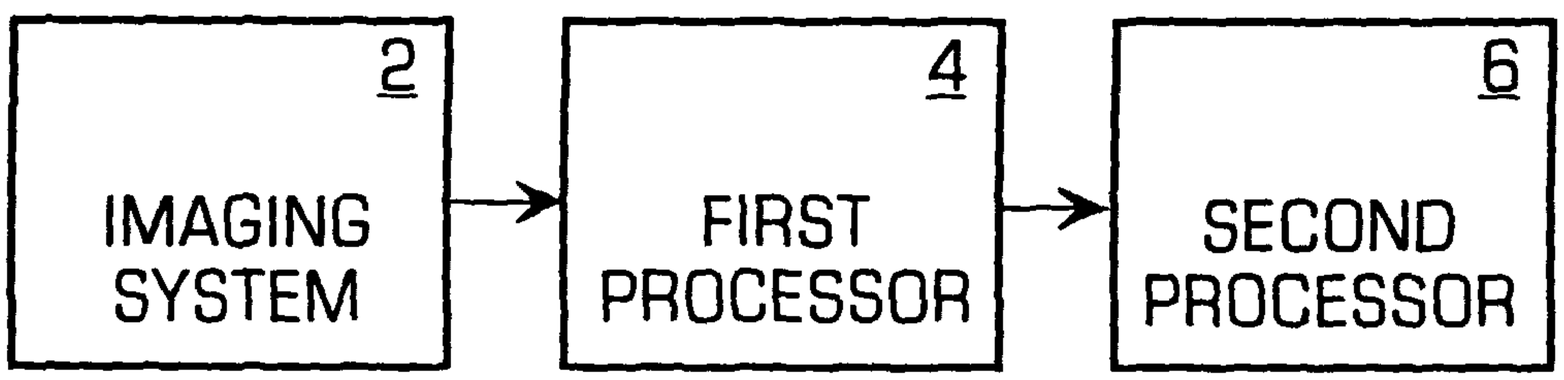

(57) Abstract: A multi-neural net imaging apparatus (2) and method for classification of image elements, such as biological particles. The multi-net structure utilizes subgroups of particle features to partition the decision space by an attribute or physical characteristic of the particle and/or by individual and group particle classification that includes an unknown category. Preprocessing (6) classifies particles as artifacts based on certain physical characteristics. Post processing (6) enables the use of contextual information either available from other sources or gleaned from the actual decision making process to further process the probability factors and enhance the decisions.

WO 01/82216 A1

MULTI-NEURAL NET IMAGING APPARATUS AND METHOD

Technical Field

The present invention relates to an imaging apparatus having a plurality of neural nets, and a method of training the neural nets and a method of operating such an imaging apparatus. The apparatus can be used to detect and classify biological particles and more particularly, for detecting and classifying biological particles from human urine.

BACKGROUND OF THE INVENTION

Biological particle analysis apparatuses are well known in the art. See for example U.S. Patent No: 4,338,024, assigned to the present assignee, which describes a prior art machine that uses a computer having a stored fixed program to detect and to classify detected biological particles.

Standard decision theory that is used to sort biological particle images is well known, and tends to sort particles by classification in a serial fashion. More specifically, for a urine sample containing a plurality of particle types, the particle images are searched for one or more particle features unique to a single particle type, and those images are extracted. This process is repeated for other particles one particle type at a time. The problem with this methodology is that each particle type can exhibit a range of values for the searched for particle feature(s), and the range of values can overlap with those of other particle types. There is also the problem of artifacts, which are particle images that have no clinical significance, e.g. talc or hair, or cannot be classified due to the sensitivity of the imaging device or other problems with the image (e.g. boundary of particle undefined due to partial capture). Artifact particle images need to be disregarded from the analysis in such a way as to not

adversely affect the overall accuracy of the particle analysis. Thus, it can be difficult to accurately but reliably classify particles in a sample containing artifacts .

Most biological particle classification devices further necessitate manual manipulation to accurately classify the particles in the sample. While particle features can be used to segregate particle images by particle type, a trained user is needed to verify the result.

Neural net computers are also well known. The advantage of a neural net computer is its ability to "learn" from its experiences, and thus a neural net computer, in theory, can become more intelligent as it is trained.

There is a need for a biological particle classification method and apparatus for accurate and automated classification of biological particles in a sample, such as a urine sample.

SUMMARY OF THE INVENTION

In some embodiments of the present invention, a multi-neural net image detecting and classification apparatus is disclosed. The multi-neural net more efficiently uses the available information, which of necessity is finite, in that it more effectively partitions the decision space, thereby allowing this information to be used to make fewer decisions at each stage while still covering all outcomes with its totality of decisions. In addition, the neural net measures certainty at multiple stages of processing in order to force images to an abstention class, e.g. artifact. In some sense one can view this multi neural network as forcing the image data to run a gauntlet where at each stage of the gauntlet it is quite likely to be placed in an "I don't know" category. This is much more powerful than simply running through a single net because in essence what is accomplished is multiple fits of the data to templates which are much better defined than a single template could be because of the more effective use of the information.

Some embodiments of the present invention also relate to a large set of particle features and a training method, which involves not simply a single pass through the training set, but

selecting from a number of nets and then reducing the feature vector size. Finally, the present invention provides for preprocessing and post processing that enables heuristic information to be included as part of the decision making process. Post processing enables contextual information either available from other sources or gleaned from the actual decision making process to be used to further enhance the decisions.

One aspect of the present invention is a method of classifying an element in an image into one of a plurality of classification classes, wherein the element has a plurality of features. The method includes the steps of extracting the plurality of features from the image, determining a classification class of the element, and modifying the determined classification class of the element based upon a plurality of previously determined classification class determinations. The determination of the element classification class includes at least one of:

selecting and processing a first subgroup of the extracted features to determine a physical characteristic of the element, and selecting and processing a second subgroup of the extracted features using the physical characteristic determined to determine a classification class of the element; and

selecting and processing a third subgroup of the extracted features to determine a group of classification classes of the element, and selecting and processing a fourth subgroup of the extracted features using the determined classification class group to determine a classification class of the element.

In other aspect of the present invention, an imaging apparatus for classifying an element in an image into one of a plurality of classification classes, wherein the element has a plurality of features, includes means for extracting the plurality of features from the image, means for determining a classification class of the element, and means for modifying the determined classification class of the element based upon a plurality of previously determined classification class determinations. The determining means includes at least one of:

means for selecting and processing a first subgroup of the extracted features to determine a physical characteristic of the element, and means for selecting and processing a second subgroup of the extracted features using the physical characteristic determined to determine a classification class of the element, and

means for selecting and processing a third subgroup of the extracted features to determine a group of classification classes of the element, and means for selecting and processing a fourth subgroup of the extracted features using the determined classification class group to determine a classification class of the element.

In yet another aspect of the present invention, a method of classifying an element in an image into one of a plurality of classifications, wherein the element has a plurality of features, includes the steps of extracting the plurality of features from the image, determining a classification of the element based upon the plurality of features extracted by a first determination criteria wherein the first determination criteria includes the classification of the element as an unknown classification, determining a classification of the element by a second determination criteria, different from the first determination criteria, in the event the element is classified as an unknown classification by the first determination criteria, and determining the classification of the element by a third determination criteria, different from the first and second determination criteria, in the event the element is classified as one of a plurality of classifications by the first determination criteria.

In yet one more aspect of the present invention, an imaging apparatus for classifying an element in an image into one of a plurality of classification classes, wherein the element has a plurality of features, includes: an extractor for extracting the plurality of features from the image of the element; a first processor that determines a classification class of the element, and a second processor that modifies the determined classification class of the element based upon a plurality of previously

determined classification class determinations. The first processor determines the classification class of the element by at least one of:

selecting and processing a first subgroup of the extracted features to determine a physical characteristic of the element, and selecting and processing a second subgroup of the extracted features in response to the physical characteristic determined to determine a classification class of the element; and

selecting and processing a third subgroup of the extracted features to determine a group of classification classes of the element, and selecting and processing a fourth subgroup of the extracted features in response to the determined classification class group to determine a classification class of the element.

Other objects and features of embodiments of the present invention will become apparent by a review of the specification, claims and appended figures.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 is a flow diagram showing the method of an embodiment of the present invention.

Figure 2 is a schematic diagram of the apparatus of an embodiment of the present invention.

Figures 3A and 3B are flow diagrams illustrating the boundary enhancement of an embodiment of the present invention.

Figure 4 is a diagram illustrating the symmetry feature extraction of an embodiment of the present invention.

Figures 5A to 5D are drawings illustrating the skeletonization of various shapes.

Figure 6A is a flow diagram showing the LPF scan process of an embodiment of the present invention.

Figure 6B is a flow diagram of the neural net classification used with the LPF scan process of an embodiment of the present invention.

Figure 7A is a flow diagram showing the HPF scan process of an embodiment of the present invention.

Figure 7B is a flow diagram of the neural net classification used with the HPF scan process of an embodiment of the present invention.

Figure 8 is a schematic diagram of the neural net used with an embodiment of the present invention.

Figures 9A to 9C are tables showing the particle features used with the various neural nets in the LPF and HPF scan processes of some embodiments of the present invention.

DETAILED DESCRIPTION

Some embodiments of the present invention comprise a method and apparatus for making decisions about the classification of individual particle images in an ensemble of images of biological particles for the purpose of identifying each individual image, and determining the number of images in each given class of particles.

Basic Method and Apparatus

The method is generally shown schematically in Figure 1, and comprises 5 basic steps:

1) collect individual images,

2) extract particle features from each individual image,

3) apply certain pre-processing rules to determine classifications of individual images or how the classification process will be performed,

4) classify the individual images using a multiple neural net decision making structure, and

5) analyze the ensemble of decisions or a subset of the ensemble of decisions to determine the overall classification of the ensemble or changes to classifications of certain subsets or individual images.

The method of the present invention further includes steps that train the individual neural nets used to make decisions, as well as steps that select the nets used in the final decision-making from among multiple nets produced by the training procedure.

There are three major hardware elements that are used to implement the present invention: an imaging system 2, a first processor 4 and a second processor 6. These hardware elements are schematically illustrated in Fig. 2.

Imaging system 2 is used to produce images of fields of view of a sample containing the particles of interest. Imaging system 2 is preferably a well known flow microscope as described in U.S. Patents 4,338,024, 4,393,466, 4,538,299 and 4,612,614. The flow microscope produces images of successive fields containing particles as they flow through a flow cell.

First processor 4 analyzes the images of successive fields, and isolates the particles in individual patches. A patch extraction apparatus (such as that described in U.S. Patents 4,538,299 and 5,625,709) is used to analyze the images produced by the imaging system and to define local areas (patches) containing particles of interest. The boundary of each particle is identified and defined, and used to extract the picture data for each particle from the larger field, thereby producing digital patch images that each contain the image of an individual particle of interest (resulting in a significant compression of the data subsequently required for processing). Imaging system 2 and first processor 4 combine to perform the first step (collection of individual images) shown in Fig. 1.

Second processor 6 analyzes each particle image to determine the classification of the particle image. Second processor 6 performs the last four steps shown in Fig. 1, as described below.

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Boundary Enhancement – Mask Images

To enhance the particle feature extraction, the particle boundary is further refined, and black and white mask images of the particles are created. This process effectively changes all the digital image pixels outside the boundary of the particle (background pixels) to black pixels, and the pixels inside the particle boundary to white pixels. The resulting white images of the particles against a black background conveys the particles' shape and size very clearly, and are easy to operate on for particle features based on shape and size only (given that the pixels are either white or black).

Figs. 3A-3B illustrate the basic steps for transforming the particle image into a mask image. First, a Shen-Castan edge detector (as described in Parker, James R., Algorithms for Image Processing and Computer Vision, ISBN 0-471-14056-2, John Wiley & Sons, 1997, pp 29-32) is used to define the edges of particles of interest, as illustrated in Fig. 3A. A particle image 10 typically contains images of particles of interest 12 and other particles 14. The particle image 10 is smoothed, and a band limited Laplacian image is created, followed by a gradient image. A threshold routine is used to detect the edges, whereby the locations where the intensity crosses a predetermined threshold are defined as edges. The detected edges are connected together to result in an edges image 16, which contains lines that correspond to detected boundaries that outline the various particles.

A mask image is created from the edge image 16 in the manner illustrated in Fig. 3B. The edge image 16 is inverted so the boundary lines are white and the background is black. Then, the image is cleaned of all small specks and particles too small to be of interest. Small gaps in the boundary lines are filled to connect some of the boundary lines together. The boundary lines are dilated to increase their width. This dilation is on the outer edges of the boundary lines, since the inner edges define the actual size of the particles. Disconnected pixels are bridged to create complete lines that enclose the particles. The inside of the boundaries are filled in to create

blobs that represent the particles. The blobs are eroded to remove the pixels that had formed the boundary lines, so that the blobs have the correct size. Finally, the largest blob is detected, and all the remaining blobs are discarded. The resulting image is a mask image of the particle, where the white blob against the black background accurately corresponds to the size and shape of the particle of interest.

Particle Feature Extraction

Once the image of a particle of interest has been localized within a patch image, and its boundary further refined by creating a white mask image of the particle, the patch and mask images are further processed in order to extract particle features (feature data) from the particle image. Generally, the particle features numerically describe the size, shape, texture and color of the particles in numerous different ways that aid in the accurate classification of particle type. The particle features can be grouped in families that are related to one of these numerical descriptions, and can be extracted from the patch image, the mask image, or both.

The first family of particle features all relate to the shape of the particle, which aid in differentiating red and white blood cells which tend to be round, crystals which tend to be square or rectangular, and casts with tend to be elongated. The first family of particle features are:

1. Particle Area: the number of pixels contained within the particle boundary. Preferably, this particle feature is derived from the mask image of the particle.
2. Perimeter Length: the length of the particle boundary in pixels. Preferably, this is derived from the particle mask image by creating a 4-neighborhood perimeter image of the mask, and counting the number of non-zero pixels.

3. Shape Factor: an indication of the roundness of the particle. This is calculated as the square of the Perimeter Length, divided by the Particle Area.

4. Area to Perimeter Ratio: another indication of the roundness of the particle. This is calculated as the Particle Area divided by the Perimeter Length.

The second family of particle features relates to the symmetry of the particle, and in particular the determination of the number of lines of symmetry for any given shaped particle. This family of particle features are quite useful in distinguishing casts (typically having a line of symmetry along its long axis) and squamous epithelial cells (SQEPs, which generally have no line of symmetry). This family of particle features utilizes information derived from line segments applied at different angular orientations to the particle. As illustrated in Fig. 4, a line segment 20 is drawn through the centroid 22 of the mask image 19. For each point along the line segment 20, line segments 24a and 24b perpendicular thereto are drawn to extend away from the line segment 20 until they intersect the particle boundary, and the difference in length of the opposing perpendicular line segments 24a and 24b are calculated and stored. This calculation is repeated for each point along the line segment 20, where all the difference values are then summed and stored as a Symmetry Value for line segment 20. For a perfect circle, the Symmetry Value is zero for any line segment 20. The calculation of the Symmetry Value is then repeated for each angular rotation of line segment 20, resulting in a plurality of Symmetry Values, each one corresponding to a particular angular orientation of line segment 20. The Symmetry Values are then normalized by the Particle Area value, and sorted into an ordered list of Symmetry Values from low to high.

The second family of particle features are:

5. Minimum Symmetry: the lowest Symmetry Value in the ordered list, which represents the maximum symmetry exhibited by the particle at some value of rotation.
6. 20% Symmetry: the Symmetry Value that constitutes the 20th percentile of the ordered list of Symmetry Values.
7. 50% Symmetry: the Symmetry Value that constitutes the 50th percentile of the ordered list of Symmetry Values.
8. 80% Symmetry: the Symmetry Value that constitutes the 80th percentile of the ordered list of Symmetry Values.
9. Maximum Symmetry: the highest Symmetry Value in the ordered list, which represents the minimum symmetry exhibited by the particle at some value of rotation.
10. Average Symmetry: the average value of the Symmetry Values.
11. Standard Deviation Symmetry: the standard deviation of the Symmetry Values.

The third family of particle features relate to skeletonization of the particle image, which produces one or more line segments that characterize both the size and the shape of the particle. These particle features are ideal in identifying analytes having multiple components in a cluster, such as budding yeast, hyphae yeast, and white blood cell clumps. These analytes will have skeletons with multiple branches, which are easy to differentiate from analytes having single branch skeletons. Creation of skeleton images is well known in the art of image processing, and is disclosed in Parker, James R., Algorithms for Image Processing and Computer Vision, ISBN 0-471-14056-2, John Wiley & Sons, 1997, pp 176-210).

Skeletonization essentially involves collapsing each portion of the particle boundary inwardly in a direction perpendicular to itself. For example, a perfect circle collapses to a single point; a crescent moon collapses to a curved line, a figure-8 collapses to 2 straight line segments, and a cell with an indentation collapses

to a curved line, as illustrated in Figs. 5A – 5D respectively. The preferred embodiment utilizes two skeletonization algorithms: ZSH and BZS. ZSH is the Zhang-Suen thinning algorithm using Holt's variation plus staircase removal. BZS is the Zhang-Suen thinning algorithm using Holt's variation. Figure 5.11 in Parker (p. 182) shows the difference between results when these algorithms are applied, along with C-code for each algorithm.

The third family of particle features are:

12. ZSH Skeleton Size: the size of the skeleton, preferably determined by counting the number of pixels forming the skeleton. The Skeleton Size for a perfect circle is 1, and for a crescent moon would be the length of the curved line.
13. ZSH Normalized Skeleton Size: Skeleton Size normalized by the size of the particle, determined by dividing Skeleton Size by Particle Area.
14. BZS Skeleton Size: the size of the skeleton, preferably determined by counting the number of pixels forming the skeleton. The Skeleton Size for a perfect circle is 1, and for a crescent moon would be the length of the curved line.
15. BZS Normalized Skeleton Size: Skeleton Size normalized by the size of the particle, determined by dividing Skeleton Size by Particle Area.

The fourth family of particle features relate to measuring the shape of the particle using radial lengths of radii that fit in the particle, and the quantile rankings of these values. Specifically, a centroid is defined inside the particle, preferably using the mask image, and a plurality of radii emanating from the centroid at different angles extend out to the particle boundary. The lengths of the radii are collected into a list of Radii Values, and the list is sorted from low to high values. A certain % quantile of an ordered list of values represents the value having a position in the list that corresponds

to the certain percentage from the bottom of the list. For example, a 30% quantile of a list is the value that is positioned 30% up from bottom of the list, with 70% of the values being above it in the list. So, in an order list of 10 values, the 30% quantile value is the seventh value from the top of the list, and the 50% quantile is the median value of the list.

The fourth family of particle features are:

16. 25% Radii Value: the value corresponding to the 25% quantile of the list of Radii Values.
17. 50% Radii Value: the value corresponding to the 50% quantile of the list of Radii Values.
18. 75% Radii Value: the value corresponding to the 75% quantile of the list of Radii Values.
19. Smallest Mean Ratio: the ratio of the smallest Radii Value to the mean Radii Value.
20. Largest Mean Ratio: the ratio of the largest Radii Value to the mean Radii Value.
21. Average Radii Value: the average of the Radii Values.
22. Standard Deviation Radii Value: the standard deviation of the Radii Values.

The fifth family of particle features measures the intensity of the particle image. Light absorption properties of different analytes differ significantly. For example, crystals are generally refractive and may actually "concentrate" light so that their interior may be brighter than the background. Stained white blood cells, however, will typically be substantially darker than the background. The average intensity reveals the overall light absorbing quality of the particle, while the standard deviation of intensity measures the uniformity of the particle's absorbing quality. In order to measure intensity, the particle is preferably isolated by using the mask image

in order to mask the patch image of the particle. Thus, the only pixels left (inside the mask) are those pixels contained inside the particle boundary. This family of particle features includes:

23. Average Pixel Value: the average pixel value for all the pixels inside the particle boundary.
24. Standard Deviation of Pixel Values: the standard deviation of pixel values for pixels inside the particle boundary.

The sixth family of particle features use the Fourier Transform of the particle to measure the radial distribution of the particle. The Fourier Transform depends on the size, shape and texture (i.e. fine grain structure) of the particle. In addition to adding texture, the Fourier Transform magnitude is independent of the position of the particle, and particle rotation is directly reflected as a rotation of the transform. Finding clusters of energy at one rotation is an indication of linear aspects of the particle (i.e. the particle has linear portions). This finding helps discriminate between particles such as crystals versus red blood cells. The Fourier Transform of the patch image of the particle is preferably calculated using a well known Fast Fourier Transform (FFT) algorithm with a window of 128x128 pixels. The following particle features are then calculated:

25. FFT Average Intensity of Rotated 128 Pixel Line: a queue listing of average pixel values along a 128 pixel line as a function of rotation angle. This is calculated by placing a radial line of length 128 pixels over the transform, and rotating the radial line through an arc of 180 degrees by increments of N degrees. For each increment of N degrees, the average of the pixel values along the radial line is calculated. The average pixel values for the N degree increments are stored in a queue as Average Intensity along with the corresponding angular increment.

26. FFT Maximum/Minimum 128 Pixel Angular Difference: the difference between the angular values that correspond to the highest and lowest Average Intensity values stored in the queue.

27. FFT 128 Pixel Average Intensity Standard Deviation: the standard deviation of the Average Intensity values stored in the queue.

28. FFT Average Intensity of Rotated 64 Pixel Line: same as the FFT Average Intensity of Rotated 128 Pixel Line, but instead using a 64 pixel length radial line.

29. FFT Maximum/Minimum 64 Pixel Angular Difference: same as the FFT Maximum/Minimum 128 Pixel Angular Difference, but instead using a 64 pixel length radial line.

30. FFT 64 Pixel Average Intensity Standard Deviation: same as the FFT 128 Pixel Average Intensity Standard Deviation, but instead using a 64 pixel length radial line.

31. FFT Average Intensity of Rotated 32 Pixel Line: same as the FFT Average Intensity of Rotated 128 Pixel Line, but instead using a 32 pixel length radial line.

32. FFT Maximum/Minimum 32 Pixel Angular Difference: same as the FFT Maximum/Minimum 128 Pixel Angular Difference, but instead using a 32 pixel length radial line.

33. FFT 32 Pixel Average Intensity Standard Deviation: same as the FFT 128 Pixel Average Intensity Standard Deviation, but instead using a 32 pixel length radial line.

Additional FFT particle features all related to standard deviation values based upon a rotated radial line of varying lengths are as follows:

34. FFT 128 Pixel Average Intensity Standard Deviation Sort: a sorted queue listing of the standard deviation of average pixel values along a 128 pixel line for different rotations. This is calculated by placing a radial line of length 128 pixels over the transform, and rotating the radial line through an arc of 180 degrees by increments of N degrees. For each increment of N degrees, the standard deviation value of the pixels on the line is calculated. The standard deviation values for all the N degree increments are sorted from low to high, and stored in a queue.

35. FFT 128 Pixel Minimum Radial Standard Deviation: the minimum radial standard deviation value retrieved from the sorted queue listing of standard deviation values.

36. FFT 128 Pixel Maximum Radial Standard Deviation: the maximum radial standard deviation value retrieved from the sorted queue listing of standard deviation values.

37. FFT 128 Pixel 25% Quantile Radial Standard Deviation: the radial standard deviation value from the queue corresponding to the 25% quantile of the values stored in the queue.

38. FFT 128 Pixel 50% Quantile Radial Standard Deviation: the radial standard deviation value from the queue corresponding to the 50% quantile of the values stored in the queue.

39. FFT 128 Pixel 75% Quantile Radial Standard Deviation: the radial standard deviation value from the queue corresponding to the 75% quantile of the values stored in the queue.

40. FFT 128 Pixel Minimum to Average Radial Standard Deviation Ratio: the ratio of the minimum to average radial standard deviation values stored in the queue.

41. FFT 128 Pixel Maximum to Average Radial Standard Deviation Ratio: the ratio of the maximum to average radial standard deviation values stored in the queue.

42. FFT 128 Pixel Average Radial Standard Deviation: the average radial standard deviation value of the values stored in the queue.

43. FFT 128 Pixel Standard Deviation of the Radial Standard Deviation: the standard deviation of all of the radial standard deviation values stored in the queue.

44. FFT 64 Pixel Average Intensity Standard Deviation Sort: the same as the FFT 128 Pixel Average Intensity Standard Deviation Sort, but instead using a 64 pixel length radial line.

45. FFT 64 Pixel Minimum Radial Standard Deviation: the same as the FFT 128 Pixel Minimum Radial Standard Deviation, but instead using a 64 pixel length radial line.

46. FFT 64 Pixel Maximum Radial Standard Deviation: the same as the FFT 128 Pixel Maximum Radial Standard Deviation, but instead using a 64 pixel length radial line.

47. FFT 64 Pixel 25% Quantile Radial Standard Deviation: the same as the FFT 128 Pixel 25% Quantile Radial Standard Deviation, but instead using a 64 pixel length radial line.

48. FFT 64 Pixel 50% Quantile Radial Standard Deviation: the same as the FFT 128 Pixel 50% Quantile Radial Standard Deviation, but instead using a 64 pixel length radial line.

49. FFT 64 Pixel 75% Quantile Radial Standard Deviation: the same as the FFT 128 Pixel 75% Quantile Radial Standard Deviation, but instead using a 64 pixel length radial line.

50. FFT 64 Pixel Minimum to Average Radial Standard Deviation Ratio: the same as the FFT 128 Pixel Minimum to Average Radial Standard Deviation Ratio, but instead using a 64 pixel length radial line.

51. FFT 64 Pixel Maximum to Average Radial Standard Deviation Ratio: the same as the FFT 128 Pixel Maximum to Average Radial Standard Deviation Ratio, but instead using a 64 pixel length radial line.

52. FFT 64 Pixel Average Radial Standard Deviation: the same as the FFT 128 Pixel Average Radial Standard Deviation, but instead using a 64 pixel length radial line.

53. FFT 64 Pixel Standard Deviation of the Radial Standard Deviation: the same as the FFT 128 Pixel Standard Deviation of the Radial Standard Deviation, but instead using a 64 pixel length radial line.

54. FFT 32 Pixel Average Intensity Standard Deviation Sort: the same as the FFT 128 Pixel Average Intensity Standard Deviation Sort, but instead using a 32 pixel length radial line.

55. FFT 32 Pixel Minimum Radial Standard Deviation: the same as the FFT 128 Pixel Minimum Radial Standard Deviation, but instead using a 32 pixel length radial line.

56. FFT 32 Pixel Maximum Radial Standard Deviation: the same as the FFT 128 Pixel Maximum Radial Standard Deviation, but instead using a 32 pixel length radial line.

57. FFT 32 Pixel 25% Quantile Radial Standard Deviation: the same as the FFT 128 Pixel 25% Quantile Radial Standard Deviation, but instead using a 32 pixel length radial line.

58. FFT 32 Pixel 50% Quantile Radial Standard Deviation: the same as the FFT 128 Pixel 50% Quantile Radial Standard Deviation, but instead using a 32 pixel length radial line.

59. FFT 32 Pixel 75% Quantile Radial Standard Deviation: the same as the FFT 128 Pixel 75% Quantile Radial Standard Deviation, but instead using a 32 pixel length radial line.

60. FFT 32 Pixel Minimum to Average Radial Standard Deviation Ratio: the same as the FFT 128 Pixel Minimum to Average Radial Standard Deviation Ratio, but instead using a 32 pixel length radial line.

61. FFT 32 Pixel Maximum to Average Radial Standard Deviation Ratio: the same as the FFT 128 Pixel Maximum to Average Radial Standard Deviation Ratio, but instead using a 32 pixel length radial line.

62. FFT 32 Pixel Average Radial Standard Deviation: the same as the FFT 128 Pixel Average Radial Standard Deviation, but instead using a 32 pixel length radial line.

63. FFT 32 Pixel Standard Deviation of the Radial Standard Deviation: the same as the FFT 128 Pixel Standard Deviation of the Radial Standard Deviation, but instead using a 32 pixel length radial line.

Even more FFT particle features are used, all related to average values based upon a rotated radial line of varying lengths:

64. FFT 128 Pixel Average Intensity Sort: a sorted queue listing of the average pixel values along a 128 pixel line for different rotations. This is calculated by placing a radial line of length 128 pixels over the transform, and rotating the radial line through an arc of 180 degrees by increments of N degrees. For each increment of N degrees, the average value of the

pixels on the line is calculated. The average pixel values for all the N degree increments are sorted from low to high, and stored in a queue.

65. FFT 128 Pixel Minimum Average Value: the minimum radial average value retrieved from the sorted queue listing of average values.

66. FFT 128 Pixel Maximum Radial Value: the maximum radial average value retrieved from the sorted queue listing of average values.

67. FFT 128 Pixel 25% Quantile Radial Average Value: the radial average value from the queue corresponding to the 25% quantile of the average values stored in the queue.

68. FFT 128 Pixel 50% Quantile Radial Average Value: the radial average value from the queue corresponding to the 50% quantile of the average values stored in the queue.

69. FFT 128 Pixel 75% Quantile Radial Average Value: the radial average value from the queue corresponding to the 75% quantile of the average values stored in the queue.

70. FFT 128 Pixel Minimum to Average Radial Average Value Ratio: the ratio of the minimum to average radial average values stored in the queue.

71. FFT 128 Pixel Maximum to Average Radial Average Value Ratio: the ratio of the maximum to average radial average values stored in the queue.

72. FFT 128 Pixel Average Radial Standard Deviation: the average radial standard deviation value of the average values stored in the queue.

73. FFT 128 Pixel Standard Deviation of the Average Values: the standard deviation of all of the radial average values stored in the queue.

The seventh family of particle features use grayscale and color histogram quantiles of image intensities, which provide additional information about the intensity variation within the particle boundary. Specifically, grayscale, red, green and blue histogram quantiles provide intensity characterization in different spectral bands. Further, stains used with particle analysis cause some particles to absorb certain colors, such as green, while others exhibit refractive qualities at certain wavelengths. Thus, using all these particle features allows one to discriminate between a stained particle such as white blood cells that absorb the green, and crystals that refract yellow light.

Histograms, cumulative histograms and quantile calculations are disclosed in U.S. Patent 5,343,538. The particle image is typically captured using a CCD camera that breaks down the image into three color components. The preferred embodiment uses an RGB camera that separately captures the red, green and blue components of the particle image. The following particle features are calculated based upon the grayscale, red, green and blue components of the image:

74. Grayscale Pixel Intensities: a sorted queue listing of the grayscale pixel intensities inside the particle boundary. The grayscale value is a summation of the three color components. For each pixel inside the particle boundary (as masked by the mask image), the grayscale pixel value is added to a grayscale queue, which is then sorted (e.g. from low to high).

75. Minimum Grayscale Image Intensity: the minimum grayscale pixel value stored in the queue.

76. 25% Grayscale Intensity: the value corresponding to the 25% quantile of the grayscale pixel values stored in the queue.

77. 50% Grayscale Intensity: the value corresponding to the 50% quantile of the grayscale pixel values stored in the queue.

78. 75% Grayscale Intensity: the value corresponding to the 75% quantile of the grayscale pixel values stored in the queue.

79. Maximum Grayscale Image Intensity: the maximum grayscale pixel value stored in the queue.

80. Red Pixel Intensities: a sorted queue listing of the red pixel intensities inside the particle boundary. The particle image is converted so that only the red component of each pixel value remains. For each pixel inside the particle boundary (as masked by the mask image), the red pixel value is added to a red queue, which is then sorted from low to high.

81. Minimum Red Image Intensity: the minimum red pixel value stored in the queue.

82. 25% Red Intensity: the value corresponding to the 25% quantile of the red pixel values stored in the queue.

83. 50% Red Intensity: the value corresponding to the 50% quantile of the red pixel values stored in the queue.

84. 75% Red Intensity: the value corresponding to the 75% quantile of the red pixel values stored in the queue.

85. Maximum Red Image Intensity: the maximum red pixel value stored in the queue.

86. Green Pixel Intensities: a sorted queue listing of the green pixel intensities inside the particle boundary. The particle image is converted so that only the green component of the pixel value remains. For each

pixel inside the particle boundary (as masked by the mask image), the green pixel value is added to a green queue, which is then sorted from low to high.

87. Minimum Green Image Intensity: the minimum green pixel value stored in the queue.
88. 25% Green Intensity: the value corresponding to the 25% quantile of the green pixel values stored in the queue.
89. 50% Green Intensity: the value corresponding to the 50% quantile of the green pixel values stored in the queue.
90. 75% Green Intensity: the value corresponding to the 75% quantile of the green pixel values stored in the queue.
91. Maximum Green Image Intensity: the maximum green pixel value stored in the queue.
92. Blue Pixel Intensities: a sorted queue listing of the blue pixel intensities inside the particle boundary. The particle image is converted so that only the blue component of the pixel value remains. For each pixel inside the particle boundary (as masked by the mask image), the blue pixel value is added to a blue queue, which is then sorted from low to high.
93. Minimum Blue Image Intensity: the minimum blue pixel value stored in the queue.
94. 25% Blue Intensity: the value corresponding to the 25% quantile of the blue pixel values stored in the queue.
95. 50% Blue Intensity: the value corresponding to the 50% quantile of the blue pixel values stored in the queue.
96. 75% Blue Intensity: the value corresponding to the 75% quantile of the blue pixel values stored in the queue.
97. Maximum Blue Image Intensity: the maximum blue pixel value stored in the queue.

The eighth family of particle features use concentric circles and annuli to further characterize the variation in the FFT magnitude distribution, which is affected by the size, shape and texture of the original analyte image. A center circle is defined over a centroid of the FFT, along with seven annuli (in the shape of a washer) of progressively increasing diameters outside of and concentric with the center circle. The first annulus has an inner diameter equal to the outer diameter of the center circle, and an outer diameter that is equal to the inner diameter of the second annulus, and so on. The following particle features are calculated from the center circle and seven annuli over the FFT:

98. Center Circle Mean Value: the mean value of the magnitude of the FFT inside the center circle.
99. Center Circle Standard Deviation: the standard deviation of the magnitude of the FFT inside the center circle.
100. Annulus to Center Circle Mean Value: the ratio of the mean value of the magnitude of the FFT inside the first annulus to that in the center circle.
101. Annulus to Center Circle Standard Deviation: the ratio of the standard deviation of the magnitude of the FFT inside the first annulus to that in the center circle.
102. Annulus to Circle Mean Value: the ratio of the mean value of the magnitude of the FFT inside the first annulus to that of a circle defined by the outer diameter of the annulus.
103. Annulus to Circle Standard Deviation: the ratio of the standard deviation of the magnitude of the FFT inside the first annulus to that of a circle defined by the outer diameter of the annulus.
104. Annulus to Annulus Mean Value: the ratio of the mean value of the magnitude of the FFT inside the first annulus to that of the annulus or

center circle having the next smaller diameter (in the case of the first annulus, it would be the center circle).

105. Annulus to Annulus Standard Deviation: the ratio of the standard deviation of the magnitude of the FFT inside the first annulus to that of the annulus or center circle having the next smaller diameter (in the case of the first annulus, it would be the center circle).

106-111: Same as features 100-104, except the second annulus is used instead of the first annulus.

112-117: Same as features 100-104, except the third annulus is used instead of the first annulus.

118-123: Same as features 100-104, except the fourth annulus is used instead of the first annulus.

124-129: Same as features 100-104, except the fifth annulus is used instead of the first annulus.

130-135: Same as features 100-104, except the sixth annulus is used instead of the first annulus.

136-141: Same as features 100-104, except the seventh annulus is used instead of the first annulus.

154-197 is the same as 98-141, except they are applied to an FFT of the FFT of the particle image.

The last family of particle features use concentric squares with sides equal to 11%, 22%, 33%, 44%, 55%, and 66% of the FFT window size (e.g. 128) to further characterize the variation in the FFT magnitude distribution, which is affected by the size, shape and texture of the original analyte image. There are two well known texture analysis algorithms that characterize the texture of an FFT. The first is entitled Vector Dispersion, which involves fitting a planar to teach regions using normals, and is described on pages 165-168 of Parker. The

second is entitled Surface Curvature Metric, which involves conforming a polynomial

to the region, and is described on pages 168-171 of Parker.

The following particle features are calculated from different sized windows over the FFT:

142-147: Application of the Vector Dispersion algorithm to the 11%, 22%, 33%, 44%, 55%, and 66% FFT windows, respectively.

148-153: Application of the Surface Curvature Metric algorithm to the 11%, 22%, 33%, 44%, 55%, and 66% FFT windows, respectively.

Processing and Decision Making

Once the foregoing particle features are computed, processing rules are applied to determine the classification of certain particles or how all of the particles in the ensemble from the sample will be treated. The preferred embodiment acquires the particle images using a low power objective lens (e.g. 10X) to perform low power field (LPF) scans with a larger field of view to capture larger particles, and a high power objective lens (e.g. 40X) to perform high power field (HPF) scans with greater sensitivity to capture the more minute details of smaller particles.

The system of the present invention utilizes separate multi neural net decision structures to classify particles captured in the LPF scan and HPF scan. Since most particles of interest will appear in one of the LPF or HPF scans, but not both, the separate decision structures minimize the number of particles of interest that each structure must classify.

Neural Net Structure

Figure 8 illustrates the basic neural net structure used for all the neural nets in the LPF and HPF scans. The net includes an input layer with inputs X_1 to X_d, each corresponding to one of the particle features described above that are selected for use with the net. Each input is connected to each one of a plurality of neurons Z_1 to Z_J in a hidden layer. Each of these hidden layer neurons Z_1 to Z_J sums all the values received

from the input layer in a weighted fashion, whereby the actual weight for each neuron is individually assignable. Each hidden layer neuron Z_1 to Z_J also applies a non-linear function to the weighted sum. The output from each hidden layer neuron Z_1 to Z_J is supplied each one of a second (output) layer of neurons Y_1 to Y_K. Each of the output layer neurons Y_1 to Y_K also sums the inputs received from the hidden layer in a weighted fashion, and applies a non-linear function to the weighted sum. The output layer neurons provide the output of the net, and therefore the number of these output neurons corresponds to the number of decision classes that the net produces. The number of inputs equals the number of particle features that are chosen for input into the net.

As described later, each net is 'trained' to produce an accurate result. For each decision to be made, only those particle features that are appropriate to the decision of the net are selected for input into the net. The training procedure involves modifying the various weights for the neurons until a satisfactory result is achieved from the net as a whole. In the preferred embodiment, the various nets were trained using NeuralWorks, product version 5.30, which is produced by NeuralWare of Carnegie, Pa, and in particular the Extended Delta Bar Delta Back-propagation algorithm. The non-linear function used for all the neurons in all of the nets in the preferred embodiment is the hyperbolic tangent function, where the input range is constrained between –0.8 and +0.8 to avoid the low slope region.

LPF Scan Process

The LPF scan process is illustrated in Fig. 6A, and starts by getting the next particle image (analyte) using the low power objective lens. A neural net classification is then performed, which involves the process of applying a cascading structure of neural nets to the analyte image, as illustrated in Fig. 6B. Each neural net takes a selected subgroup of the calculated 198 particle features discussed above, and calculates a classification probability factor ranging from zero to one that the particle

meets the criteria of the net. The cascading configuration of the nets helps improve the accuracy of each neural net result downstream, because each net can be specifically designed for more accuracy given that the particle types it operates on have been prescreened to have or not have certain characteristics. For system efficiency, all 198 particle features are preferably calculated for each particle image, and then the neural net classification process of Fig. 6B is applied.

The first neural net applied to the particle image is the AMOR Classifier Net, which decides whether or not the particle is amorphous. For the preferred embodiment, this net includes 42 inputs for a selected subset of the 198 particle features described above, 20 neurons in the hidden layer, and two neurons in the output layer. The column entitled LPF AMOR2 in the table of Figs. 9A-9C shows the numbers of the 42 particle features described above that were selected for use with this net. The first and second outputs of this net correspond to the probabilities that the particle is or is not amorphous, respectively. Whichever probability is higher constitutes the decision of the net. If the net decides the particle is amorphous, then the analysis of the particle ends.

If it is decided that the particle is not amorphous, then the SQEP/CAST/OTHER Classifier Net is applied, which decides whether the particle is a Squamous Epithelial cell (SQEP), a Cast cell (CAST), or another type of cell. For the preferred embodiment, this net includes 48 inputs for a selected subset of the 198 particle features described above, 20 neurons in the hidden layer, and three neurons in the output layer. The column entitled LPF CAST/SQEP/OTHER3 in the table of Figs. 9A-9C shows the numbers of the 48 particle features described above that were selected for use with this net. The first, second and third outputs of this net correspond to the probabilities that the particle a Cast, a SQEP, or another particle type, respectively. Whichever probability is highest constitutes the decision of the net.

If it is decided that the particle is a Cast cell, then the CAST Classifier Net is applied, which decides whether the particle is a White Blood Cell Clump (WBCC), a

Hyaline Cast Cell (HYAL), or an unclassified cast (UNCC) such as a pathological cast cell . For the preferred embodiment, this net includes 36 inputs for a selected subset of the 198 particle features described above, 10 neurons in the hidden layer, and three neurons in the output layer. The column entitled LPF CAST3 in the table of Figs. 9A-9C shows the numbers of the 36 particle features described above that were selected for use with this net. The first, second and third outputs of this net correspond to the probabilities that the particle is a WBCC, HYAL or UNCC. Whichever probability is highest constitutes the decision of the net.

If it is decided that the particle is a Squamous Epithelial cell, then the decision is left alone.

If it is decided that the particle is another type of cell, then the OTHER Classifier Net is applied, which decides whether the particle is a Non-Squamous Epithelial cell (NSE) such as a Renal Epithelial cell or a transitional Epithelial cell, an Unclassified Crystal (UNCX), Yeast (YEAST), or Mucus (MUCS). For the preferred embodiment, this net includes 46 inputs for a selected subset of the 198 particle features described above, 20 neurons in the hidden layer, and four neurons in the output layer. The column entitled LPF OTHER4 in the table of Figs. 9A-9C shows the numbers of the 46 particle features described above that were selected for use with this net. The first, second, third and fourth outputs of this net correspond to the probabilities that the particle is a NSE, UNCX, YEAST, or MUCS. Whichever probability is highest constitutes the decision of the net.

Referring back to Fig. 6A, once the Neural Net Classification has decided the particle type, an ART by Abstention Rule is applied, to determine if the particle should be classified as an artifact because none of the nets gave a high enough classification probability factor to warrant a particle classification. The ART by Abstention Rule applied by the preferred embodiment is as follows: if the final classification by the net structure is HYAL, and the CAST probability was less than 0.98 at the SQEP/CAST/Other net, then the particle is reclassified as an artifact. Also, if the final

classification by the net structure was a UNCC, and the CAST probability was less then 0.95 at the SQEP/CAST/Other net, then the particle is reclassified as an artifact.

The next step shown in Fig. 6A applies to particles surviving the ART by Abstention Rule. If the particle was classified by the net structure as a UNCC, a HYAL or a SQEP, then that classification is accepted unconditionally. If the particle was classified as another type of particle, then a partial capture test is applied to determine if the particle should be classified as an artifact. Partial capture test determines if the particle boundary hits one or more particle image patch boundaries, and thus only part of the particle image was captured by the patch image. The partial capture test of the preferred embodiment basically looks at the pixels forming the boundary of the patch to ensure they represent background pixels. This is done by collecting a cumulative intensity histogram on the patch boundaries, and calculating Lower and Upper limits of these intensities. The Lower limit in the preferred embodiment is either the third value from the bottom of the histogram, or the value 2% from the bottom of the histogram, whichever is greater. The Upper limit is either the third value from the top of the histogram, or the value 2% from the top of the histogram, whichever is greater. The patch image is deemed a partial capture if the lower limit is less than 185 (e.g. of a pixel intensity that ranges from 0 to 255). The patch is also deemed a partial capture if the upper limit is less than or equal to 250 and the lower limit is less than 200 (this is to take care of the case where the halo of a particle image touches the patch image boundary). All particles surviving the partial capture test maintain their classification, and the LPF scan process is complete.

In the preferred embodiment, the partial capture test is also used as one of the particle features used by some of the neural nets. The feature value is 1 if the particle boundary is found to hit one or more particle image patch boundaries, and a zero if not. This particle feature is numbered "0" in Figs. 9A-9C.

HPF Scan Process

The HPF scan process is illustrated in Fig. 7A, and starts by getting the next particle image (analyte) using the high power objective lens. Two pre-processing artifact classification steps are performed before submitting the particles to neural net classification. The first preprocessing step begins by defining five size boxes (HPF1-HPF5), with each of the particles being associated with the smallest box that it can completely fit in to. In the preferred embodiment, the smallest box HPF5 is 12 by 12 pixels, and the largest box HPF1 is 50 by 50 pixels. All particles associated with the HPF5 box are classified as an artifact and removed from further consideration, because those particles are too small for accurate classification given the resolution of the system.

The second pre-processing step finds all remaining particles that are associated with the HPF3 or HPF4 boxes, that have a cell area that is less than 50 square pixels, and that are not long and thin, and classifies them as artifacts. This second preprocessing step combines size and aspect ratio criteria, which eliminates those smaller particles which tend to be round. Once particles associated with the HPF3 or HPF4 boxes and with a cell area under 50 square pixels have been segregated, each such particle is classified as an artifact if either of the following two criteria are met. First, if the square of the particle perimeter divided by the particle area is less than 20, then the particle is not long and thin and is classified an artifact. Second, if the ratio of eigenvalues of the covariance matrix of X and Y moments (which is also called the Stretch Value) is less than 20, then the particle is not long and thin and is classified an artifact.

Particle images that survive the two preprocessing steps described above are subjected to the cascading structure of neural nets illustrated in Fig. 7B. Each neural net takes a selected subgroup of the calculated 198 particle features discussed above, and calculates a classification probability factor ranging from zero to one that the particle meets the criteria of net. As with the cascading configuration of the nets, this helps improve the accuracy of each neural net result downstream, and preferably all

198 particle features are calculated for each particle image before the HPF scan commences.

The first neural net applied to the particle image is the AMOR Classifier Net, which decides whether or not the particle is amorphous. For the preferred embodiment, this net includes 50 inputs for a selected subset of the 198 particle features described above, 10 neurons in the hidden layer, and two neurons in the output layer. The column entitled HPF AMOR2 in the table of Figs. 9A-9C shows the numbers of the 50 particle features described above that were selected for use with this net. The first and second outputs of this net correspond to the probabilities that the particle is or is not amorphous. Whichever probability is higher constitutes the decision of the net. If the net decides the particle is amorphous, then the analysis of the particle ends.

If it is decided that the particle is not amorphous, then the Round/Not Round Classifier Net is applied, which decides whether the particle shape exhibits a predetermined amount of roundness. For the preferred embodiment, this net includes 39 inputs for a selected subset of the 198 particle features described above, 20 neurons in the hidden layer, and two neurons in the output layer. The column entitled HPF ROUND/NOT ROUND2 in the table of Figs. 9A-9C shows the numbers of the 39 particle features described above that were selected for use with this net. The first and second outputs of this net correspond to the probabilities that the particle is or is not 'round'. Whichever probability is highest constitutes the decision of the net.

If it is decided that the particle is 'round', then the Round Cells Classifier Net is applied, which decides whether the particle is a Red Blood Cell (RBC), a White Blood Cell (WBC), a Non-Squamous Epithelial cell (NSE) such as a Renal Epithelial cell or a transitional Epithelial cell, or Yeast (YEAST). For the preferred embodiment, this net includes 18 inputs for a selected subset of the 198 particle features described above, 3 neurons in the hidden layer, and three neurons in the output layer. The column entitled HPF Round4 in the table of Figs. 9A-9C shows the

numbers of the 18 particle features described above that were selected for use with this net. The first, second, third and fourth outputs of this net correspond to the probabilities that the particle is a RBC, a WBC, a NSE or YEAST, respectively. Whichever probability is highest constitutes the decision of the net.

If it is decided that the particle is not 'round', then the Not Round Cells Classifier Net is applied, which decides whether the particle is a Red Blood Cell (RBC), a White Blood Cell (WBC), a Non-Squamous Epithelial cell (NSE) such as a Renal Epithelial cell or a transitional Epithelial cell, an Unclassified Crystal (UNCX), Yeast (YEAST), Sperm (SPRM) or Bacteria (BACT). For the preferred embodiment, this net includes 100 inputs for a selected subset of the 198 particle features described above, 20 neurons in the hidden layer, and seven neurons in the output layer. The column entitled HPF NOT ROUND7 in the table of Figs. 9A-9C shows the numbers of the 100 particle features described above that were selected for use with this net. The seven outputs of this net correspond to the probabilities that the particle is a RBC, a WBC, a NSE, a UNCX, a YEAST, a SPRM or a BACT. Whichever probability is highest constitutes the decision of the net.

Referring back to Fig. 7A, once the Neural Net Classification has decided the particle type, an ART by Abstention Rule is applied, to determine if the particle should be classified as an artifact because none of the nets gave a high enough classification probability factor to warrant a particle classification. The ART by Abstention Rule applied by the preferred embodiment reclassifies four types of particles as artifacts if certain criteria are met. First, if the final classification by the net structure is Yeast, and the YEAST probability was less than 0.9 at the Not Round Cells Classification Net, then the particle is reclassified as an artifact. Second, if the final classification by the net structure was a NSE, and the NSE probability was less than 0.9 at the Round Cells Classifier Net, or the round probability was less than 0.9 at the Round/Not Round Classifier Net, then the particle is reclassified as an artifact. Third, if the final classification by the net structure was a not round NSE, and the NSE probability was

less than 0.9 at the Not Round Cells Classifier Net, then the particle is reclassified as an artifact. Fourth, if the final classification by the net structure was a UNCX, and the UNCX probability was less than 0.9 at the Not Round Cells Classifier Net, or the round probability was less than 0.9 at the Round/Not Round Classifier Net, then the particle is reclassified as an artifact.

The next step shown in Fig. 7A is a partial capture test, which is applied to all particles surviving the ART by Abstention Rule. The partial capture test determines if the particle should be classified as an artifact because the particle boundary hits one or more particle image patch boundaries, and thus only part of the particle image was captured by the patch image. As with the LPF scan, the partial capture test of the preferred embodiment basically looks at the pixels forming the boundary of the patch to ensure they represent background pixels. This is done by collecting a cumulative intensity histogram on the patch boundaries, and calculating lower and upper limits of these intensities. The lower limit in the preferred embodiment is either the third value from the bottom of the histogram, or the value 2% from the bottom of the histogram, whichever is greater. The upper limit is either the third value from the top of the histogram, or the value 2% from the top of the histogram, whichever is greater. The patch image is deemed a partial capture if the lower limit is less than 185 (e.g. of a pixel intensity that ranges from 0 to 255). The patch is also deemed a partial capture if the upper limit is less than or equal to 250 and the lower limit is less than 200 to take care of the case where the halo of a particle image touches the patch image boundary.

All particles surviving the partial capture test maintain their classification. All particles deemed a partial capture are further subjected to an ART by Partial Capture Rule, which reclassifies such particles as an artifact if any of the following 6 criteria are met:

1. If it was associated with the HPF1 size box.
2. If it was not classified as either a RBC, WBC, BYST, OR UNCX.

3. If it was classified as a RBC, and if it was associated with the HPF2 size box or had a Stretch Value greater than or equal to 5.0.
4. If it was classified as a WBC, and had a Stretch Value greater than or equal to 5.0.
5. If it was classified as a UNCX, and had a Stretch Value greater than or equal to 10.0.
6. If it was classified as a BYST, and had a Stretch Value greater than or equal to 20.0.

If none of these six criteria are met by the particle image, then the neural net classification is allowed to stand even though the particle was deemed a partial capture, and the HPF scan process is complete. These six rules were selected to keep particle classification decisions in cases where partial capture does not distort the neural net decision making process, while eliminating those particles where a partial capture would likely lead to an incorrect decision.

To best determine which features should be used for each of the neural nets described above, the feature values input to any given neural net are modified one at a time by a small amount, and the effect on the neural net output is recorded. Those features having the greatest affect on the output of the neural net should be used.

Post Processing Decision Making

Once all the particles images are classified by particle type, post decision processing is performed to further increase the accuracy of the classification results. This processing considers the complete set of results, and removes classification results that as a whole are not considered trustworthy.

User settable concentration thresholds are one type of post decision processing that establishes a noise level threshold for the overall results. These thresholds are settable by the user. If the neural net classified image concentration is lower than the threshold, then all the particles in the category are reclassified as artifacts. For

example, if the HPF scan finds only a few RBC's in the entire sample, it is likely these are erroneous results, and these particles are reclassified as artifacts.

Excessive amorphous detection is another post decision process that discards questionable results if too many particles are classified as amorphous. In the preferred embodiment, if there are more than 10 non-amorphous HPF patches, and more than 60% of them are classified to be amorphous by the neural nets, then the results for the entire specimen are discarded as unreliable.

The preferred embodiment also includes a number of LPF false positive filters, which discard results that are contradictory or questionable. Unlike HPF particles, LPF artifacts come in all shapes and sizes. In many cases, given the resolution of the system, it is impossible to distinguish LPF artifacts from true clinically significant analytes. In order to reduce false positives due to LPF artifacts, a number of filters are used to look at the aggregate decisions made by the nets, and discard those results that simply make no sense. For example, if the HPF WBC count is less than 9, then all LPF WBCC's should be reclassified as artifacts, since clumps of white blood cells are probably not present if white blood cells are not found in significant numbers. Further, the detection of just a few particles of certain types should be disregarded, since it is unlikely that these particles are present in such low numbers. In the preferred embodiment, the system must find more than 3 LPF UNCX detected particles, or more than 2 LPF NSE detected particles, or more than 3 LPF MUC detected particles, or more than 2 HPF SPRM detected particles, or more than 3 LPF YEAST detected particles. If these thresholds are not met, then the respective particles are re-classified as artifacts. Moreover, there must be at least 2 HPF BYST detected particles to accept any LPF YEAST detected particles.

Neural Net Training and Selection

Each neural net is trained using a training set of pre-classified images. In addition to the training set, a second smaller set of pre-classified images is reserved as

the test set. In the preferred embodiment, the commercial program NeuralWare, published by NeuralWorks, is used to perform the training. Training stops when the average error on the test set is minimized.

This process is repeated for multiple starting seeds and net structures (i.e. number of hidden layers and elements in each layer). The final choice is based not only on the overall average error rate, but also to satisfy constraints on errors between specific classes. For example, it is undesirable to identify a squamous epithelial cell as a pathological cast because squamous epithelial cells occur normally in female urine specimens, but pathological casts would indicate an abnormal situation. Therefore, the preferred embodiment favors nets with SQEP to UNCC error rates less than 0.03 at the expense of a greater misclassification rate of UNCC as SQEP. This situation somewhat decreases the sensitivity to UNCC detection, but minimizes false positives in female specimens, which with sufficiently high rate of occurrence would render the system useless since a high proportion of female urine samples would be called abnormal. Thus, it is preferable to employ a method that not only minimizes the overall error rate, but also considers the cost of specific error rates in the selection of the "optimal" nets, and build this selection criterion into the net training.

As can be seen from the forgoing, the method and apparatus of the present invention differs from the prior art in the following respect. In the prior art, at each stage of processing, a classification of a particle is made, with the remaining unclassified particles considered artifacts or unknowns. In order to minimize the classification of particles as artifacts or unknowns, the range of values for classification at each stage is large. This can cause misclassification of particles.

In contrast, the range of values for classification at each stage of the present invention is narrow, resulting in only particles having greater probability of certainty being so classified, and the remainder being classified in a classification for further processing that is related to the previous stage of processing. The multi-net structure of the present invention utilizes subgroups of the particle features to partition the

decision space by an attribute or physical characteristic of the particle (e.g. its roundness) and/or by individual and group particle classification that includes an unknown category. This partitioned decision space, which produces probability factors at each decision, more efficiently uses the available information, which of necessity is finite, and effectively allows this information to be used to make the same number of total decisions, but with fewer possible outcomes at each stage. Preprocessing and post processing enables heuristic information to be included as part of the decision making process. Post processing enables the use of contextual information either available from other sources or gleaned from the actual decision making process to further process the probability factors and enhance the decisions. The use of neural net certainty measures at multiple stages of processing forces images to an abstention class, i.e. artifact. In some sense one can view this multi network approach as forcing the image data to run a gauntlet where at each stage of the gauntlet it is quite likely to be placed in an "I don't know" category. This is much more powerful than simply running through a single net because in essence what is accomplished is multiple fits of the data to templates which are much better defined than a single template could be, which allows effective use of the information. Another way to think about this is that data in different subspaces is analyzed, and is required it to fit perfectly in some sense, or well enough, with the characteristics of that subspace or else it falls out of the race. The training method of the present invention involves not simply a single pass through the training set, but selecting from a number of nets and then reducing the feature vector size. The high number of features themselves, each focussing on a particular set of physical characteristics, increases the accuracy the system.

It is to be understood that the present invention is not limited to the embodiments described above and illustrated herein, but encompasses any and all variations falling within the scope of the appended claims. Therefore, it should be understood that while the present invention is described with respect to the

classification of images of biological samples, it also includes image analysis for any image having features that can be extracted and used to classify the image. For example, the present invention can be used for facial recognition. Features can be extracted to identify and classify the shape, size, location and dimension of the eyes, nose, mouth, etc., or more general features such as face shape and size, so that the facial images can be identified and classified into predetermined classifications.

79150-25

CLAIMS:

1. A method of classifying an element in an image into one of a plurality of classification classes, wherein the element has a plurality of features, the method comprising the steps of:

extracting the plurality of features from the image;

determining a classification class of the element by at least one of:

selecting and processing a first subgroup of the extracted features to determine a physical characteristic of the element, and selecting and processing a second subgroup of the extracted features using the physical characteristic determined to determine a classification class of the element; and

selecting and processing a third subgroup of the extracted features to determine a group of classification classes of the element, and selecting and processing a fourth subgroup of the extracted features using the determined classification class group to determine a classification class of the element; and

modifying the determined classification class of the element based upon a plurality of previously determined classification class determinations.

2. The method of claim 1, wherein the element is a biological particle.

3. The method of claim 1, wherein each of the determinations includes assigning a probability factor, and further including the step of modifying the determined classification class to an artifact classification in the event one or more of the probability factors used to classify the element fails to exceed a predetermined threshold value.

4. The method of claim 1, further comprising the step of:

classifying the element as an artifact based on the physical characteristic of the element, wherein the artifact element bypasses the determination of the classification class of the element.

5. The method of claim 1, further comprising the steps of:

determining whether a boundary of the element intersects a border of an image containing the element, and

modifying the determined classification class of the element to an artifact classification in the event the element boundary and image border are determined to intersect.

6. The method of claim 1, wherein the processing of the first, second, third and fourth subgroups of the extracted features is performed using neural nets.

7. The method of claim 6, further comprising the steps of:

training the neural nets by selecting and processing the first, second, third and fourth subgroups of the extracted features using a training set of known elements along with a test set of elements, wherein the training of the neural nets is repeatedly performed until an accuracy rate of the determination of classification class of the test set of elements reaches a predetermined value.

8. The method of claim 6, wherein the first, second, third and fourth subgroups of the plurality of features are selected by modifying feature values thereof by a predetermined amount, and selecting those features that affect an output of the respective neural net the most.

9. The method of claim 1, wherein one of the plurality of extracted features is symmetry of the element, and the extraction of the symmetry feature includes:

defining a first line segment that crosses a centroid of the element;

defining a second and third line segments for points along the first line segment that orthogonally extend away from the first line segment in opposite directions;

utilizing a difference between lengths of the second and third line segments to calculate the extracted symmetry feature of the element.

10. The method of claim 1, wherein one of the plurality of extracted features is skeletonization of the element image, and the extraction of the skeletonization feature includes orthogonally collapsing a boundary of the element to form one or more line segments.

11. The method of claim 1, wherein at least one of the plurality of extracted features is a measure of a spatial distribution of the element image, and at least another one of the plurality of extracted features is a measure of a spatial frequency domain of the element image.

12. An imaging apparatus for classifying an element in an image into one of a plurality of classification classes, wherein the element has a plurality of features, the apparatus comprising:

means for extracting the plurality of features from the image;

means for determining a classification class of the element, the determining means including at least one of:

means for selecting and processing a first subgroup of the extracted features to determine a physical characteristic of the element, and means for selecting and processing a second subgroup of the extracted features using

the physical characteristic determined to determine a classification class of the element; and

means for selecting and processing a third subgroup of the extracted features to determine a group of classification classes of the element, and

means for selecting and processing a fourth subgroup of the extracted features using the determined classification class group to determine a classification class of the element; and

means for modifying the determined classification class of the element based upon a plurality of previously determined classification class determinations.

13. The apparatus of claim 12, wherein the element is a biological particle.

14. The apparatus of claim 12, wherein each of the determinations includes assigning a probability factor, and wherein the determining means further includes means for modifying the determined classification class to an artifact classification in the event one or more of the probability factors used to classify the element fails to exceed a predetermined threshold value.

15. The apparatus of claim 12, further comprising:

means for classifying the element as an artifact based on the physical characteristic of the element, wherein the artifact element bypasses the determining means.

16. The apparatus of claim 12, further comprising:

means for determining whether a boundary of the element intersects a border of an image containing the element, and

means for modifying the determined classification class of the element to an artifact classification in the event the element boundary and image border are determined to intersect.

17. The apparatus of claim 12, wherein the processing of the first, second, third and fourth subgroups of the extracted features is performed using neural nets.

18. The apparatus of claim 17, further comprising:

means for training the neural nets by selecting and processing the first, second, third and fourth subgroups of the extracted features using a training set of known elements along with a test set of elements, wherein the training means repeatedly trains the neural nets until an accuracy rate of the determination of classification class of the test set of elements reaches a predetermined value.

19. The apparatus of claim 17, wherein the first, second, third and fourth subgroups of the plurality of features are selected by modifying feature values thereof by a predetermined amount, and selecting those features that affect an output of the respective neural net the most.

20. The apparatus of claim 12, wherein one of the plurality of extracted features is symmetry of the element, and the extraction means includes:

means for defining a first line segment that crosses a centroid of the element;

means for defining a second and third line segments for points along the first line segment that orthogonally extend away from the first line segment in opposite directions;

means for utilizing a difference between lengths of the second and third line segments to calculate the extracted symmetry feature of the element.

21. The apparatus of claim 12, wherein one of the plurality of extracted features is skeletonization of the element image, and the extraction means further includes means for orthogonally collapsing a boundary of the element to form one or more line segments.

22. The apparatus of claim 12, wherein at least one of the plurality of extracted features is a measure of a spatial distribution of the element image, and at least another one of the plurality of extracted features is a measure of a spatial frequency domain of the element image.

23. A method of classifying an element in an image into one of a plurality of classifications, wherein the element has a plurality of features, the method comprising the steps of:

extracting the plurality of features from the image;

determining a classification of the element based upon the plurality of features extracted by a first determination criteria, wherein the first determination criteria includes the classification of the element as an unknown classification;

determining a classification of the element by a second determination criteria, different from the first determination criteria, in the event the element is classified as an unknown classification by the first determination criteria; and

determining the classification of the element by a third determination criteria, different from the first and second determination criteria, in the event the element is classified as one of a plurality of classifications by the first determination criteria.

24. An imaging apparatus for classifying an element in an image into one of a plurality of classification classes, wherein the element has a plurality of features, the apparatus comprising:

an extractor for extracting the plurality of features from the image of the element;

a first processor that determines a classification class of the element by at least one of:

selecting and processing a first subgroup of the extracted features to determine a physical characteristic of the element, and selecting and processing a second subgroup of the extracted features in response to the physical characteristic determined to determine a classification class of the element; and

selecting and processing a third subgroup of the extracted features to determine a group of classification classes of the element, and selecting and processing a fourth subgroup of the extracted features in response to the determined classification class group to determine a classification class of the element; and

a second processor that modifies the determined classification class of the element based upon a plurality of previously determined classification class determinations.

79150-25

25. The method of claim 1, further comprising the step of:

classifying the element as an artifact based on a further physical characteristic of the element, wherein the artifact element bypasses the determination of the classification class of the element.

26. The apparatus of claim 12, further comprising:

means for classifying the element as an artifact based on a further physical characteristic of the element, wherein the artifact element bypasses the determining means.

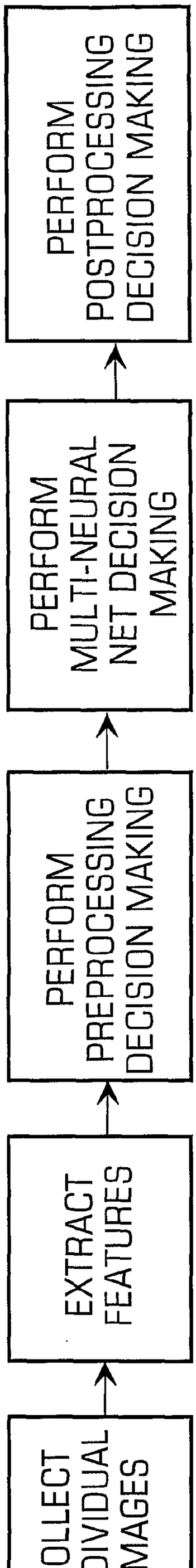

PERFORM POSTPROCESSING DECISION MAKING
PERFORM MULTI-NEURAL NET DECISION MAKING
PERFORM PREPROCESSING DECISION MAKING
EXTRACT FEATURES
COLLECT INDIVIDUAL IMAGES

FIG. 1

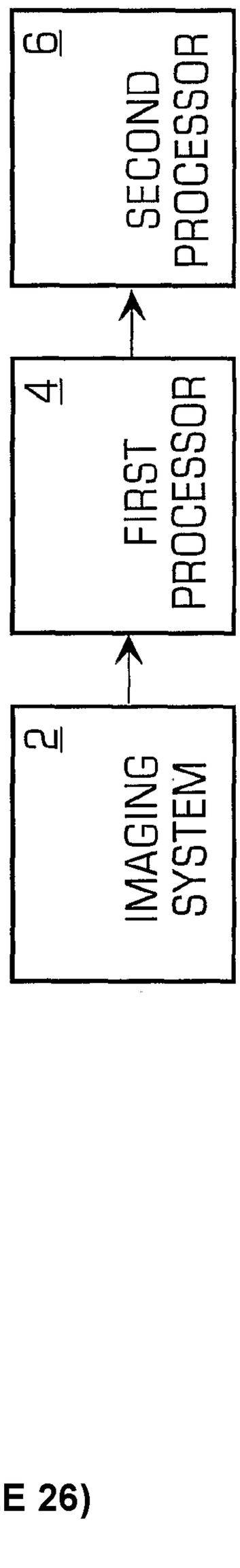

6
SECOND PROCESSOR
4
FIRST PROCESSOR
2
IMAGING SYSTEM

FIG. 2

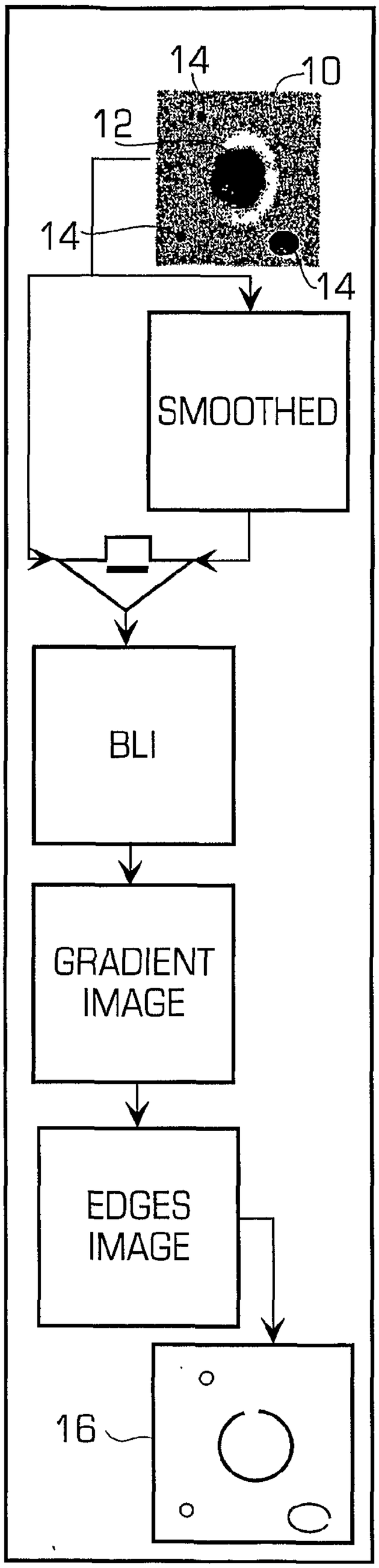

14
10
12
14
14
SMOOTHED
BLI
GRADIENT IMAGE
EDGES IMAGE
16

FIG. 3A

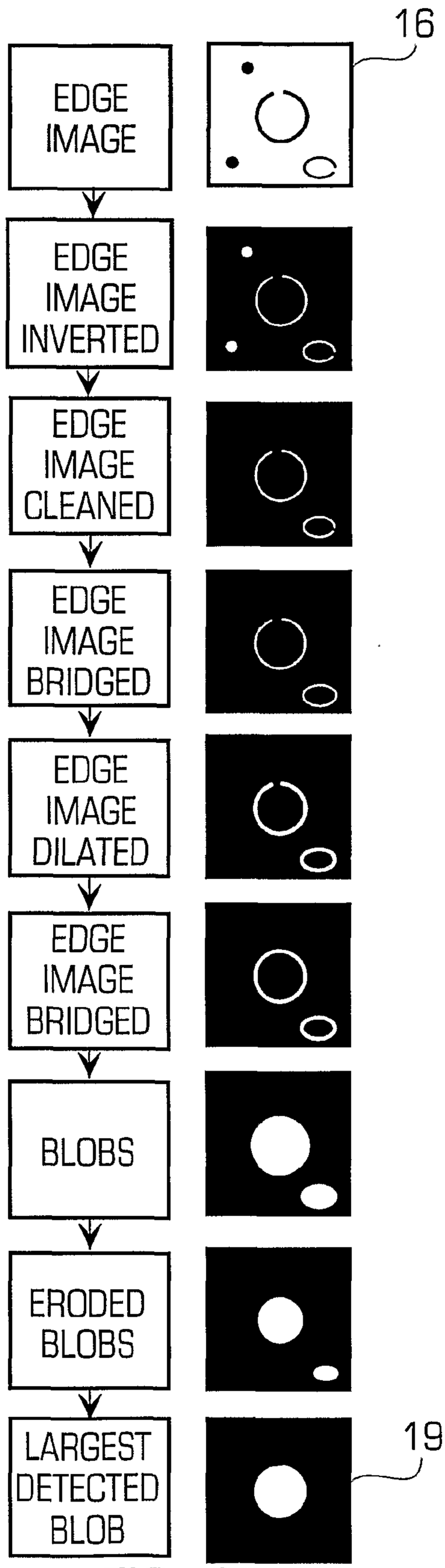

16
EDGE IMAGE
EDGE IMAGE INVERTED
EDGE IMAGE CLEANED
EDGE IMAGE BRIDGED
EDGE IMAGE DILATED
EDGE IMAGE BRIDGED
BLOBS
ERODED BLOBS
LARGEST DETECTED BLOB
19

FIG. 3B

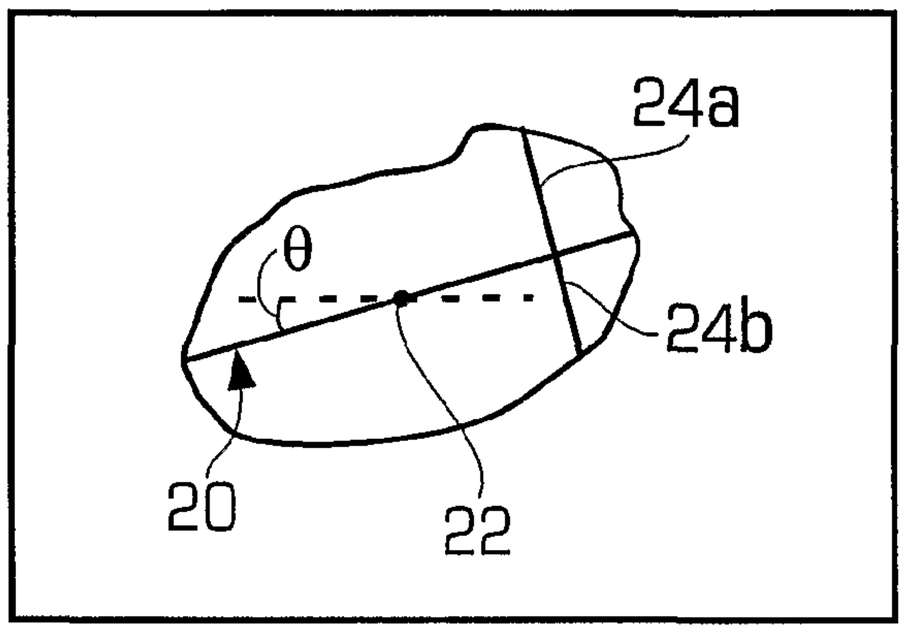


FIG. 4

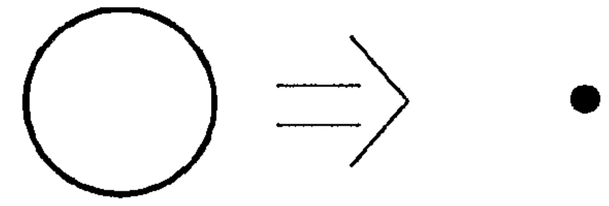


FIG. 5A

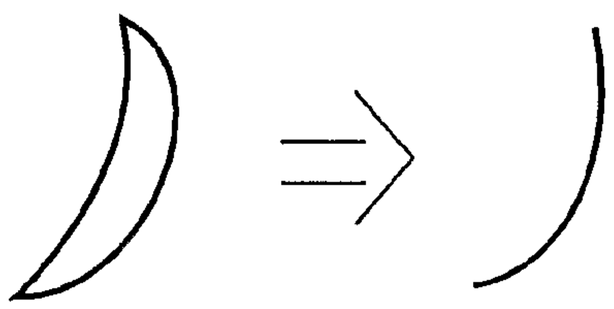


FIG. 5B

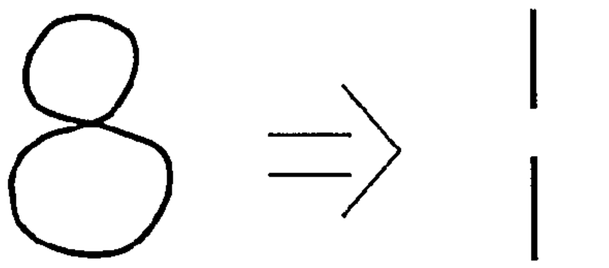


FIG. 5C

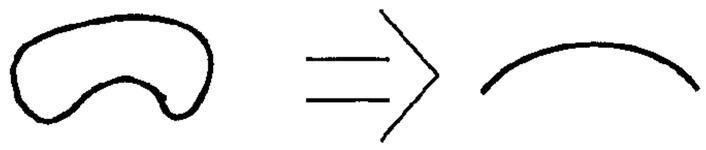


FIG. 5D

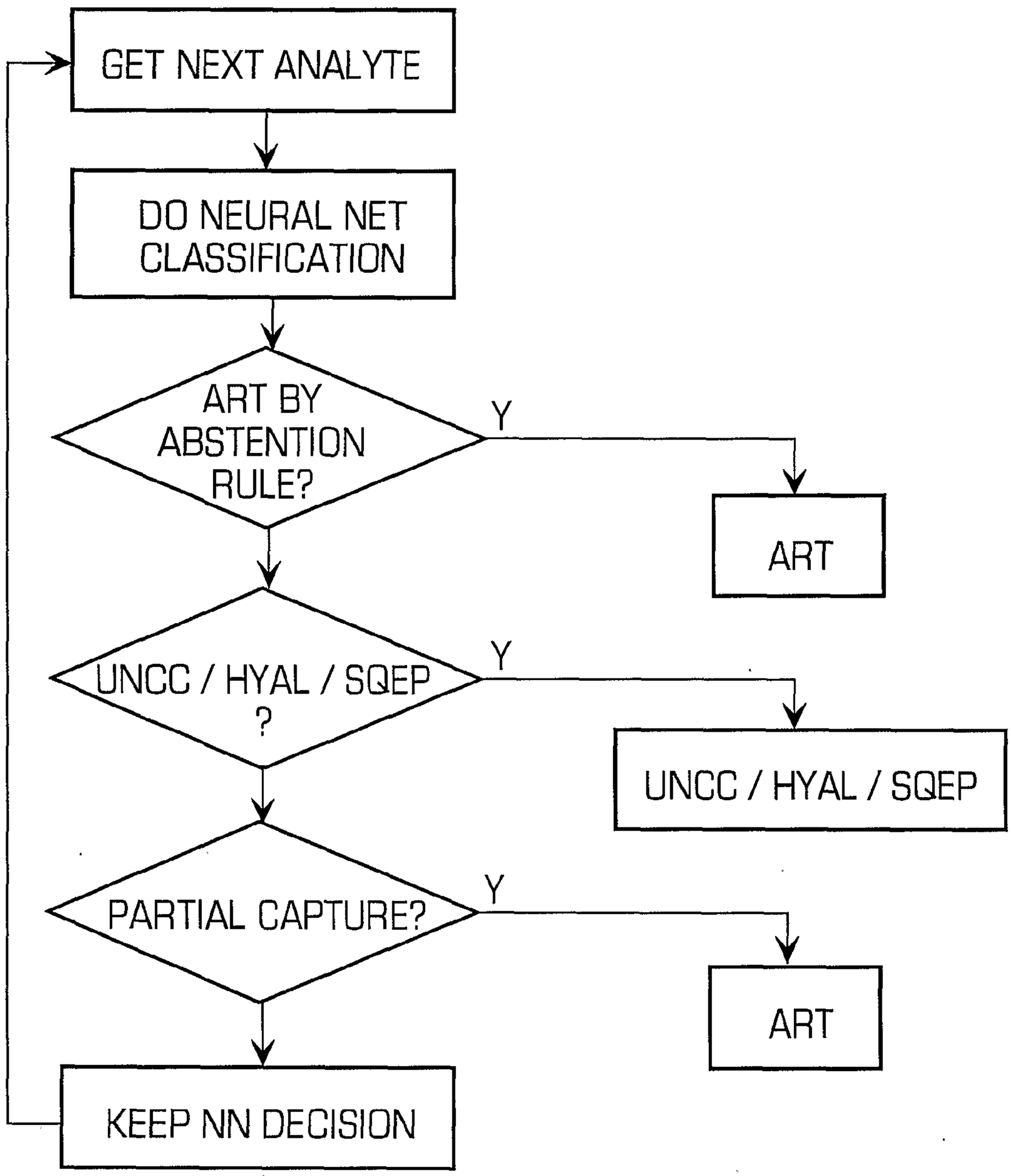

GET NEXT ANALYTE
DO NEURAL NET CLASSIFICATION
ART BY ABSTENTION RULE?
Y
ART
UNCC / HYAL / SQEP ?
Y
UNCC / HYAL / SQEP
PARTIAL CAPTURE?
Y
ART
KEEP NN DECISION

FIG. 6A

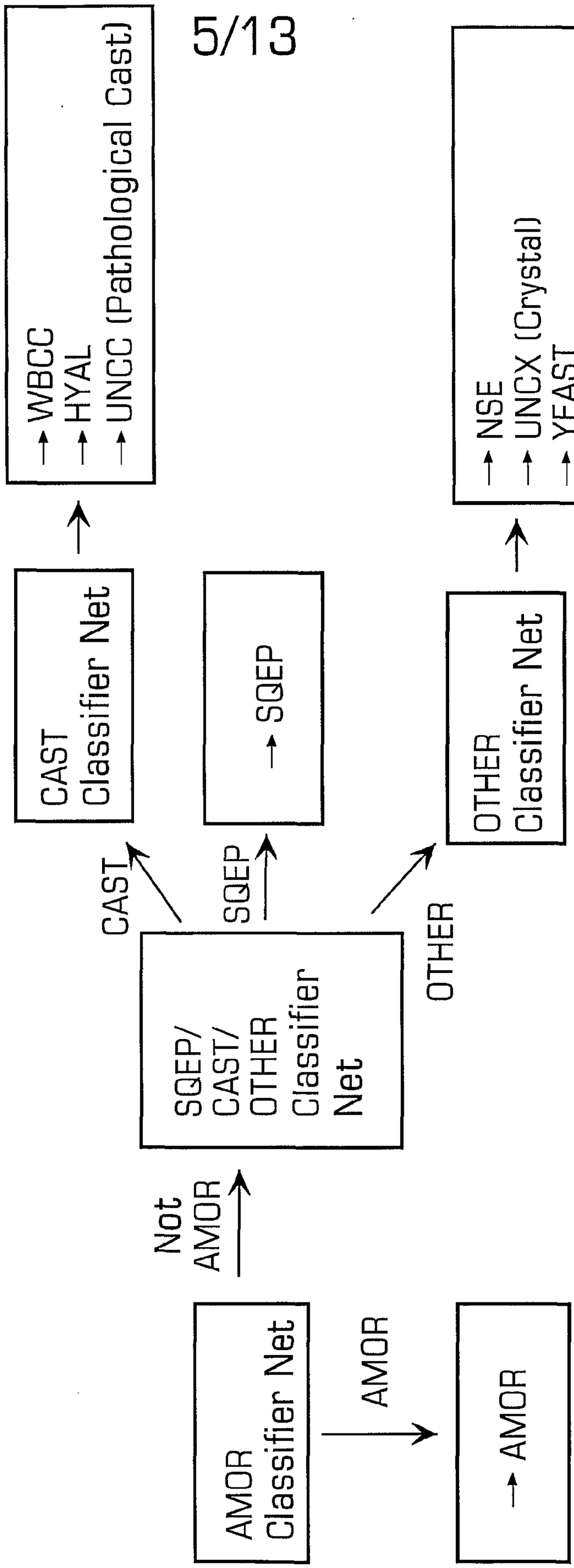

Not AMOR
SQEP/ CAST/ OTHER Classifier Net
CAST
SQEP
OTHER
CAST Classifier Net
→ WBCC
→ HYAL
→ UNCC (Pathological Cast)
→ SQEP
OTHER Classifier Net
→ NSE
→ UNCX (Crystal)
→ YEAST
→ MUCS
AMOR Classifier Net
AMOR
→ AMOR

FIG. 6B

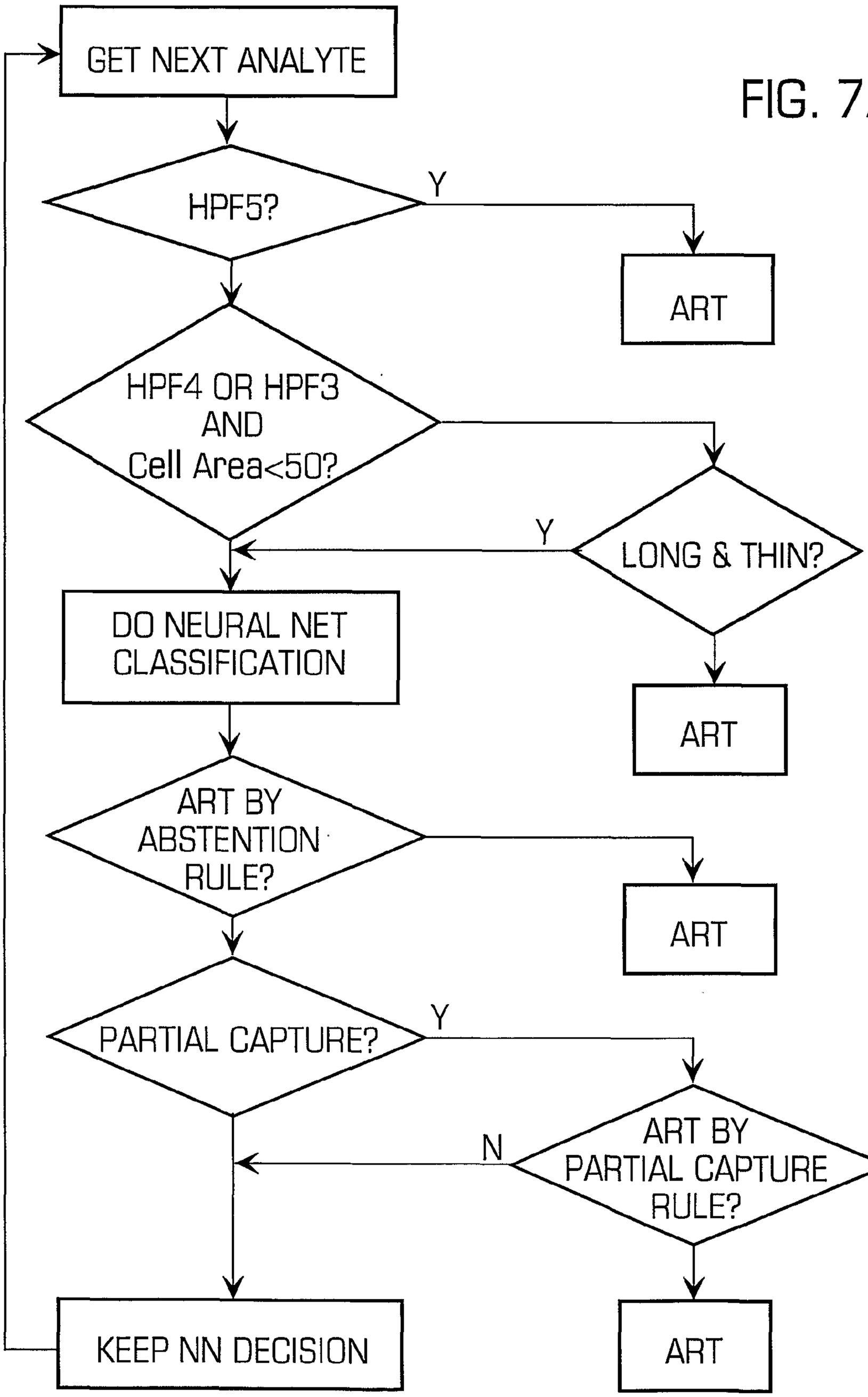

GET NEXT ANALYTE
HPF5?
Y
ART
HPF4 OR HPF3
AND
Cell Area<50?
Y
LONG & THIN?
ART
DO NEURAL NET
CLASSIFICATION
ART BY
ABSTENTION
RULE?
ART
PARTIAL CAPTURE?
Y
ART BY
PARTIAL CAPTURE
RULE?
N
KEEP NN DECISION
ART

FIG. 7A

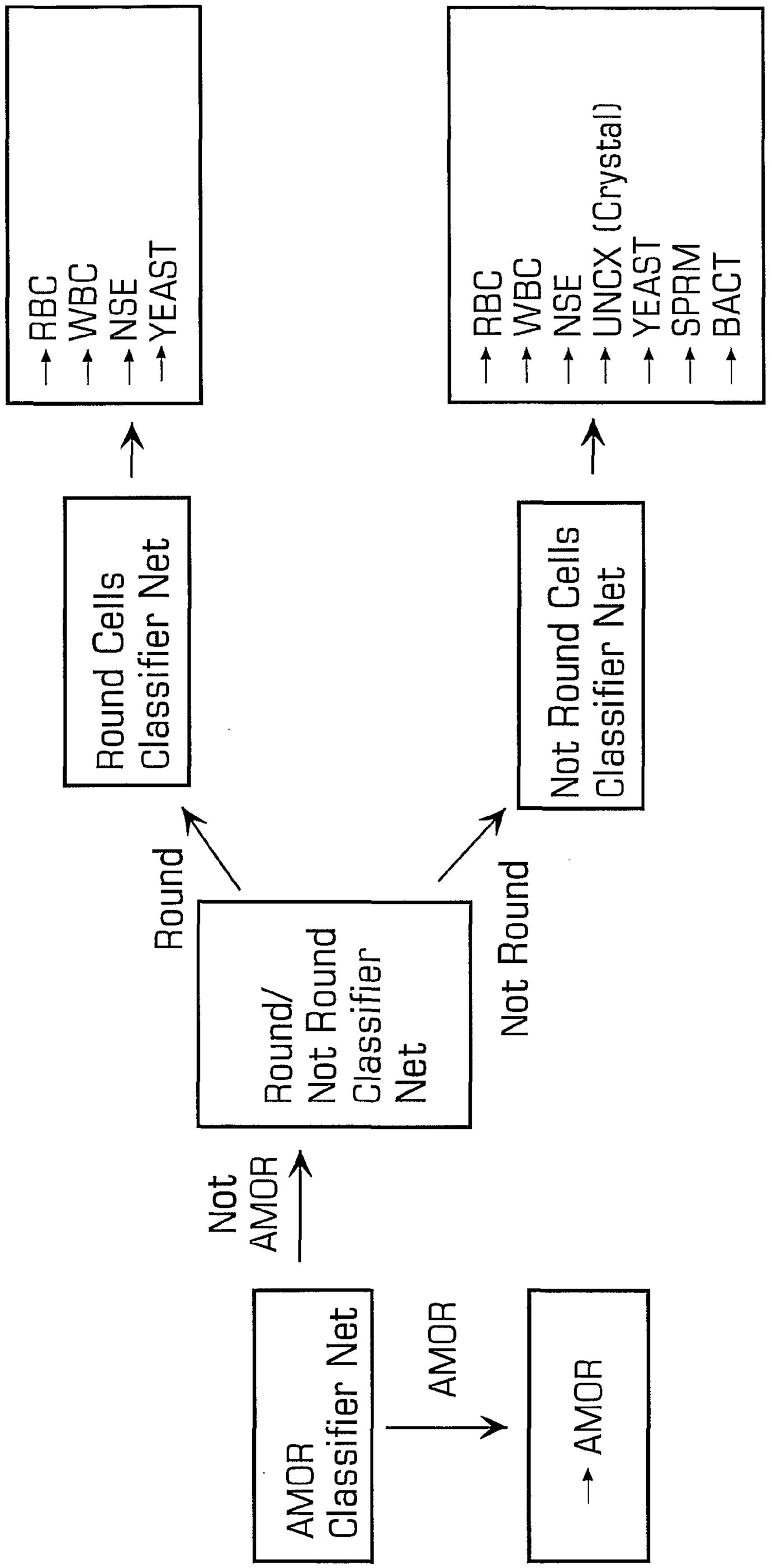

Not AMOR
Round/ Not Round Classifier Net
Round
Not Round
Round Cells Classifier Net
Not Round Cells Classifier Net
RBC
WBC
NSE
YEAST
RBC
WBC
NSE
UNCX (Crystal)
YEAST
SPRM
BACT
AMOR Classifier Net
AMOR
AMOR

FIG. 7B

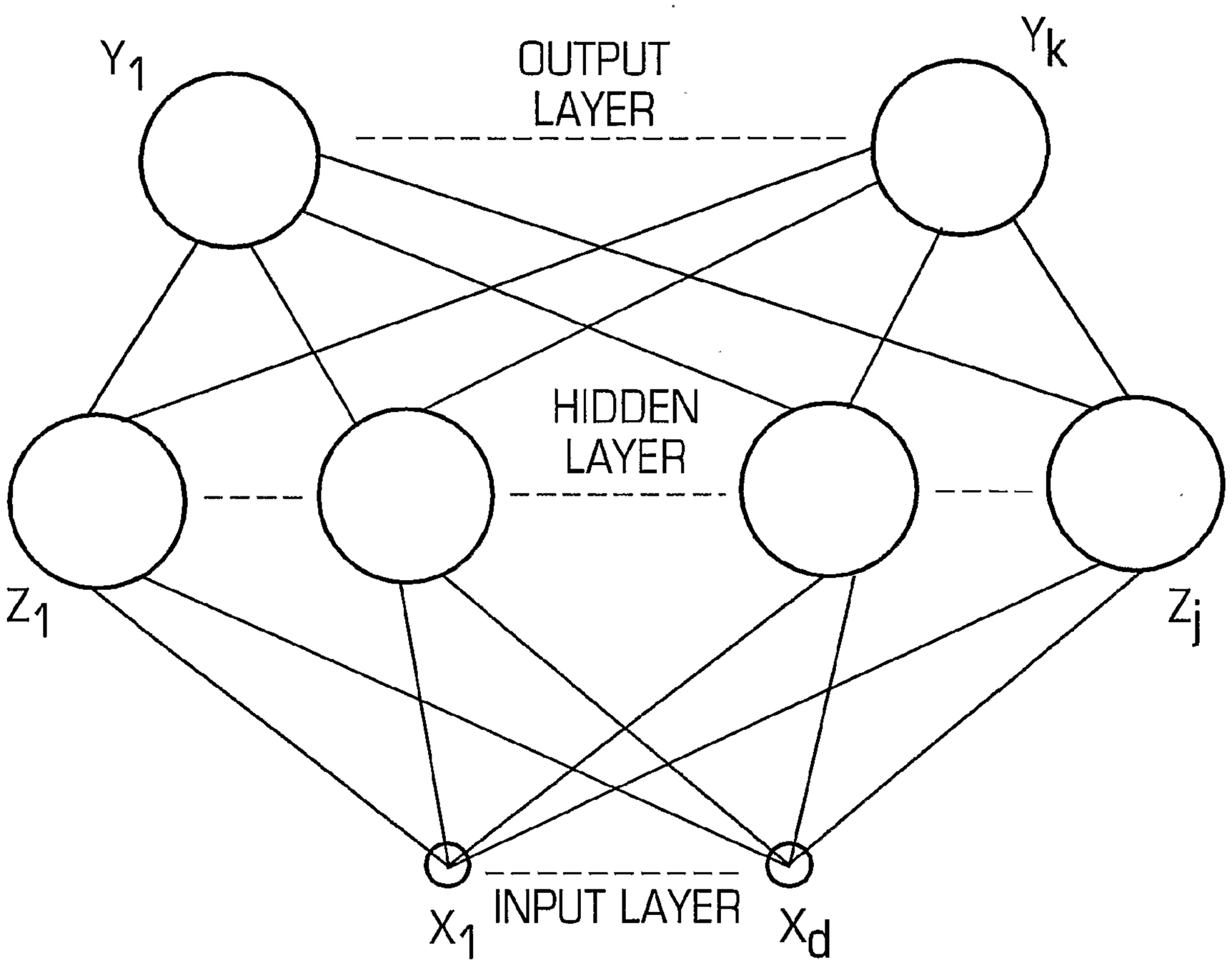


FIG. 8

FIG. 9A

FEATURE NO.	HPF AMOR2	PF ROUND/NOT ROUND	HPF ROUND4	HPF NOT ROUND7	LPF AMOR2	LPF CAST/SQEP/OTHER3	LPF CAST3	LPF OTHER4
0		X						
1	X	X	X	X	X	X		X
2	X	X		X	X	X		X
3	X	X		X	X	X		X
4	X	X						
5		X						
6	X	X		X	X	X		
7		X						
8		X						
9		X						
10		X			X		X	
11		X	X	X				
12		X			X	X		
13		X	X	X				
14		X			X	X		
15		X	X	X				
16		X	X	X				
17		X			X	X		
18		X						
19	X	X	X	X	X	X		
20		X						
21	X	X		X	X	X		
22	X	X		X	X	X		
23		X						
24		X						
25		X						
26		X			X	X		
27		X			X	X		
28		X						
29		X		X	X	X		
30		X						
31		X						
32		X						
33		X						
34		X						
35	X	X		X			X	
36		X		X				
37		X		X				
38	X	X			X	X		X
39		X			X	X		X
40		X		X				

FIG. 9B

FEATURE NO.	HPF AMOR2	PF ROUND/NOT ROUND	HPF ROUND4	HPF NOT ROUND7	LPF AMOR2	LPF CAST/SQEP/OTHER3	LPF CAST3	LPF OTHER4
41		X		X				X
42		X		X				X
43								
44								
45				X		X		
46	X				X			
47								
48	X			X		X		
49	X			X				
50	X			X			X	
51								
52								
53								
54						X		
55	X			X	X			
56	X			X				
57	X			X				
58	X							X
59	X			X				
60	X			X				
61	X			X				
62								
63								
64								
65				X				
66	X			X				
67	X		X	X				
68								
69	X			X				
70								
71	X			X				
72	X			X				
73								
74								
75	X			X				
76	X			X				
77			X					
78				X				
79				X				

FIG. 9C

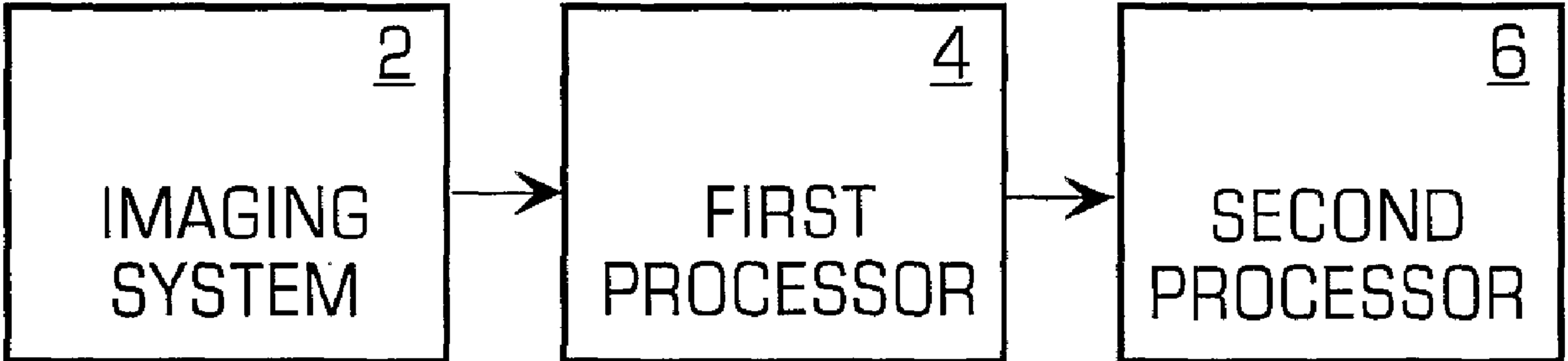
FEATURE NO.	HPF AMOR2	PF ROUND/NOT ROUND	HPF ROUND4	HPF NOT ROUND7	LPF AMOR2	LPF CAST/SQEP/OTHER3	LPF CAST3	LPF OTHER4
80				X	X	X	X	X
81	X		X	X	X	X	X	X
82	X		X	X		X	X	X
83	X			X		X	X	X
84	X			X	X	X	X	X
85				X				
86				X			X	
87	X		X	X	X	X	X	X
88				X		X	X	X
89	X		X	X	X	X		X
90				X				
91				X	X			
92				X		X	X	X
93			X	X	X	X	X	X
94			X	X		X	X	X
95	X		X	X		X		X
96				X				
97				X		X		X
98				X	X	X		X
99	X			X				
100	X			X	X			
101								
102				X		X		
103				X				
104	X			X	X			
105								
106				X			X	
107	X			X	X			
108				X				
109	X			X				
110				X				
111								
112							X	
113	X							
114								
115				X				
116	X							
117								
118				X			X	
119								
120				X	X			

FIG. 9D

FEATURE NO.	HPF AMOR2	PF ROUND/NOT ROUND	HPF ROUND4	HPF NOT ROUND7	LPF AMOR2	LPF CAST/SQEP/OTHER3	LPF CAST3	LPF OTHER4
121								
122								
123						X		
124				X				
125							X	
126	X				X			
127							X	
128								
129				X				
130			X	X				
131				X			X	
132				X			X	
133							X	
134								
135				X				
136								
137				X				
138								
139				X		X		
140				X				
141				X		X		
142				X		X		
143	X			X				
144	X		X	X				
145								
146						X		
147				X		X		
148				X		X		
149				X				
150			X	X				
151				X		X		
152				X		X		
153				X				
154				X		X		
155								
156			X	X				
157						X		
158				X				
159								
160								

FEATURE NO.	HPF AMOR2	PF ROUND/NOT ROUND	HPF ROUND4	HPF NOT ROUND7	LPF AMOR2	LPF CAST/SQEP/OTHER3	LPF CAST3	LPF OTHER4
161				X		X		
162				X		X		
163	X			X		X		
164				X			X	
165				X				
166								
167				X				
168							X	
169				X				
170				X		X		
171								
172						X		
173						X	X	
174								
175								
176							X	
177								
178								
179				X				
180				X				
181								
182	X			X		X		
183								
184	X			X				
185								
186								
187						X		
188	X							
189						X		
190								
191								
192								
193								
194	X			X				
195								
196								
197								
TOTAL:	50	39	18	100	42	48	36	46

FIG. 9E


2
IMAGING SYSTEM
4
FIRST PROCESSOR
6
SECOND PROCESSOR