Intelligent Image Processing Techniques for Cancer Progression Detection, Recognition and Prediction in the Human Liver

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***Abstract*-Clinical Decision Support (CDS) aids in early diagnosis of liver cancer, a potentially fatal disease prevalent in both developed and developing countries. Our research aims to develop a robust and intelligent clinical decision support framework for disease management of cancer based on legacy Ultrasound (US) image data collected during various stages of liver cancer. The proposed intelligent CDS framework will automate real-time image enhancement, segmentation, disease classification and progression in order to enable efficient diagnosis of cancer patients at early stages. The CDS framework is inspired by the human interpretation of US images from the image acquisition stage to cancer progression prediction. Specifically, the proposed framework is composed of a number of stages where images are first acquired from an imaging source and pre-processed before running through an image enhancement algorithm. The detection of cancer and its segmentation is considered as the second stage in which different image segmentation techniques are utilized to partition and extract objects from the enhanced image. The third stage involves disease classification of segmented objects, in which the meanings of an investigated object are matched with the disease dictionary defined by physicians and radiologists. In the final stage; cancer progression, an array of US images is used to evaluate and predict the future stages of the disease. For experiment purposes, we applied the framework and classifiers to liver cancer dataset for 200 patients. Class distributions are 120 benign and 80 malignant in this dataset.**

Keywords—CDS; Image Segmentation; Classification; SVM; LESH; WEKA; Ultrasound; Liver Cancer;

I. INTRODUCTION

Liver cancer is the sixth most common malignant tumour and the third most common cause of cancer-related deaths worldwide. The chronic Liver damage affects up to 20% of our population. It has many causes - viral infections (Hepatitis B and C), toxins, genetic, metabolic and autoimmune diseases [1]. The diagnosis of liver cancer usually occurs in later stages in the disease when there are few effective treatment options and the prognosis for patients with Hepatocellular Carcinoma (HCC) remains very poor. Currently, hepatic excision remains the standard for treatment of HCC; however, the procedure is somewhat not sufficient due to low respectability rate. In addition, recurrence often happens in most of the cases (>60%) after resection with short life expectancy of about 6 months from the time of diagnosis [2]. In the liver cancer treatment domain, accurate selection of a personalised treatment plan can be of critical importance for the patient's health or even survival. In order to pursue a better disease management there is an urgent need in developing models for early cancer detection, as well as understanding the underlying mechanisms of liver cancer development. Computer-aided diagnosis (CAD) has become one of the major research subjects in medical imaging and diagnostic radiology. In this research, the motivation and philosophy for early development of CAD are presented together with the current status and future potential of CAD.

The general research framework (see Figure 2) is proposed to further investigation and development. This framework is inspired by road sign detection [3] and is being extended and applied this work for liver cancer diagnosis and progression. In addition to this section in which the research problem was introduced and its practical relevance was highlighted, Section-II provides exiting State of the Art, Section-III presents the proposed framework and providing details about each operational stage. Section-IV provides the experimental results obtained and an analysis of the results leading to the conclusions that are provided in Section-V.

II. STATE OF THE ART

This section introduces existing literature in the application domain of CAD. The study of these approaches will conceptually compare the performance of the state of the art to

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the performance of the proposed algorithm in the following section. This allows fair comparison, particularly when no standard dataset is available for researchers to carry out performance analysis. Fig. 1 illustrates the general framework used in the majority of the CAD approaches proposed in the literature. These approaches largely differ due to the differences in the algorithms used within each of the four functional blocks of Fig. 1.

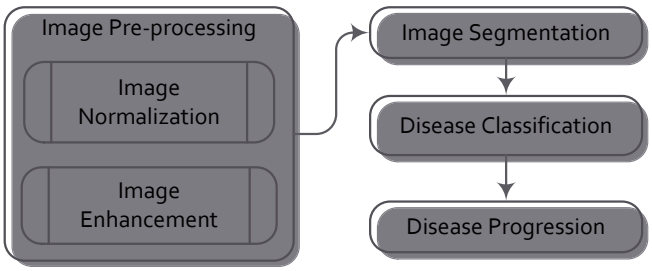


Fig. 1. General framework of CAD

The credibility of a high-quality liver US examination depends on the scanner (that is, the quality of the original image) and the experience of the examiner. At first stage Image Preprocessing is introduced to deal with the issue of guaranteeing the homogeneity of the original US images, which thus subsequently improves the chances of lesion Region of Interest (ROI) detection being more accurate. Image normalization which is a sub process in image processing stage has been achieved by using Mean Filter [4], Wiener Filter [5], Median Filter [6] and Hybrid Filtering [7]. Image Enhancement is also performed for enhancing the appearance of the image as part of image preprocessing. Histogram Equalization [4] to stretch the contrast by redistributing the gray-level values uniformly and Log Transformation [5] for enhancing details in the darker regions of the image; are commonly used techniques by the researchers. At second stage, Image Segmentation is considered as a fundamental task in image analysis responsible for partitioning an image into multiple sub-regions based on a desired feature(s). Canny Edge Detector [8] is introduced to approximate and optimize the edge-searching problem. In order to make the edges more prominent, two dimensional Gaussian and Magnitude and Direction of the gradient are computed at each pixel level. Otsu's thresholding method [8] is utilised to find ROI and proven to be efficient than other local and global thresholding methods. Region Growing [9] is used firstly to obtain homogeneous seeds via histogram analysis. The histogram of each band is analysed to obtain a set of representative pixel values, and the seeds are generated with all the image pixels with representative grey values. Secondly, a modified seeded region growing algorithm is applied to perform the segmentation. This algorithm makes use of instance based learning as similarity criteria. According to Fig. 1, Disease Classification is considered as third stage in the CAD framework. Accurate diagnosis for different types of cancer plays an important role for doctors to assist them in determining and choosing the proper treatment. The survival rate is strongly influenced by stage of the malignancy (malignant tumour) at the point of diagnosis. Thus, an early diagnosis is needed in order to give the proper treatment to the patients and to help reduce the mortality and morbidity rate. There are many types of classification algorithm or commonly known as classifiers have been used for cancer diagnosis by the researchers. Some of them are Artificial Neural Network (ANN), Support Vector Machine (SVM), Bayesian classifier and K-Nearest Neighbours (KNN). An experimental study [2] consisting of a proteomic dataset of 132 HCC related tumour and non-tumour samples where each comprises of 1433 variables were used for construction and evaluation of classification models based on ANN and classification and regression trees (CART) algorithm. Both algorithms successfully segregate samples into corresponding phenotypes with high sensitivities and specificities (ANN: 89.4%, 89.4%; CART: 80.3%, 80.3%), enlightening the usefulness and possibilities of data mining techniques in genomic and proteomic expression profiling studies. The discriminative performance of CART was slightly lower than that of ANN by 9.1% in both sensitivity and specificity. However, in terms of training time complexity and ease of use, CART may have outperformed ANN. A group of SVM [14] with basic kernel functions are used where 5 fold Cross Validation (CV) is carried out for SVM in the training data set to tune their parameters. This study includes CV accuracy for all of the data sets and selects the smallest CV error. In another study [15], SVMP was trained with a degree range of [1: 5] and the SVMR was implemented with a radius close to 1 ([0.1, 0.2... 2]). The best result of the SVM corresponds to a degree of 1, attaining an error rate of 45.45% for the optimal contour set, 25.0% for the optimal clinical set and 23.86% for the feature set. With the SVMR the best performance for the optimal contour set was obtained with a radius of 1 showing an error of 48.86%, an error rate of 21.59% for the optimal clinical set with a radius of 1.9, and a radius of 1.8, for the case of the optimal feature set, with an error of 27.27%. SVM classifier for identification of liver cancer tumour from different textural features method used for segmentation and classification [16]. The texture features are extracted from the high intensity value using Otsu's thresholding method. In fourth and final stage Disease Progression is measured by range of liver cancer US images gathered over a period of time period will be used to assess and predict the future stages of the disease. The event-based disease progression model [18] develops a timeline of disease progression that can be used to position each within the event sequence. An integrative hierarchical analysis of tumour progression [19] that discovers which a priori defined pathway is relevant either throughout or in particular steps of progression. The next section aims to overcome previous research gaps in designing a robust CAD system.

III. Proposed Framework

In this proposed research model, general research framework (see Fig. 2) is proposed for further investigation and

development of CDS. This framework is inspired by recently developed algorithm [3] which has been extended and applied to this work for liver cancer diagnosis and progression. The proposed CDS system comprises of four key stages, which are detailed in this section. For better understanding of proposed CDS, Fig. 2 is given to describe a complete CDS framework.

A. Image Preprocessing

Images acquired from US devices are not always appropriate to perform the desired image processing tasks. Due to presence speckles and noise in the US electrographic images, noise filtering and image enhancement are required. An image pre-processing step normalizes the image by reducing noise, adjusting the contrast and by removing blurriness at the same time. The noise and blurriness in the image can hinder the true detection. US images require preprocessing to suppress the noise and enhance important image features. We have adopted two techniques in Image Preprocessing stage, Image Normalization and Image Enhancement. Median Filter is employed for image normalization which helps to get rid of small noise particles and blurriness of the image. We have introduced Contrast Limited Adaptive Histogram Equalization (CLAHE) for image enhancement. This approach has gained reasonable popularity and used quite frequently to enhance medical images. It first divides an image into contextual blocks and then applies Histogram Equalization to each block sub regions of an image. Later, it generates a histogram for each block using a specific number of bins and then clips the histogram at a certain threshold. It also maps each region according to the new histogram results. At the end, it interpolates grey level mapping to reconstruct the final CLAHE image which will be our enhanced image ready for ROI segmentation.

B. Image Segmentation

Image segmentation divides the image into non-overlapping regions and then separates the objects (lesions) from the background. The boundaries of the lesions are delineated for feature extraction which will be helpful in classification stage. The pre-processed images are further analysed in this stage in finding accurate ROI. Firstly, CLAHE images are transformed from grey level images to binary images so that clear distinction can be formed with background representing pixel 0 and foreground representing with pixel 1. Active Contour model is utilised to separate out ROI with minimum interactions from medical experts. This helps in accurate segmentation of the ROI that are further normalised as 128×128 dimensional blob and collected as array of ROIs representing same US liver images. The extracted blobs are then passed to the classification stage where disease classification is measured.

C. Disease Classification

The primary objective is to propose efficient cancer classification techniques which provide reliable and accurate classifications. The research goal can be achieved by finding best solutions that can ensure high accuracy in classification using supervised and un-supervised machine learning algorithms. Based on the selected features, the suspicious regions will be classified into different categories, such as benign findings and malignancy.

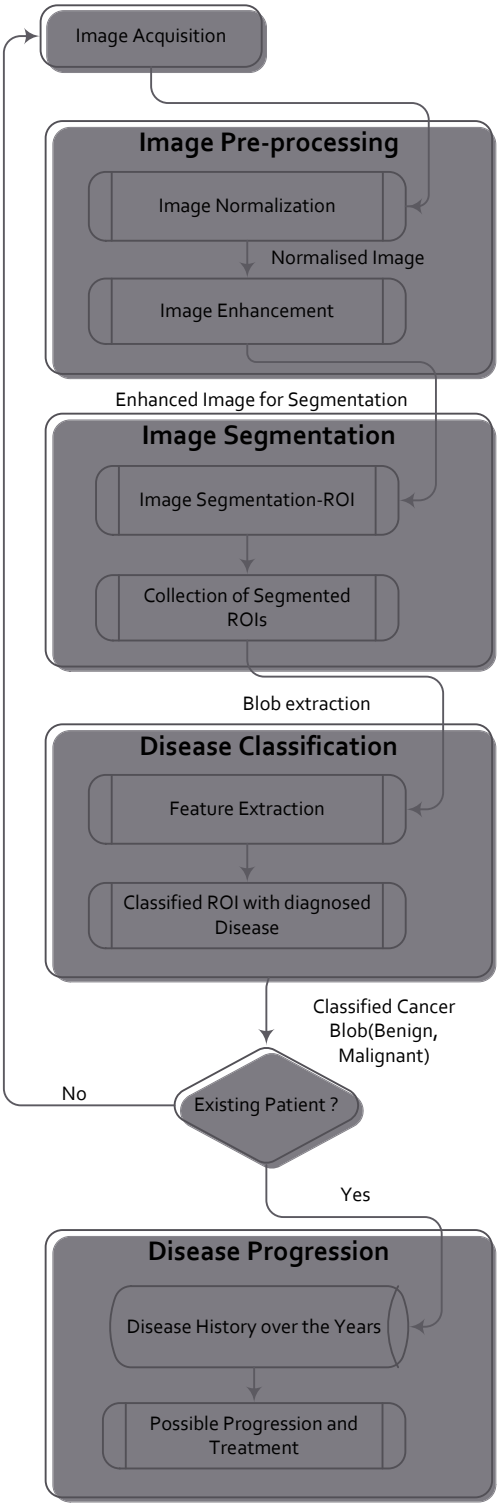


Fig. 2. Proposed Framework

We have employed Local Energy Based Shape Histogram (LESH) to gather features from the output of the Image Segmentation stage. The image(s) are normalised to a square dimensional image of size 128×128 if not done already and at the same time converted to grey level image. It should be reminded that the image normalisation to a fixed dimensional size and its grey level conversion, are the valid input requirements for LESH feature extraction. The next stage is to extract the LESH features of the normalized images. LESH features are obtained by computing the local energy along each filter orientation of image sub-region. The overall histogram represents the concatenated histograms, which are computed along each sub-region of the image. These extracted LESH features from different classes of liver cancers are trained manually and classified with the help of multiclass SVM polynomial kernel. The training samples of US Liver cancer images are correctly marked initially by the experts and 25 to 30 different samples per class were trained by using SVM. We have also experimented different classifiers i.e. MLP to evaluate their performance and comparison between them.

D. Disease Progression

Range of liver cancer US images over time period will be used to assess and predict the future stages of the disease as an effective method for monitoring the progression of liver cancer disease. To achieve this task we have introduced a functionality to check the patient status whether he/she is an existing patient who has liver cancer history. In case patient has history found in the database its previous US scan results are compared with the newly diagnosed results. This helps in predicting the disease progression and relevant treatment can be suggested accordingly. This should be reminded that Disease Progression stage is semi-automated, where experts have to view the diagnostic results and agree with the progression predictions produced by CDS. The next section provides details of the experimental setup and acquired results by utilizing aforementioned algorithm.

IV. EXPERIMENTAL SETUP AND RESULTS

A number of preliminary simulation experiments have been carried out aimed to evaluate each stage of the proposed framework from pre-processing to disease classification. This paper does not cover Disease Progression stage which will be evaluated in the future research work. Our study samples include 200 patients data with various types of cancers randomly selected from the clinical population. This US image dataset were acquired from Radiology department of Crosshouse Hospital Kilmarnock United Kingdom. Images acquired from the Hospital were in DICOM format with length L = 128.00 and width W = 255. The DICOM images were transformed to JPEG for later computer based processing. All experiments were conducted on an Intel Core i5 Pentium processor of 5 GHz and 8GB of RAM. Microsoft Visual Studio 2008, OpenCV, WEKA Experimenter and Matlab R2013a were used for the software development and experimental purposes.

A. Image Preprocessing

To perform desired image processing tasks on images acquired in DICOM format, are initially converted to JPEG. This procedure involves retaining only the image information and discarding the patient information at the same time. The resultant US images are not always suitable to directly perform segmentation tasks due to salt and pepper noise present in the image. 2D Median Filter is an ideal choice to clear the images from this sort of noise, which involves removal of tiny particles from images which have no connection with other particles or objects in the image. This procedure not only removes the noise from the image but it also helps sharpening the edges and makes possible cyst or cancer areas more visible for later image segmentation tasks. Image Enhancement is an important preprocessing performed after Image Normalization, to enhance the darker pixel areas. CLAHE is adopted to perform such enhancement tasks due to its capabilities to enhance low-contrast images such as US. It enhances the contrast of the grayscale image by transforming the values using contrast-limited adaptive histogram equalization. Following step were carried out to implement CLAHE to enhance images.

1. Calculate a grid size based on the maximum dimension of the image. If a window size is not specified chose the grid size as the default window size.
2. Identify grid points on the image, starting from top-left corner. Each grid point is separated by grid size pixels.
3. For each grid point calculate the histogram of the region around it, having area equal to window size and cantered at the grid point.
4. If a clipping level is specified clip the histogram computed above to that level and then uses the new histogram to calculate the cumulative distribution function**.**
5. After calculating the mappings for each grid point, repeat steps 6 to 8 for each pixel in the input image.
6. For each pixel find the four closest neighbouring grid points that surround that pixel.
7. Using the intensity value of the pixel as an index, find its mapping at the four grid points based on their cdfs.
8. Interpolate among these values to get the mapping at the current pixel location. Map this intensity to the range [min: max) and put it in the output image.

B. Image Segmentation

After completion of Image Preprocessing stage, Active Contour model based image segmentation is applied to segment cancerous parts (i.e. ROI) from enhanced image. In active contour model, we utilized the technique of matching a deformable model to an image by means of energy minimization. A snake or active contour model initialized near the target gets refined iteratively and is attracted towards the salient contour. A snake in the image is represented the curve with a set of *n* points.

$$V_i = (x_i, y_i) \quad (1)$$

Where $i = 0 \ldots\ldots\ldots n-1$

Energy function as

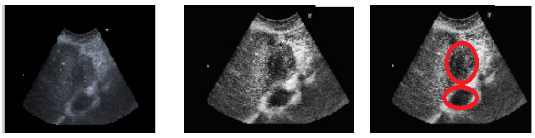
$$E_{total} = \int_0^1 E(V(s))\, ds = \int_0^1 [\![E_{int}(V(s)) + E_{ext}(V(s))]\!] ds \quad (2)$$

Where E_{int} (V(s)) is internal energy and E_{ext} (V(s)) external energy

$$E_{external} = E_{limage} + E_{con} \quad (3)$$

The energy function for snake is in two parts, the internal and external energies. The internal energy is the part that depends on intrinsic properties of the snake, such as its length or curvature and the external energy depends on factors such as image structure. $E_{external}$ represents the external energy of the spline (snake) due to bending, E_{limage} denotes the image forces acting on spline and E_{con} serves as external constraint forces introduced by user. The combination of E_{limage} and E_{con} can be represented as $E_{external}$, that denotes the external energy acting on the spline. Following steps were carried out to implement active contour model to segment cancer blob from liver US image.

- Liver Image acquisition from ultrasound
- Convert RGB image to greyscale- for desired inputs.
- Convert image to binary image, based on adaptive threshold-Masking.
- Apply active contour model with help of greyscale images and masked images.
- Take a compliment of binary image- Another masking, black pixel convert into white and vice versa.
- Regions properties of resulting image are under investigation, where segmented ROI can be cropped for further classification and progression estimation.



Original image Enhanced Image Segmented image (ROI)

C. Disease Classification

At the Disease classification stage, experiments were performed to evaluate different commonly used classifier techniques for liver cancer classification. WEKA tool has been utilised to evaluate performances of various classifiers on LESH features obtained from normalised ROI. To measure and investigate the performance on the selected classification methods namely Bayesian Logistic regression, Multi-Layer Perception, KNN, J48graft and SVM classifier, we found that WEKA provides better framework to compare performances of various classifiers. 66% of data are used for training and remaining for testing purpose that is shown in TABLE 1.In this study, all data is considered as instances and features in the data are known as attributes. The simulation results are portioned into several sub items for easier analysis and evaluation. Different performance matrix like True Positive (TP) rate, False Positive (FP) rate, Precision, Recall, F measure and Receiver Operative Curve (ROC) area are presented in numeric value during training and testing phase. The summary of those results by running the techniques in WEKA is reported in TABLE-2. According to TABLE 3, we can clearly see the highest accuracy is 95.29% belongs to SVM and lowest accuracy is 51.43% that belongs to Bayesian logistic regression. Based on TABLE 4, we can compare errors among different classifiers in WEKA. We have found out that SVM is the best (13.873%), second best is the MLP (17.608 %). An algorithm which has a lower error rate will be preferred as it has more powerful classification capability and ability in terms of medical and bioinformatics fields. From TABLE 5, we see that SVM classifier requires the shortest time which is around 0.01 seconds compared to others. MLP algorithm requires the longest model building time which is around 1.02 seconds. The second one in the list is Bayesian logistic regression with 0.06 seconds. Keppa statistic is used to assess the accuracy of any particular measuring cases. It is usually to distinguish between the reliability of data collected and their validity. The average Kappa score from the selected around 0.00-0.87. Based on the Kappa Statistic criteria, the accuracy of the classification purposes is substantial [10]. So according to best average Kappa statistics SVM classifier is 0.87. The objective of this study is to evaluate and investigate nine selected classification algorithms based on WEKA. These results suggest that among all machine learning algorithms Bayesian Logistic regression, Multi-Layer Perception, KNN , J48graft and SVM has the potential to significantly improve over the conventional classification methods for use in medical or in general, bioinformatics field. However there is chance of improvement by involving different feature selection methods and test the performance of each classifier. First, the misclassification cost is not considered explicitly in this research. In future, cost sensitive learning might make the study more practical and valuable.

TABLE 1. NUMBER OF INSTANCES IN THE TRAINING AND TEST DATASET

Data set	No of training data	%Training Data	No of test data	% Test Data	Total
Liver cancer	130	66%	70	34%	200

TABLE 2. SUMMARY OF DIFFERENCE CLASSIFIERS PERFORMANCE

Classifier	TP Rate	FP Rate	Precision	Recall	F-measure	ROC Area	Class
Bayesian Logistic regression	0	0	0	0	0	0.5	B
	1	1	0.627	1	0.771	0.5	M
Multi Layer	0.959	0.077	0.904	0.959	0.931	0.982	B

Perceptio n	0.92 3	0.04 1	0.968	0.923	0.945	0.98 2	M
KNN	0.75 5	0.06 7	0.87	0.755	0.808	0.90 6	B
	0.93 3	0.24 5	0.865	0.933	0.898	0.91 7	M
J48graft	0.91 9	0.05 9	0.907	0.919	0.913	0.89 9	M
	0.94	0.08	0.949	0.94	0.945	0.89	B
SVM	1	1	0.85	1	0.919	0.5	M
	0	0	0	0	0	0.50	B

TABLE 3. PERFORMANCE MEASURING IN CORRECTLY CLASSIFIED INSTANCES

Classifier	Accuracy	Kappa Statistics
Bayesian logistic regression	62.74 %	0
MLP	93.85 %	0.8957
KNN	86.64 %	0.9064
J48graft	93.26 %	0.8979
SVM	95.29%	0.8743

TABLE 4. ERROR MEASUREMENT FOR DIFFERENT CLASSIFIER

Classifier	Mean Absolu te Error	Root Mean Squared Error	Relative Absolute Error	Root relative Squared Error
Bayesian Logistic regression	0.3726	0.6104	79.6725 %	126.2472 %
Multi Layer Perception	0.0769	0.2427	16.0116 %	48.521 %
KNN	0.1428	0.3525	30.5301 %	72.9055 %
J48graft	0.0826	0.2579	17.608 %	53.0185 %
SVM	0.15	0.3873	13.873%	44.545%

TABLE 5. PERFORMANCE MEASURING IN TIME TAKEN TO BUILD MODEL

Classifier	Time taken to build model(seconds)
Bayesian logistic regression	0.06
MLP	1.02
KNN	0.50
J48graft	0.2
SVM	0.01

V. CONCLUSIONS

In this paper an efficient CDS framework inspired by the human interpretation of US images is presented. The proposed framework is composed of a number of stages where images are first acquired from an imaging source and pre-processed before running through an image enhancement algorithm. 2D Median Filter and CLAHE are employed for Image Normalization and Image Enhancement respectively. The detection of cancer and its segmentation is considered as the second stage in which different image segmentation techniques are utilized to partition and extract objects from the enhanced image. Active Contour Model is used for the purpose of Region of Interest segmentation. The third stage involves disease classification of segmented objects, in which the meanings of an investigated object are matched with the disease dictionary defined by physicians and radiologists. At this stage LESH features were obtained of normalized ROI. Classifiers performance is measured by introducing WEKA Explorer where several classifiers such as Bayesian Logistic regression, Multi-Layer Perception, KNN, J48graft and SVM classifier were tested on LESH features. SVM produced 95.29% accuracy results and performed better among the machine learning algorithms tested. In future work, disease prediction using US and Magnetic Resonance Imaging (MRI) Fusion along with cost-sensitive learning is hoped to further improve the effectiveness and value of the study.

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