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Automatic Prostate Cancer Grading System Based on 3-D Histo-pathological Images

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Abstract

In this paper we have breifly described a machine vision system for grading the prostate cancer based on 3-D histo-pathological images. The 3-D images are obtained from confocal microscope as a stack of optical sections. Various heuristics and conventional image enhancement techniques are used to enhance the image features. Different image segmentation methods including high-level methods are employed to isolated the cells in a volumetric image. We have presented various methods for quantitation of the tissue architecture and cell distribution pattern. This system can be used as a supporting tool for prognosis and diagnosis of the prostate cancer patients.

1. Introduction

Automatic analysis of images of a tissue specimen is a complex process owing to the inherent difficulties in microscopy images. Some of the artifacts in the images include uneven illumination, improper specimen preparation, specimen photodamage, instrumentation noise, etc.. The cells are arranged closely and compactly where they are touching one another and overlapping. The touching or overlapping cell boundaries exhibits a very low and uneven intensity gradient magnitude that is difficult to recognise by low level image processing. Presence of dense inter-cellular matters, highly textured cell chromatin and intra cellular objects makes it very difficult to completely automate the process of tissue image analysis. In the recent literature [1], [2], it has been observed that the analysis of two dimensional images of tissue specimen is not enough for measuring various features such as malignancy level of a cancer tumor based on variation in the chromosome density [3], spread of the malignancy, etc.. While grading the cancer tumor based on cytological features, precise measurement of size, shape, orientation, etc. of individual cells is called for. This can be done only by 3D image analysis.

In this paper we have described an expert system built in our institute to grade the prostate cancer tumor based on the three dimensional image analyses. The three dimensional images of the thick tissue specimens are obtained using Confocal Laser beam Scanning Microscope (CLSM). CLSM produces a stack of 2D optical sections that gives the three dimensional information of the tissue specimen. Such a stack of optical sections suffers from uneven illumination, non-isotropic voxels due to relatively poor axial resolution, instrumentation noise, etc..

2. Image Enhancement and Noise Reduction

This is an important step towards reducing the error and interactiveness in further processing and feature extraction. First step is to reduce the effect of photobleaching. *Photobleaching* causes the considerable variation in the image intensity along the depth of the stack of optical sections. A local threshold is automatically chosen based on the histogram concavity analysis. If $I_1, I_2, \ldots I_n$ are the average image intensities of optical sections 1, 2,..., n then a scale factor β_i is calculated as $\beta_i = max\{I_1, I_2, \ldots, I_n\} - I_i$ for i = 1 to n. If there are N_i voxels in the foreground of image slice i, then the intensity value of each image voxel is enhanced by a factor $\frac{\beta_i}{N_i}$. This is a simple scaling of the intensity of foreground voxels to get a better visualization. The next enhancement step is to increase the axial resolution. This step is done by *interpolation using morphing*. This technique has the advantage of both intensity based and contour based interpolation methods. The two tone versions of the images are subjected to Ex-OR operation. The skeleton of the resulting image gives the overall boundary contour of the object in the interpolated image slice. The objects in the source images are then deformed towards the contour in the interpolated image slice. The intensity of the objects in the interpolated image slice is determined by the weighted averaging of the voxels intensities in the source image. This process of

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intensity filling is called morphing [4],[5]. The resulting images are subjected to *window slicing, size and shape filtering, morphological opening and closing, surface enhancement and directional smoothing* techniques. These conventional and heuristic methods enhance the boundary features of the cells while suppressing the spurious noisy signals.

3. Segmentation

Segmentation is a process of isolation of the objects in the image to facilitate the automatic feature measurement values. Segmentation is the key to any computer vision based expert system. There are as many segmentation algorithms proposed in the literature as there are segmentation problems. Most of these methods are problem specific. The low-level methods such as *Sobel and Laplacian edge detectors* and region growing methods fail to achieve the complete segmentation in case of Histo-pathological images. This is because, the gradient magnitude at the overlapping or touching cell boundary is very low and uneven. We have modified and implemented some of the region based low level methods such as *constrained seeded volume growing* [6], [7], *successive erosion dilation* [8], *3-D watershed techniques*, etc. to get the initial segmentation result. We have included a merging technique to 3-D watershed to reduce the over segmentation of the cells and to avoid detection of the spurious objects as cells [7]. The low-level segmentation results are used as a priori information in high-level segmentation methods. We have designed and implemented segmentation methods based *on successive optimization of active contour models in surface following* [4],[5],[6], *3-D deformable models* [9],[10], *layered segmentation* by local search [11],[12], etc.. In the active contour model method, we have initialized the contour model in one optical section and the optimum contour is propagated to its neighboring sections as an initial contour. Energy derived from image gradient, distance map, image intensity and externally imposed penalty terms are used to force the convergence of the contour to far off points in the cell surface. We have also provided many other heuristics low-level segmentation methods as well as edge detectors for segmentation of the cells. As the volumetric histo-pathological images falls in a complex image category where precision in processing is required to achieve any considerable utility of automatic analysis, more often we have used more than one method including interactive corrections to get the precise segmentation results.

4. FISH Signal Evaluation

Fluorescence in situ Hybridization (FISH) signals indicated the loss or gain of particular chromosome in a cell nucleus. It has been found that the variation in the chromosome numbers can be directly related to the malignancy level. We have develop a tool based on simple image analysis to automatically identify, segment and count the FISH signals per cell nucleus. Segmented and labeled cells are used to confer the cell membership of these signals. After using conventional filters to reduce the noise, top-hat filter is used to enhance the FISH signals. A *three dimensional component labelling* technique is applied to a region within the cell and maximum number of label is taken as the maximum FISH signals present in the cell nucleus [5],[9],[13],.

5. Feature Selection and Measurement

One can select many features of the cells and tissue based on which the tissue image can be classified into different grades. We have selected few major features of the cell that exhibit large variation in its value for different grades for our purpose. Algorithms are developed to calculate all possible features separately if needed for further diagnosis and prognosis. The major cytological features selected are cellularity, dyshesion, nuclear irregularity, anisonucleosis, macronucleoli, polarity loss, crowding, cell enlargement, etc.. Based on each feature the tissue image is classified. A linear combination of the grading result based on different features is used to make the final decision about the carcinoma tissue specimen. Histological feature such as disruption in the tissue architecture is majorly used by the pathologists to grade the prostate cancer. We have developed heuristic methods to quantitate the breakdown of the tissue architecture. Some of the tissue features which are used to decide the grade of the prostate tumor are variation in size and shape properties of the cells in a tissue, disruption of cell architecture, presence of outliers, cell distribution pattern, variation in the orientation and the most dominant direction of the cells, etc..

The tissue images are separately graded based on the Cytological features and Histological features. We have found that Cytological features can alone be quite enough for automatic grading of the prostate tumor specimen [14]. We have *implemented Expectile-Quantile (EQ) plot* to differentiate between different patterns of cell distribution as well as clustering of the cells and presence of individual cells far from the clusters in the tissue specimen image.

A simple classification technique based on look-up table is used to grade the prostate tissue images. A manual grading result by pathologist is first used as a gold standard. Different cytological and histological features of the tissue image are calculated and grouped based on manual grading results. The

features that clearly confirm to pathologists view by showing large variation in its value from one grade to another is considered with maximum weightage. A lookup table is prepared based on the range of values of these features within each grade. About two hundred experimental data sets with nearly similar distribution of number of data sets in each grade of the cancer is used to form the look up table. The feature values of the new data sets are calculated and compared with the look up table and a crisp grade is given to the data set. The uncertainty of the data set's belongingness to particular grade is quantified as the distance of the feature value from the cluster center of the particular grade.

It has been observed that the crisp grading does not provide the accurate position of the grading in a continuo's scale. We have also implemented continuous class classification scheme to show the exact position of the grade on a continuous scale.

5. Results and Discussion

We have tested our system on relatively large number of data sets. Around 70% of the data sets were classified correctly. Same number of data sets was classified correctly by using only cytological features for grading. In the early literature it has been reported that the pathologists grading of the tumor differ from one pathologist to another. Our next attempt is bring the variation in grading using the expert system within the level of variation between different pathologists. The expert system produces reliable and reproducible results and can be used to regulate the grading in general as well as to in depth diagnosis by knowing quantitative feature values of the tissue specimen under inspection.

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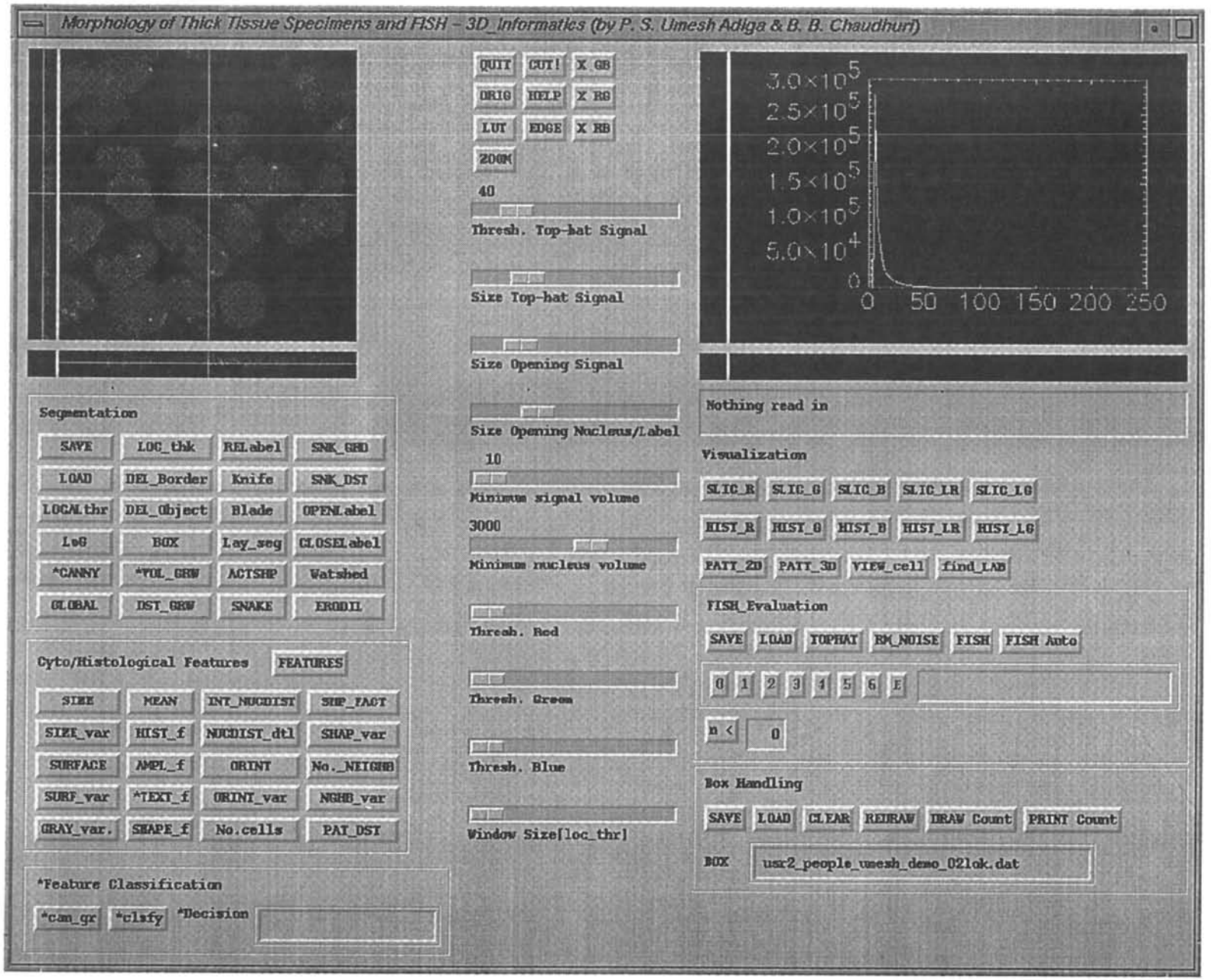
Morphology of Thick Tissue Specimens and FISH – 3D_Informatics (by P. S. Umesh Adiga & B. B. Chaudhuri)
QUIT
CUT!
X GB
ORIG
HELP
X RG
LUT
EDGE
X RB
ZOOM
40
Thresh. Top-hat Signal
Size Top-hat Signal
Size Opening Signal
Size Opening Nucleus/Label
10
Minimum signal volume
3000
Minimum nucleus volume
Thresh. Red
Thresh. Green
Thresh. Blue
Window Size[loc_thr]
3.0×10^5
2.5×10^5
2.0×10^5
1.5×10^5
1.0×10^5
5.0×10^4
0
0 50 100 150 200 250
Nothing read in
Visualization
SLIC_R
SLIC_G
SLIC_B
SLIC_LR
SLIC_LG
HIST_R
HIST_G
HIST_B
HIST_LR
HIST_LG
PATT_2D
PATT_3D
VIEW_cell
find_LAB
FISH_Evaluation
SAVE
LOAD
TOPHAT
RM_NOISE
FISH
FISH Auto
0 1 2 3 4 5 6 E
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Box Handling
SAVE
LOAD
CLEAR
REDRAW
DRAW Count
PRINT Count
BOX
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Segmentation
SAVE
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RELabel
SNK_GRD
LOAD
DEL_Border
Knife
SNK_DST
LOCALthr
DEL_Object
Blade
OPENLabel
LoG
BOX
Lay_seg
CLOSELabel
*CANNY
*VOL_GRW
ACTSHP
Watshed
GLOBAL
DST_GRW
SNAKE
ERODIL
Cyto/Histological Features
FEATURES
SIZE
MEAN
INT_NUCDIST
SHP_FACT
SIZE_var
HIST_f
NUCDIST_dtl
SHAP_var
SURFACE
AMPL_f
ORINT
No._NEIGHB
SURF_var
*TEXT_f
ORINT_var
NGHB_var
GRAY_var.
SHAPE_f
No.cells
PAT_DST
*Feature Classification
*can_gr
*clsfy
*Decision