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C-Filler: An Method for Filling of ...

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C-FILTER: A METHOD FOR FILTERING OF BIOMEDICAL SPECIMENS.

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Abstract. A method to filter 'good metaphase' cells in biomedical specimens is given. The filtering is done with a C-Filter. C-Filter is based on C-Calculus. It seems that this Calculus gives us two devices: C-Filter and C-Transform, well suited for analysis of textures in general, and in particular of biomedical specimens, which can be considered as textures too. We analysed more than one hundred of biomedical specimens - that of peripheral blood and of spinal cord. For computer the slides or films of specimens were digitized and input as 512x512 matrices with 64 levels of gray. Our results were fully confirmed by experiments.

INTRODUCTION.

After a rather painful and difficult beginning the use of a digital computer in the field of biomedicine now enjoys a complete recognition and wide application.

The use of the computer not only gives undisputably reliable results, but also opens new vistas for further and a more profound research. Indeed the application of the computer for white-corpuses analysis, for chromosomes classification, for detection of different kinds of cancer such as cervical, cancer of the breast, abdomen, brain, stomach, and of other organs and parts of the human body, not only supplies with absolutely unambiguous results, but they are obtained much faster than in diagnosis of a pathologist and moreover, are less costly (1).

The studies of the mechanism of different cell diseases, whether the causes of them are known or not, and whether they are congenital or acquired later in life, are carried out all over the world.

The modern pathology subdivides the diseases into two categories: hereditary and acquired. For the latter it is thought that they are caused by a unfavorable environment.

Let us discuss briefly the first category: a genetic basis of a disease can be viewed in the light of Mendelian laws of heredity. It is established, without any doubt, now that certain traits in an individual are determined by the genes, he inherited, and in replication of these genes.

We also know that the cause in many hereditary diseases can be a defective gene, or an altered one, or the absence of certain genes.

However there is another cause for a genetic anomaly, which has nothing to do either with a mutation of a gene, or with the absence of certain ones, but deals with some anomaly in chromosomes. The anomaly can be in the number, or form, or size of the chromosomes. A classic example here is the disease called

Mongolism (Down's syndrome). It occurs as often as once in each 700 newborn babies. Finally there is a group of diseases in which the genetic anomaly is restricted to somatic cells, or rather, to the cells "correct". These cells, figuratively speaking, appear on the stage after the fertilization took place; they are distinct from the germinal cells responsible for the initiation of the foetus formation.

It can also happen that a carcinogenic cell, whether a somatic one or of some other kind, becomes anomalous as result of mutation in one or several of its genes. From this moment on the entire progeny of this cell can also be carcinogenic (2).

With the new techniques and the use of computer new methods, simple and accurate, for the determination of numbers and configurations of the chromosomes have been developed, accelerating the research of today and enabling further progress.

These methods led to discovery of new diseases, continue to lead to discovery of the new ones, the causes of which should be sought in the mutations of genes, as above mentioned. There is, thus a great need of further studies in this direction, as well as in the studies concerned with the classification of the human chromosomes, or, in brief, there is a great need of research in the field of "good" mitoses.

In these studies we propose to use a C-Calculus and a filtering procedure with a C-Filter. We have introduced these methods, applied them to many cases of "image processing", in particular, search of a "good" mitosis in the biomedical specimens.

C-CALCULUS

In a numerical system each of its elements (numbers) has two values: one - the intrinsic value of number itself, and the other - the

there and plotting them in C-Space, or, in other words, forming C-Transforms, will immediately indicate the type of the patterns or signals present in the image. Peaks in the C-Space, i.e. similar values of 'u' (difference in extreme values - amplitude) will indicate on presence of periodic or quasi-periodic signals with frequency 'w' in the image, whereas scattered points - on irregularities, on the noise in the image.

APPLICATION

a) Texture.

A concept of texture is paramount for the discrimination of objects in a visual field. Each object has its texture, hence to discern the textures means to be able to distinguish the objects. Moreover the texture gives the information on the depth of the background, the distances of the objects from the observer (8). Hence the texture analysis is vitally important. This analysis presents also a very complex problem and therefore it is imperative to do it on a digital computer.

To use a digital computer in the texture analysis presents in its turn a very complex task. There are attempts (9,10) to analyse the texture on a digital computer using certain models. These models however are such that they could not be described in exact terms. As result difficulties arise when they are used.

For a purpose of an analysis and classification one can think a texture as a repetitive layout of some subpatterns, some subareas. Such a notion of a texture suggests two approaches: a structural and a statistical one.

From the point of view of the structural approach a texture can be imagined as if assembled of 'patches' (small areas of similar size) of subpatterns. These areas (patches) then repeat themselves periodically over the entire visual field (11). From the point of view of statistics a texture is a set of statistical parameters evaluated from numerous measurements carried out over a picture, or texture.

At this point it is necessary to observe that for the grey tones in the patterns the first order of statistics (i.e. the average and the standard deviation) is not sufficient. The second order of statistics here is also necessary, so Julesz (12), for instance, has used the transition probability between the different tones - levels of greyness.

Other techniques with the transition probability have been also developed (13,14,15,16,17, 18,19).

One can think of textures as of patterns with the following characteristics:

1) they consist of 'patches' or 'pieces' roughly uniform, whether in size, or in variation in the tones of grey.

2) The number of such 'pieces' is very high as compared to the occurrences of other characteristics which can be extracted from patterns.

For such a description of a texture we obtained a C-Transform with the points extremely clustered in the C-Space.

Already in our previous paper (20) we presented several experimental results, those of classification of textures, of extraction of the object outlines from a textured background, as well, as finally, we gave the examples of the

filtering of overlapping textures.

b) Biomedical specimens.

Form, size and density in a biomedical specimen can thought of as sufficient parameters for a human observer to distinguish different types of cells.

To some of the observers, however, the idea occurred to think a specimen as a complex texture and make use there the difference in their textures for the classification of the cells (21, 22,23).

The good results we have obtained with the C-Transform for discrimination and classification of textures prompted us to apply this method to biomedical specimens in order to filter there the 'good' metaphase.

We worked with specimens of the peripheral blood and of spinal cord. They have been given to us in two different forms, as:

a) a film taken with a microscope, with a camera of 24x36mm.

b) glass-slides of a microscope.

For the input of specimens (b) a telecamera was optically linked to a microscope, then this camera was connected to a computer, giving there a matrix of 256x256 with 16 levels of grey.

We applied the C-Transform to this input using the well-known algorithm of clusterization (24, 25).

Two distinct peaks were noticeable in the C-Space, one much higher than the other.

It also had low values of 'u's' and 'v's; hence corresponding to the high level of noise in the specimen.

The second peak had not only much higher values of 'u' than the first, but the values of 'v' in it have been much more consistent than in the first peak.

The latter peculiarity prompted us to modify the manner of operation of our C-Filter (26). Indeed, until now we worked not only modifying frequency by choosing the size of the window (u^0) but we also imposed constraints that the variations of the signal within the window had to exceed a certain value (v^0).

The selection of u^0 and v^0 has been done automatically by the program, in fact, these values have been determined by the algorithm of clusterization from a relationship between the accuracy and the dimensions of the spikes in the plane u,v.

It is necessary to point out, that as for the input of the film - so long the magnification of the microscope remained constant, so - for the routine input by a human operator, always the same values of u and v have been obtained. The constant values of u^0 and v^0 for numerous images (100), we have examined, induced us to think about application of a special hardware for our filter.

The Fig.1 gives a photograph of a specimen of peripheral blood taken through microscope (input-picture). In this picture one can see 6 cells, from which 4, close to the edge of picture, are in metaphase. The Fig.2 shows the result of filtering. In it one can notice that the noise has been completely eliminated - leaving only mitoses.

CONCLUSIONS

The results we have obtained prompt us to the next stage of application of our method. In the future we intend to apply our method for

position of the number in system. Thinking of that an idea came to mind that, if to combine separate numbers into groups, or sets with some common coordinates, then manipulations on such sets might reveal certain trends in runs of numbers and, thus, to show some features in the system, which otherwise would remain hidden when system is described by separate numbers only (3,4,5).

We decided to combine separate numbers into strings, such that numbers there would be monotonously increasing and/or decreasing, also that each string would never contain more than a pair of extreme values, and to ascribe to each of these strings the coordinates of maximum and minimum there.

Such a string

$$a_n a_{n-1} \dots a_0$$

we named a "comosite set", or, simply, a "C-set", therefore the name - C-Calculus.

We used formal rules of arithmetics for operations on these string-set. From all operations we chose two: the product and the sum, or, in terms of ordinary set-calculus, intersection and union:

We reasoned, that if several descriptions of system in terms of such C-set will be made, in each description the strings-sets being formed in the same direction slightly overlapping on ly each other, then the products (intersections) of such sets would enhance the trends in the runs of numbers more intensely than when they were expressed in separate descriptions. Repe titions of this procedure might lead then to convergence of these trends to local maxima and minima and thus reveal the pattern/s in the system.

This procedure developed for a digital computer for a purpose of pattern recognition was: a function 'y', as a digitized image, was fed into the computer as a square matrix of order n

$$A = [y_{i,j}] \quad i, j = 1, 2, \dots, n$$

The matrix was scanned horizontally (row-by-row) beginning from a certain position in a row, with a device, a "reader" with a window "w". This "reader" read only extreme values of the function 'y' in the area "w" of the matrix, "seen" through this window "w". The distance between the points of extreme values was recorded too, as well as ordinate of the row. The window 'w' was applied contiguously in a row and over the entire matrix. Such a scanning of the entire matrix can be thought as partitioning of the original matrix A by submatrices "w". For each position of the window a quadruple of values was obtained: the maximum and minimum values of the function in side of the window, the distance between these values, and the ordinate of row. The ordering of these quadruples into a string gave then a description of the matrix A, as a C-set - the first - C.

The scanning was repeated for a slightly shifted (fraction of the width of the window "w") position of the window in respect to the first scanning, and another C-set - C₁ - was obtained. The product of these C-sets gave then a finer partitioning of the original matrix and a more detailed description of the function 'y'. Consecutive application of such procedure: scanning and forming of the products, for an

appropriate size of the window, lead the trends in the descriptions of the function to converge to the points of local maxima and minima. Hence the characteristic features in the pattern could be extracted.

It has been shown (6) that the condition for convergence for one-dimensional case is:

$$w \leq D/2 + 1 \quad (1)$$

here D is the shortest interval in the image, where the 'y' is still monotone.

C-FILTER

The existence of condition (1), that is, that in order to obtain convergence to local maxima and minima in an image, the width of the scanning window should be less or equal to the shortest interval of monotonicity between two extreme values - clearly indicates on the possibility of application of C-Calculus as a filter. Indeed stipulating the size of the window will stipulate the convergence for that pattern or signal in the image for which the shortest interval between the local extremes will be greater or equal to the size of that window "w". All patterns or signal in the image with the distances between extreme values smaller than the width 'w' would give identical values of differences in consecutive scanings and, hence, no convergence for them would take place. With a proper size of the window a C-Filter can be used for extraction of a signal from an image, i.e. to filter a signal out of a noisy background, and, also for filtering different patterns from an image.

C-TRANSFORM

In the above exposition it was tacitly assumed that the image in question contained numerous maxima and minima, a feature typical for textures and periodic signals. However the application of C-Calculus is in no way limited to this kind of patterns.

C-Calculus allows to extract not only textured patterns from images, but also such patterns as object outlines. Moreover it allows to judge the form and type of the pattern/signal present in an image. This is done with the C-Transform for the image.

In the exposition of the C-Calculus (7) the C-Space was defined. It is a three-dimensional space with the axes:

axis 'v' - for the width of scanning window
axis 'u' - for the difference between the extreme values (k-m), for each position of the window during scanning, and
axis 't' - for the frequency with which the points of equal 'v' and 'u' are encountered. To illustrate a C-Transform consider a signal with a constant period ('v') and amplitude (k-m, hence, 'u'), as e.g. a sinus curve - such a signal will be represented just by a single point in the C-Space (however, any other regular periodic signal with the same constant period and amplitude as this sinusoidal signal will be as well represented by the same point in the C-Space).

A signal with a constant period (w), but with a varying amplitude ('u') will have its C-Transform as a straight line parallel to axis 'u' in a plane parallel to the plane 'u,t' at a distance 'w' from it. Scanning an image, computing the differences between extreme values

the chromosome classification profiting there by bands or stripes typical for the textures of chromosomes.

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