

Discrimination of Cancer Cells by Dominant Feature Parameters Method in Thyroid Gland Cells

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=Abstract=

A new method of digital image analysis technique for discrimination of cancer cell was presented in this paper. The object image was the Thyroid Gland cells image that was diagnosed as normal and abnormal (two types of abnormal: follicular neoplastic cell, and papillary neoplastic cell), respectively. By using the proposed region segmentation algorithm, the cells were segmented into nucleus. The 16 feature parameters were used to calculate the features of each nucleus. As a consequence of using dominant feature parameters method proposed in this paper, discrimination rate of 91.11 % was obtained for Thyroid Gland cells.

Introduction

Pattern Recognition Technique has attracted considerable attention in the recent years. This is mostly due because it plays an important role in human visual perception and provides information which is used in recognition and interpretation. Pattern Recognition has a wide variety of applications in medical image, remote-sensing, geology, and robotics¹⁾. An example of application in medical image is the evaluation of roentgenograms to classify normal and abnormal interstitial pulmonary patterns²⁾.

This paper deals with the cancer cell discrimination that calls attentions to the pathologists. The object cell images were Thyroid Gland cells image that diagnosed as normal cell, follicular neoplastic cell, and papillary neoplastic cell, respectively.

The Clinical Cytology which detects the cancer cells by analyze the microscopic images was introduced by Papanicolaou³⁾. However, discriminations were achieved by human

visual system. The digital process of medical image began early 1960' dealing with the microscopic images, X-ray images, and Computer Tomographic images. Digital image processing methods has been applied to Clinical Cytology⁴⁾. But, the Clinical Cytology has many problems to the engineers. Medical features are difficult to understanding for engineer. And there are various features in every types of cells.

In this paper, features are extracted in the nucleus instead of DNA which include the main features of cell. Experiment was carried out by microscopic image. Because the microscopic image is more clear than ultrasonic echography. The discrimination experiment uses the multiple parameters instead of simple parameters to increase the discrimination rate. The segmentation for separation of nucleus is carried out by contour following method with directional angle. The features of nucleus are extracted from microscopic images. Used feature parameters are 16. And the discrimination experiment is carried out by dominant

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feature parameters method which proposed in this paper.

Clinical Cytology and Thyroid Gland Cells

1. Clinical Cytology

The Clinical Cytology is the inspection method of detecting the cancer cells by analyzing the microphotographs of cells in medical image processing. Cells are taken from the internal organs of human body and check for the existence of cancer cells. It is a necessary inspection method of detection of the various types of cancers for early diagnosis and treatments. Because of the treatment of the large amount of data in a short period of time, the automation of discrimination of cell is also necessary. The Clinical Cytology is making an observation on cells and diagnosing the cells by morphological features. Since it has to handle a large amount of object in a short peroid of time, it has been used single parameters only⁵⁾.

2. Materials

The samples used in the experiment of this paper are Thyroid Gland cells image. They are microscopic images of Thyroid Gland cells taken by surgical operation and are diagnosed as normal, follicular neoplastic and papillary neoplastic, respectively. After dying by Papanicolaou technique, images of samples of each classes were obtained by microscope and captured by camera. Size of object image was 512×512 with 8 bit resolution of gray leveled value. Actual size of sample image was $102.4 \mu\text{m}$.

Table 1. shows the main features of Thyroid Gland cells. The size of papillary neoplastic cell is biggest and the size of follicular neoplastic cell is smaller than other types. And the shape of normal and follicular neoplastic cell is round but the shape of papillary neoplastic cell is irregular. The texture pattern of nucleus of each class is different each other. Since the nucleus contains the main feature of nucleus, the other features of Table 1 are not considered in this paper. In the previously reported paper, discrimination of cells image was performed by evaluating nucleus since the main feature of cells image contained in nucleus that approach reduce the computational complexity⁶⁾.

Table 1. The main features of Thyroid Gland cells⁹⁾

Feature	Normal	Abnormal		
		Follicular	Papillary	
Cell aggregate	Loose	Dense		
Mass Formation	Absent	Present		
Cell arrangement	Normal	Follicular	Papillary (occasionally follicular)	
Nuclear membrane	Regular	Regular	Irregular	
Nuclear inclusion		Rare	Frequent	
		Artifact may mimic inclusion		
Nucleus	Shape	Round	Round or oval	Irregular
	Size	Medium	Small, uniform	Large, variable
Chromatin pattern	Chromatine clump	homogeneous	Distinct, homogeneous	Ground-glass, heterogeneous
	Texture	Coarse	Coarse	Fine

Cancer Cell Discrimination by Dominant Feature Parameters Method

1. Thresholding

Thresholding is one of the most important approaches in image segmentation. Many images can be characterized as images containing some object of interest of reasonably uniform brightness placed against a background with different brightness.

Several analytic approaches to the setting of a luminance threshold have been proposed⁷⁾. One method is to set the gray scale threshold at a level such that the cumulative gray scale count matches an a priori assumption of the gray scale probability distribution⁸⁾.

1) Mode method

Shape of the histogram of an image provides many clues to the characteristics of the image. For example, a narrowly distributed histogram indicates a low-contrast image. A bimodal histogram often suggests that the image which contains an object with a narrow amplitude range against a background with different amplitude. Where an image is clearly distinguishable into object from background, the shape of gray level histogram is bimodal. In this case, the

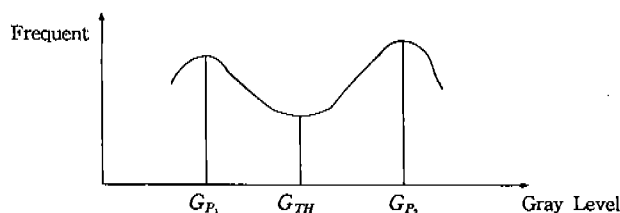


Fig. 1. Selection of threshold value in mode method.

threshold value is the valley between two summits. This local minimum selection method called as Mode Method⁹⁾. Fig. 1. shows the selection of threshold value of an image in mode method. The value of G_{TH} indicates the threshold value. In the experiment of discrimination, the G_{TH} is a variable to be calculated for each frame of medical cells images.

$$f(x, y) = \begin{cases} f(x, y) & : f(x, y) \leq G_{TH} \\ 0 & : f(x, y) > G_{TH} \end{cases} \quad (1)$$

2. Segmentation

1) Contour Following Method

Successful image segmentation will end up with labeling of each pixel that lies within a specific distinct segment. One means of labeling is to append to each pixel of an image the label number or index of its segment. A more simple method is to specify the closed contour of each segment and append a label number to all pixels in contour¹⁰⁾. Contour Following method is explained in Fig. 2. A conceptual bug begins marching from the white background to the black pixel region indicated by the closed contour.

When the bug crosses into a black pixel, it makes a right turn and proceeds to the next pixel. If that pixel is black, the bug again turns right, and if the pixel is white, the bug turns left. The procedure continues until the bug returns to the starting point. The Cartesian coordinate of each black-to-white or white-to-black crossing is recorded as the boundary location.

In this paper, segmentation by the contour following method was carried out to classify the nucleus from background.

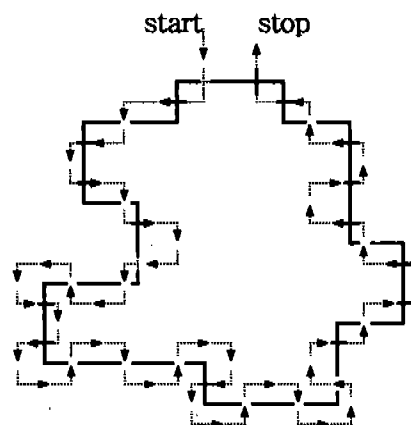


Fig. 2. Example of Contour Following.

2) Proposed region segmentation method

The cells image contains nucleus, cytoplasm, red blood cell, and extracellular materials: e. g., colloid, blood plasma. Thus segmentation for classification of the nucleus from cells image is required^{3~5)}. In this paper, an improved method of region segmentation based upon Contour Following method is proposed. The Contour Following method searches with two directions only. Searching by two directions is quite within the realms of possibility of missing the diagonal pixels. Thus, when the bug searches for the neighbor pixel, it should search for not only vertical or horizontal direction but also every other direction. A reasonable choice for the searching directions is directions with angle of multiples of $\pi/4$. If the increment of searching direction for neighbor pixel, there is no missing pixel. Thus the proposed method settles the limitation of Contour Following method.

Table 2. shows the difference between the Contour Following method and the proposed method. The main differences are search direction, searching angle, consideration of shape information, and capability of searching diagonal neighbor pixel.

3. Feature Parameters

A feature of image is a distinguishing primitive characteristic or attribute of an image. Some features are natural in the sense that they are defined by the visual appearance of an image, while others are artificial result from specific

Table 2. A comparison of the proposed method with contour following.

	contour following ⁽¹⁰⁾	proposed method ⁽⁹⁾
search direction	left or right	8 direction
searching angle	180°	45°
shape information	do not consider	consideration
diagonal neighbor	possibility of loss	search

mainpulations of an image.

1) Nuclear Area (AR)

The area of nucleus is defined as the number of pixels that was included in nucleus. This feature paramer can be obtained by simply counting the number of pixels within the boundary.

2) Nuclear x-size, and Nuclear y-size (SX and SY)

The length(x-size and y-size) of a contour is one of its simplest descriptors. Simply counting the number of pixels along the contour gives a rough approximation of the length.

3) Perimeter (PM)

The perimeter of a region is the length of its contour. For a chain-coded curve with unit spacing in both directions, it can be obtained by counting the vertical and horizontal components are counting as 1 and the diagonal components as $\sqrt{2}$.

4) Gray Level Mean (GM)

Amplitude measurements may be made at specific image points, e. g. the amplitude $F(j, k)$ at coordinate (j, k) , and amplitudes of neighborhood pixels centered at (j, k) . For example, the average or mean gray level in a $W \times W$ pixel neighborhood is given by

$$GM = \frac{1}{W^2} \sum_m \sum_n F(j + m, k + n). \quad (2)$$

5) Averaged Power (AP)

The Averaged Power of each nucleus is computed as

$$AP = [\sum \sum GV^2] / AR \quad (3)$$

where, GV is the Gray level Value of the nucleus.

6) Autocorrelation (AC)

The autocorrelation function has been suggested as the

basis of a texture measure⁽¹¹⁾. The autocorrelation function is defined as

$$AC = \sum_j \sum_k F(j, k)F(j - m, k - n) \quad (4)$$

for computation over a $W \times W$ window with $-T \leq m, n \leq T$ pixel lags.

7) Standard Deviation of Gray Level Value (SD)

The standard deviation of neighbor is one of the useful image amplitude feature of the image, which can be computed as

$$SD = \frac{1}{W^2} [\sum_m \sum_n [f(j + m, k + n) - GM]^2]^{1/2} \quad (5)$$

8) Average of X-Size and Y-Size (MS)

In the feature extraction, the nuclear X-size and the nuclear Y-siz is the simplest parameters and these are one of the important feature parameters. It is not a problem in the case when the nuclear X-size and nuclear Y-size are similar, but when they are not match in size, the discrimination by any one of them will bring a mistake on the determination of nuclear size. Therefore, the avarage of nuclear X-size and nuclear Y-size is proposed as a new feature parameter. A new parameter of average of X-Size and Y-Size will be calculated as

$$MS = (SX + SY)/2 \quad (6)$$

9) Denseness (DS)

A parameter in measuring of denseness of a nucleus can be defined as

$$DS = PM^2 / AR. \quad (7)$$

where, AR is the area of nucleus. The perimeter of a nucleus is the length of its boundary. Although area and its perimeter are sometimes used as descriptors, they apply primarily to situations in which the size of the objects of interest is invariant. A new feature parameter is required because the nucleus is not invariant.

10) Valid Rate (VR)

The Valid Rate is ratio of nuclear area to area of circum-

scribed square to the nucleus and this feature parameter can be expressed as

$$VR = AR/D * 100 [\%] \quad (8)$$

where, D is the area of the circumscribed square to the nucleus.

11) Entropy (ET)

Entropy is a statistical measure of uncertainty. For a given ensemble of pattern vectors, a good measure of intraset dispersion is the entropy, given by

$$ET = -H(\log 2 / \log P) \quad (9)$$

where, $H = \sum_m \sum_n F(j+m, k+n)$, and P is the probability density of the pattern population, and H is the expectation operator with respect to P. The entropy concept can be used as a suitable criterion in the design of feature parameters.

12) The ratio of perimeter versus average of X-size and Y-size (RP)

The ratio of the perimeter versus average of X-size and Y-size is one of the feature parameters to classify the nuclear shape. Even though the shapes of nucleus are different, the value of perimeters can have same value because the perimeter values are simply obtained the number of pixels along the contour. If the perimeters of nucleus are same but shapes are different, this parameter can distinguish the shape of nuclei. The calculation of this feature parameter expressed as

$$RP = PM/MS = PM/[(SX + SY)/2]. \quad (10)$$

13) Inactivity (IN), Inverse Difference (ID) and Absolute Value (AV)

Consider two pixels $A(j, k)$ and $A(l, m)$ that are located at coordinates (j, k) and (l, m) , respectively.

The first-order probability distribution of the amplitude of a quantized image may be expressed as

$$\begin{aligned} P(a) &= P[A(j, k) = d_a] \\ P(b) &= P[A(l, m) = d_b] \end{aligned} \quad (11)$$

where, d_a , and d_b represent quantized pixel amplitude value for $0 \leq a \leq X-1$ and $0 \leq b \leq X-1$.

If an image region contains fine texture, the two-dimensional histogram of pixel pairs will tend to be uniform, and for coarse texture the histogram values will be skewed toward the diagonal of the histogram¹⁰. Consider the pair of pixels $A(j, k)$ and $A(l, m)$ that are separated by d radial units at an angle ϕ with respect to the horizontal axis.

Let $P(a, b; j, k, d, \phi)$ represent the two dimensional histogram measurement of an image over some $W \times W$ window where each pixel is quantized over a range $0 \leq a \leq X-1$ and $0 \leq b \leq X-1$. The two dimensional histogram can be considered as an estimate of the joint probability distribution.

$$P(a, b; j, k, d, \phi) \approx P[A(j, k) = a, A(l, m) = b] \quad (12)$$

If the pixel pairs within an image are highly correlated, the entries in $P(a, b; j, k, d, \phi)$ will be clustered along the diagonal of the array. Various measures, listed below, have been proposed as measures that specify the energy spread.

* Inactivity (IN)

$$IN = \sum_a \sum_b (a-b)^2 P[A(j, k) = a, A(l, m) = b] \quad (13)$$

* Inverse Difference (ID)

$$ID = \sum_a \sum_b P[A(j, k) = a, A(l, m) = b] / [1 + (a-b)] \quad (14)$$

* Absolute Value (AV)

$$AV = \sum_a \sum_b |a-b| J(a, b) \quad (15)$$

4. Selection Algorithm of Dominant Feature Parameters

Generally, the discrimination of nucleus was carried out using single parameters in Clinical Cytology. Because the discrimination rate of some feature parameters enough to be used for automatic discrimination. Thus the parameter of having high discrimination rate was required in discrimination problems.

Pathologist do not diagnosed normal or abnormal cells

by using only one factor. The discrimination of the nucleus in the medical cells image was handled in spatial domain. From the cytological point of view, considered as a whole, the difference between normal and abnormal Thyroid Gland cells was basically caused by nuclear membrane, shape of nucleus, and the size of nucleus, as shown in Table 1. It is expected that the difference between normal and abnormal Thyroid Gland cells will be distinguished by the parameters of nuclear area, nuclear x-size and y-size, perimeter, condenseness, and entropy of nucleus.

Discrimination by multiple feature parameters is the key point of this paper. In this section, a selection algorithm of dominant feature parameters method is described. At first, read the image from the computer and compute the Look-up table of each 16 feature parameters from the thresholded image. The average value of each feature parameters are stored in the Look-up Table. After construction of Look-up table, calculate the difference from Look-up table of each class. Experimentation of discrimination is carried out by calculate the difference between Look-up Table of each class and data of nucleus. The discrimination rates by each feature parameters are also calculated by this distance. By the combination theorem, the number of different combination of 16 things is about 2.0923×10^{13} . This method find the dominant feature parameters among them. According to the combination theorem, the number of different combinations of N different things, K, at a time, without repetitions, is

$${}^N C_k = \frac{N!}{K!(N-K)!} \quad (16)$$

Starting from $K=2$, carried out experiment for discrimination and search for the combination which give the maximum discrimination rate. Increment K by one and repeat until $K=N$. The number of dominant feature parameters or combination of feature parameters will depend upon the used cell type. The combination which gives the maximum discrimination rate will have dominant K feature parameters. The experiment of discrimination by dominant feature parameters method is carried out as follows.

For example, the dominant feature parameters algorithm will increase the variable assigned for normal cell if the dis-

crimination by one feature parameter is normal. If the result is abnormal, algorithm will increase proper variable and proceeds to next parameter. Finally, the dominant feature parameters algorithm will discriminate the cell by selecting of variable with biggest value. By using the dominant feature parameters method, the discrimination rate will be highly improved.

Cancer Cell Discrimination of Thyroid Gland Cells

1. Configuration of Experimental System

The configuration of experimental system that was used in this paper is as follows. The cell images were enlarged by microscope and the microscopic image was captured by camera and stored in computer memory. The image processing board, DT-2853 manufactured by Data Translation (U.S.A.) was used for the experiment.

At first, images are enlarged by microscope stored in computer memory. Then, the gray level histogram is calculated to select a threshold value. Then, classify the nucleus from background by applying proposed region segmentation algorithm to the thresholded image. After segmentation, calculate the features by 16 feature parameters. Also calculate the Power Spectral Density function of Fast Fourier Transform (PSD of FFT) for comparison. Select the dominant feature parameters from the above feature parameters. Finally, discrimination experiment by dominant feature parameters is carried out.

2. Preparation of Look-up Table

The Look-up Table was constructed by calculating the total mean of each class (normal cells, follicular neoplastic cells, and papillary neoplastic cells). The reason of construction of Look-up table of each class is to get the standard value of each class for discrimination. In this paper, the total number of frames of input images was 93 (Normal: 13, Follicular Neoplastic: 40, Papillary Neoplastic: 40) and total number of nucleus was 1822 (Normal: 191, Follicular: 879, Papillary: 752). The Look-up Table of each class is given by Table 3. The experiment of discrimination is carried out by computing the distance between the value from the Look-up table of each class and nuclear infor-

Table 3. Look-up table of each class.

	Normal Cell	Follicular Neoplastic	Papillary Neoplastic
nuclei	14.16667	24.31579	18.80000
AR	2179.667	1723.684	2254.800
SX	53.66476	49.28215	55.89716
SY	52.80807	48.48453	54.70345
PM	216.4167	186.1947	229.26000
GM	131.63	144.57	142.49
AP	19442.23	23804.72	21933.03
AC	19379.61	23744.96	21878.30
SD	7.958333	7.763106	7.430600
AV	8.439979	8.250697	8.153776
MS	53.23642	48.88334	55.30030
DS	21.59369	21.39139	23.66372
RP	4.065200	3.788503	4.145728
VR	76.60996	76.41277	73.91451
ET	9.649108	9.493293	9.531555
IN	126.3144	120.5019	110.4319
ID	12.47926	13.01159	12.26710

mation from the nucleus.

3. Selection of Dominant Feature Parameters

The feature parameters used in this paper are 16 parameters. At the beginning of the experiment, the distance between the data of Look-up table of each feature parameter and the data of each feature parameter of nucleus was calculated, and the discrimination was carried out based upon this distance. Then, calculate the discrimination rate for all the possible combinations of 16 feature parameters in order to find the combination for the best discrimination rate. That combination will give the dominant feature parameters.

By the experimental result, the number of dominant feature parameters is 5 and the selected dominant feature parameters are ① SX, ② RP, ③ DS, ④ SD, ⑤ AV. The combinations of dominant feature parameters may be changed depend upon the object cell used because the features of other cells are not same as the features of Thyroid Gland cells used in this paper.

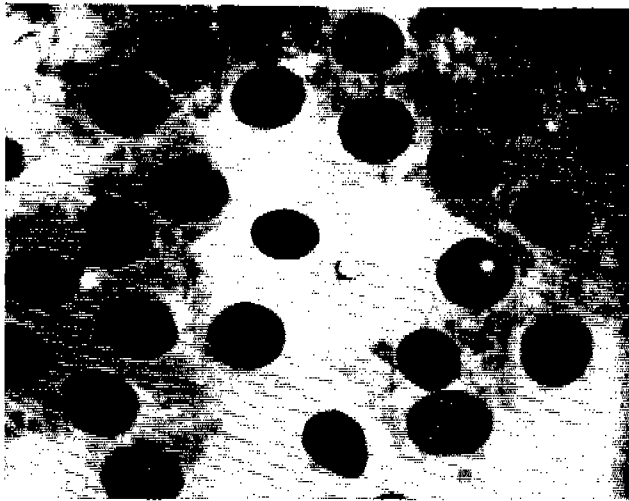
4. Discrimination of Cancer Cells

Fig. 3. shows the case of normal nucleus. In this Fig. a) express the original cells image, b) shows gray level histogram of original image, c) gives the thresholded image of a), and d) represent the segmented result. The numbers shown in d) signify the sequence number assigned to the isolated nucleus.

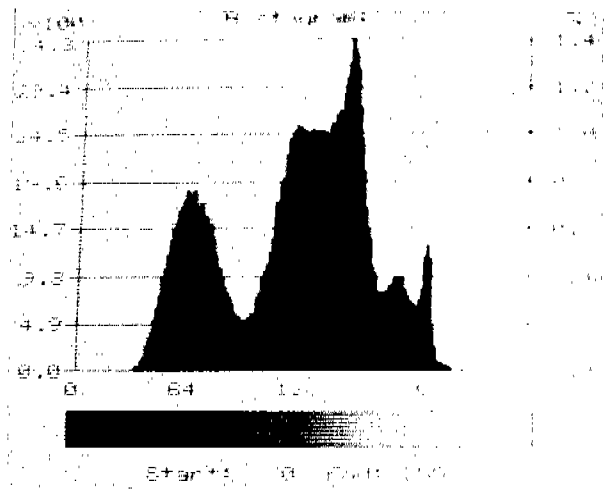
5. Experimental Results

Table 4 shows the summary of discrimination rates in each class by applying the feature parameters. The parameters of denseness (DS), entropy (ET), and absolute value (AV) gave high discrimination rate (around 78 %) for all classes. Discrimination of nucleus by averaged power (AP), inverse difference (ID), and inactivity (IN) were effective on follicular cells but not for normal or papillary cells. The standard deviation of gray level of nucleus (SD) gave high discrimination rate (around 80 %) for all class. Other parameters did not give high enough discrimination rate for all class (around 40 %). The experimental result was follows. The best discrimination rate obtained by single parameter method was 79.97 % for generally used feature parameters. The second is 79.75 % which was by nuclear X-size. The worst was 35.46 % which was obtained by averaged power of nucleus (AP). The best discrimination rate obtained by single parameter method was 79.69 % for proposed feature parameters. The second is 78.10 % which was by ratio of perimeter versus average of SX and SY (RP). The worst was 44.40 % which was obtained by inverse difference (ID). Average discrimination rate obtained by applying 16 feature parameters, single parameter at a time, was 64.66%. 80.35 % of discrimination rate obtained by Power Spectral Density function of FFT. As examined above, the discrimination rate of each parameter was high enough for automatic discrimination. However most feature parameters gave high discrimination rate for some class. According to the experimental results, discrimination of the cell by using single parameter only may be risky. The discrimination of single parameter method can be overcome by dominant feature parameters method.

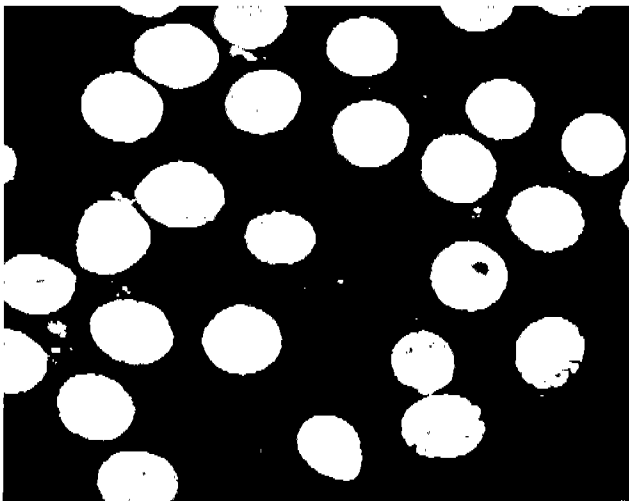
Discrimination rate obtained by dominant feature parameters method was 91.11 %. It was improved at least 10.76 %.



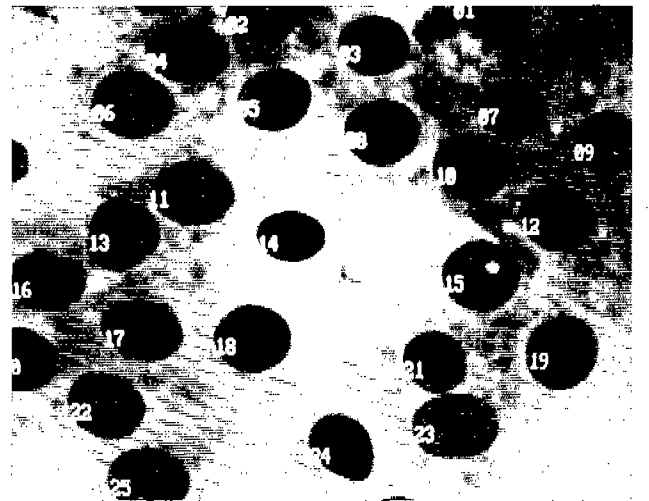
a) original image



b) gray level histogram



c) thresholded image



d) degmentation result

Fig. 3. A sample result of normal.

Conclusion

In this paper, a new method of discrimination for medical image analysis was studied which using the pattern recognition techniques. The focus of this paper is the automatic discrimination of cells into normal and abnormal cells. The object cells image used in this paper was microscopic image of Thyroid Gland cells. A new technique for segmentation of nucleus from background using contour following method with directional angle was proposed.

And new technique for discrimination of cells image which uses dominant feature parameters method was also proposed.

The thresholding by variable mode method was carried out for classifying the nucleus from medical cells image. As the result of thresholding, nucleus was effectively classified from background. The segmentation of the thresholded image into a isolated nuclei was carried out by contour following method with directional angle. The result of segmentation was very sucessfully executed. 16 parameters of Morphological features were extracted in spatial domain.

Table 4. Summary of discrimination rates.

No.	No. of Nuclei	Normal		Follicular		Papillary		Total	
		Freq.	%	Freq.	%	Freq.	%	Freq.	%
1	AR	64	33.51	814	91.61	399	53.06	1822	70.25
2	SX	84	43.98	828	94.20	541	71.94	1453	79.75
3	SY	96	50.26	804	91.47	473	62.90	1373	75.36
4	PM	76	39.79	772	87.83	570	75.80	1418	77.83
5	GM	61	31.94	372	42.32	321	42.69	754	41.38
6	AP	117	61.26	201	22.87	328	43.62	646	35.46
7	AC	110	57.59	282	32.08	316	42.62	708	38.86
8	SD	101	52.88	771	87.71	585	77.79	1457	79.97
9	AV	96	50.26	747	84.98	608	80.85	1451	79.63
10	MS	14	7.33	818	92.94	49	6.52	880	48.30
11	DS	101	52.88	739	84.07	612	81.38	1452	79.69
12	VR	23	12.04	797	90.67	318	42.29	1138	62.46
13	ET	119	62.30	733	83.39	449	59.71	1301	71.41
14	RP	102	53.40	768	87.37	553	73.54	1423	78.10
15	IN	113	59.16	638	72.58	555	73.80	1306	71.68
16	ID	88	46.07	407	46.30	314	41.76	809	44.40
17	Avg. of 1-16	85.31	44.67	656.69	74.59	436.94	58.10	1178.06	64.66
18	PSD of FFT	158	82.72	749	85.21	557	74.07	1464	80.35
19	Proposed	163	85.34	836	95.11	661	87.90	1660	91.11

Power spectral density function of FFT in frequency domain was also calculated for comparison.

As for the experimental result, average discrimination rate of 64.66% was obtained by applying single parameters at a time. Discrimination rate of 91.11% was obtained by dominant feature parameters method in spatial domain. Discrimination rate of 80.35% was obtained by PSD of

FFT method in transform domain. As a consequence of using the dominant feature parameters method proposed in this paper (K = 5, feature parameters are ① SX, ② RP, ③ DS, ④ SD, ⑤ AV), the discrimination rate was improved by at least 10.76%.

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=국문초록=

본 연구는 인간의 갑상선세포를 대상으로 암세포의 식별을 위하여 새로운 디지털 영상기술을 적용하여 해석한 것으로 이를 위하여 세포영상해석에 필요한 개선된 처리방법들을 제안하였다. 실험대상으로 정상세포와 암세포로 확인된 갑상선세포의 현미경영상을 사용하였다. 세포영상으로부터 세포핵을 구분하기 위하여 기존의 방법을 개선한 방향각을 갖는 Contour Following법을 시도하여 세포핵의 영상을 매우 효과적으로 얻을 수 있음을 입증하였고, 세포핵의 특징추출을 위하여 16개의 특징파라미터들을 사용하였고 식별율을 높이기 위하여 우수특징파라미터를 선택하여 식별율 향상을 꾀하였다. 실험결과 평균 91.11%의 식별율을 얻음으로서 효과적으로 갑상선의 암세포를 식별할 수 있음을 증명하였다.