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Automated segmentation methods for liver analysis in oncology applications

Ph. D. Thesis

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1 Motivations

The liver has important role in the digestive system. Its function is vital, which cannot be substituted by machine, and it has exceptional regenerative capability. The last property is a consequence of its modular structure that allows separating the organ into functionally independent parts. Several diseases threaten the liver. Besides poisoning and infections, the number of cancer cases is increasing in the clinical practice. In addition to primary liver tumours, the metastases of other cancer types can frequently occur in the organ. In the last decade the treatment of liver cancer became a very important filed in oncology.

The computerized medical image processing plays important role in clinical diagnosis and therapy. The 3-dimensional (3D) imaging techniques, such as Computed Tomography (CT) and Magnetic Resonance Imaging (MR) allow in vivo visualization of the liver. The CT and MR examinations can be enhanced using contrast agents. In such case more images are acquired in different times, which result multi-phase images. Due to the widespread of modern imaging techniques the number of medical images to be processed is rapidly increasing. There is significant need for software tools which make the analysis of medical images more efficient. This thesis focuses one of the most important fields of image processing: the segmentation.

There are various options for liver cancer treatment. The applied therapy depends on many conditions, like the tumour size, the number of tumours and their distribution, the stage of the disease. The treatment options involve surgery, interventional radiology, chemotherapy, radiation therapy, and the combination of these techniques. All of them can be facilitated with software tools which make the liver analysis more precise and less dependent on the operator. This thesis focuses on the segmentation of the liver, the detection of livers lesions, and the virtual liver resection.

In this work the author paid special attention to the efficiency of the proposed algorithms in addition to their accuracy. According to clinical feedbacks a software workflow is useful when the computation time between starting a function and visualizing its result does not exceed half minute. The algorithms presented in this thesis were designed to solve complex clinical problems efficiently. Another important requirement was implied by the properties of the clinical systems. Today, most applications run on servers which can execute multiple instances of a function in the same time. This software environment limits the usability of methods which need some special hardware. The algorithms presented in this thesis do not have such requirement, so they are easy to integrate in any system.

2 Liver segmentation

The basis of all computer assisted liver analysis is the liver segmentation. The author presented three approaches which represent the different phases of a long research. The first and the second algorithms were developed for single- and multi-phase contrast-enhanced CT images. These techniques were published in a journal paper [1]. The third method was developed for contrast-enhanced MR images. This technique was published in a journal paper [2]. Each method was evaluated on different datasets, which makes their comparison difficult. In order to enable their quantitative comparison, the author performed an extensive evaluation of all methods using a large CT dataset.

The accuracy of the segmentation methods was measured using various error metrics in this thesis. This summary refers only to Volumetric Overlap Error (VOE). Assume that Volumetric Overlap (VO) is equal to the intersection of the result and the reference liver divided by their union, VOE is defined by 100·(1-VO). This measure demonstrates both under- and over-segmentation and it is equal to 0% in case of perfect segmentation.

2.1 Single-phase method for CT images

The author developed an automated liver segmentation algorithm for portal-phase CT images. This method is based on basic assumptions such as the liver is the largest organ in the abdomen, the contrast-enhancement makes the liver brighter than its surrounding organs, and the liver parenchyma is nearly homogeneous in CT images. The method also incorporates information about the surrounding anatomical structures such as the lung, the heart, and the inferior vena cava (IVC). The core of the algorithm is a neighbourhood-connected region-growing technique that is facilitated by various pre- and post-processing steps. More specifically, the algorithm consists of the following steps:

- First, the liver is localized based on its volume and intensity. This is done by computing the contrast-enhanced soft-tissue intensity range based on the histogram of the image. Using this range, the image is thresholded and subsequently eroded, and the largest connected region of the result is used to initialize the segmentation.
- The second step separates the liver from the heart. It starts with segmenting the lung and identifying the bottom edge of the left and right lung lobes. Then, the bottom of the two lung lobes are connected in each coronal slice of the image, which result in a 3D surface that defines the edge between the liver and the heart.
- In the third step, the liver parenchyma is segmented using neighbourhood-connected region-growing. The initial region is used to compute the intensity of the normal liver and to start the segmentation. Due to the large radius used for connectedness the result of the region-growing is dilated after the segmentation finished.
- The fourth step corrects various types of over- and under-segmentations. An additional segmentation is performed between the liver and the lung using lower intensity statistics. Furthermore, liver veins are filled based on their characteristic geometric features, and missing lesions are added using standard cavity filling technique. The IVC is also detected based its characteristic shape and removed.

The author evaluated the proposed method using a set of 20 portal-phase CT examinations having ground-truth liver contour. The test cases were published by a liver segmentation contest, which makes the presented results comparable with other publications. The images involved a few healthy cases, but most of them were pathologic including lesions of different sizes. According to the evaluation the method can accurately (VOE=8%) segment the liver parenchyma within short time (30s per case). The visual assessment of the results showed the results excluded some lesions which were located on the boundary of the organ.

2.2 Multi-phase method for CT images

The author developed an automated approach for liver segmentation in multi-phase CT images. This algorithm is based on the previous one, but it can incorporate the information of more contrast-enhanced phases. The goal was to make the liver segmentation less dependent on the quality of the portal-phase image. The proposed approach exploits the characteristic contrast uptake of the liver. The intensity of a neighbouring organ can be similar to the liver in one particular phase, but it is very unlikely that it has the same intensity in all phases. Thus, the liver parenchyma can be localized more accurately, when the joint information of multiple phases is incorporated. More specifically, the multi-phase approach consists of the following steps:

- First, the input phases are normalized, so latter steps shall not deal with differences in slice number, voxel spacing, and image origin. As result of this step a multi-scalar image is created that represents the intensity of each voxel in all phases.
- The distribution of the contrast uptake is demonstrated by the joint histogram of the normalized images. Since the liver has the largest volume the largest peak in the joint histogram represents the liver parenchyma. All voxels are detected which have similar uptake as the liver, and the largest connected region of them is used as initial region.
- In the next step, the input phases are segmented one-by-one using the single-phase approach, which results in a set of binary volumes. The segmentation involves the separation of liver and heart, the region-growing, and the correction of under- and over-segmented areas (except for the IVC removal that is specific to the portal-phase).
- The segmentation belonging to the different phases involves the liver as well as some other regions which have similar intensity in the given phase. In the last step, the results are precisely registered and the final segmentation is defined as the combination of the results belonging to the different phases.

The author qualitatively evaluated the multi-phase algorithm on a set of 19 multi-phase examinations using a questionnaire filled by 5 physicians. According to the results the segmentation was useful for clinical purposes in 94% of the cases after some minor or no manual correction. The quantitative comparison with the single-phase method on a small set of challenging cases showed the multi-phase method performed better (VOE=11%) than the single-phase one (VOE=16%) without increasing the running time (25s per case).

2.3 Model-based method for MR images

The intensity distribution can be heterogeneous inside the liver due to pathology, which can result in under-segmentation of these areas. Addressing this problem is even more important in case of MR images which have better soft-tissue contrast. The author developed an automated approach that incorporates probabilistic liver model to increase the accuracy of the intensity based liver segmentation techniques. The model was created by registering 60 manually contoured liver exams. The novelty of the model is that it was partitioned into 8 segments according to the anatomical structure of the liver. The partitioning allows using local intensity statistics in different parts of the organ, which makes the segmentation less sensitive to local intensity differences caused by pathology or artefacts. More specifically, the algorithm consists of the following steps:

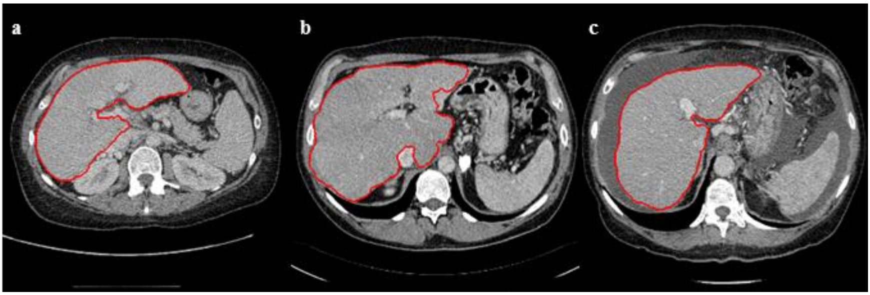
- The intensity range of the contrast-enhanced soft-tissue varies significantly among the examinations, so it is dynamically computed. In the first step, the histogram peak with the greatest mode is selected among those which represent at least 5% of the image.
- In the second step, the liver model is registered to the image to be segmented. The input image is thresholded using the contrast-enhanced soft-tissue range. Then, distance map is computed for the threshold image, which results in an image that has the large value inside the liver. The probabilistic model is registered to the distance map and the partitioning is also applied to the image.
- In the third step, the liver is segmented using neighbourhood-connected region-growing that incorporates the partitioned liver model. The initial region is created from the soft-tissue image using erosion and taking the largest connected region. Intensity statistics are computed for the initial region as well as each segment, separately. The segmentation uses voxel specific intensity condition that incorporates the statistics of the contrast-enhanced soft-tissue, the initial region, and the corresponding segment. Similar to the CT approaches, dilation and cavity filling is applied to the result of the region-growing.

The author evaluated the algorithm on a set of 8 representative contrast-enhanced MR liver exams having manually defined liver contour. The results showed the proposed approach can accurately (VOE=11%) segment the liver within short time (30s per case) despite the significant intensity heterogeneity that was characteristic for MR images.

2.4 Quantitative comparison of liver segmentation methods

The goal of this section was to present the quantitative comparison of the proposed algorithms on a large set of clinical cases. The first two approaches were tested as they were proposed, while the model-based technique was adapted to CT images. The test cases involved 83 contrast-enhanced liver CT examinations (37 portal-phase, and 46 dual-phase). The images involved healthy, tumorous, as well as some extreme (considering size or pathology) cases. The reference liver contour was defined by physician for the portal-phase image of each exam. The single-phase and the model-based methods were tested for all cases, while the multi-phase algorithm was executed for the dual-phase cases only. The test runs were performed on the same hardware, and the segmentation time was measured. In order to compare the results, the average, and the standard deviation of various error metrics were computed. Furthermore, paired T-test was performed to see whether the difference between two methods is statistically significant.

The comparison of the single-phase and the model-based algorithms on the whole dataset showed the latter has significantly better overall accuracy (VOE=13%) compared to the first one (VOE=19%). The tests with the dual-phase images demonstrated the multi-phase (VOE=15%) and the model-based (VOE=15%) approaches perform at the same level of accuracy, while the single-phase method proved to be significantly less accurate (VOE=26%). The average segmentation time was 24s, 19s, and 37s for the three methods, which indicated that both multi-phase and the model-based methods are efficient enough to be used in clinical practice. Considering the fact that the model-based method requires the portal-phase image only it has the widest usability.



Automated liver segmentation using the single-phase (a), the multi-phase (b), and the model-based (c) methods

3 Liver lesion detection

The liver lesion assessment is one of the most important functions of computer assisted liver analysis. The number of liver cancer cases is increasing in the clinical practice, which increases the number of images to be processes. Liver lesion classification and quantification can be facilitated by automated lesion detection. This is very challenging task due to the large variety of lesion size, shape, and density distribution. There is significant need for software tools which can increase the sensitivity of liver lesion detection without forcing the user to review large numbers of false positives. The author proposed an automated approach to solve this problem. The related results were published in a journal paper [3].

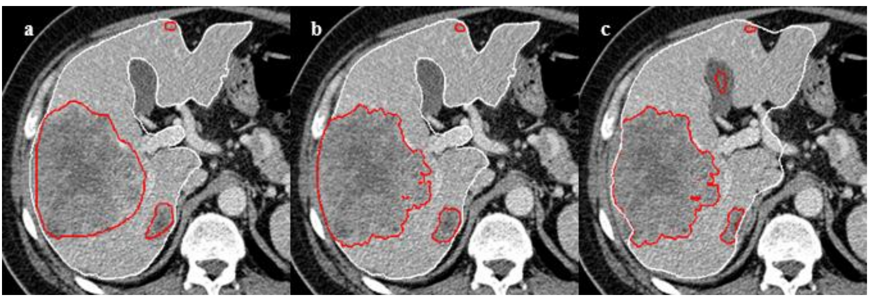
3.1 Automated liver lesion detection for contrast-enhanced CT images

The author developed a new technique for automated liver lesion detection in contrast-enhanced CT images. The proposed algorithm is based on the segmentation of abnormal regions inside the liver and the classification of these regions based on a novel multi-level shape characterization. More specifically, the algorithm consists of the following steps:

- The pre-processing step involves the morphological closing of the volume of interest (VOI) to reduce false negatives due to under-segmented lesions on the liver boundary, the resampling of the image using isotropic voxel size, the reduction of CT image noise, and the computation various features of the normal liver.
- In the second step, staring form the normal liver the abnormal regions are segmented (in an outside-in manner) and the list of candidate regions is created. This step is performed for hypo- and hyper-dense lesions, separately.
- In the last step a multi-level (inside-out) shape characterization is performed for each candidate region using standard geometric features (asymmetry, size, compactness, and volume). Based on these features a probability is defined for each level of a region, which shows the likelihood of the given level to represent a lesion. If the maximal probability level of a candidate region is above the sensitivity threshold, the region is classified as lesion and the corresponding level is used as contour.

3.2 Evaluation of automated liver lesion detection

The author evaluated the proposed method on a set of 30 contrast-enhanced liver CT exams. For each case all lesions were manually contoured by physician. Manually defined as well as automatically segmented liver was used as VOI. The algorithm was executed for all case using various sensitivity values, which allowed the Free-Response Operating Characteristic (FROC) analysis of the method. The results showed the method can achieve 92% detection rate with 1.7 false positive per case when the VOI is manually segmented. The same level of false positives was reached at lower detection rate (85%), when the VOI is segmented using automated liver segmentation technique. The detailed analysis of the false negatives demonstrated the method can miss small lesions which fade into the low density boundary of the organ. The false positives involved multiple detections of some lesion and small lesions or calcifications which were not involved in the reference in addition to other false findings. The average running time of the method was 30s per case, which demonstrates the efficiency of the method.



The ground-truth (a) and the result of the lesion detection from manual (b) and auto VOI (c)

4 Virtual volume resection

The separation of liver segments can facilitate cancer therapy. In surgical treatment planning it is very important to precisely quantify the resected and the remnant part of the liver before operation. The automated partitioning of liver segments is very challenging because the segment boundaries are not visible in medical images. There is a need for tools which allow efficient separation of liver segments based on the user's anatomical knowledge. The author proposed a novel technique to solve this problem. The related results were published in a journal paper [4].

4.1 Volume partitioning using B-spline surfaces

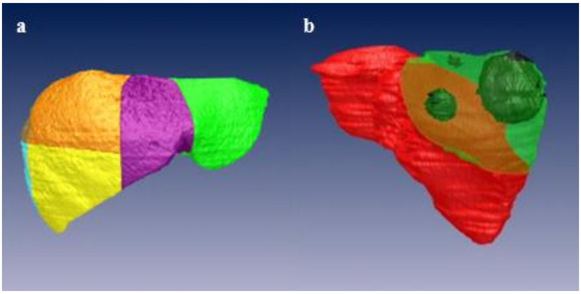
The author developed a new technique for interactive partitioning 3D binary objects using a smooth surface specified by the user. The presented volume-cutting algorithm is based on a multi-resolution triangular representation of B-spline surfaces. This representation allows computing the intersection of the surface with a scan line very efficiently. The partitioning is performed by computing the intersection of the surface with several scan lines. More specifically the algorithm consists of the following steps:

- In the first step, a normalized grid of input points is created from the user defined input traces using B-Spline curve interpolation, and a B-spline surface is interpolated that fits the normalized grid of input points.
- In the second step, the orientation of the surface and the scan lines are computed. The scan line orientation represents the axis of the 3D coordinate system which is nearly perpendicular to the surface.
- In the third step, the multi-resolution triangular representation of the surface is created by sampling the B-spline surface according to a multi-resolution grid.
- In the fourth step, the intersection of the surface with all scan lines are computed, which define the cutting edge. The intersection points are localized using a hierarchical search that is based on the multi-resolution triangular representation.
- In the last step, the cutting edge is propagated to all scan lines which do not intersect the surface.

4.2 Evaluation of virtual volume resection

The author with a radiologist performed the evaluation of the proposed tool for liver segment separation on a set of 14 CT liver exams having gold standard liver contour. Based on the Couinaud definition the liver was cut into anatomical segments using 5 surfaces which were fit to the main branches of the hepatic and the portal vein. For each test exam the physician defined the input traces for each cut. The liver was partitioned into segments according to a predefined order of cuts and the volume of each segment was quantified. The test was repeated 3 times by the operator with a few weeks of delay, and the variation of segment volumes was also computed. Having no ground-truth the segment volumes were compared with the results of another technique and the literature. The comparison demonstrated the segment volumes correlated with the result of the vessel based technique as well as the volumes reported

in the literature. The intra-operator variability was low, which indicate the liver segment separation was repeatable using the proposed technique.
Another clinical application of volume partitioning is the liver tumour resection planning. In this case the tumour is virtually cut from the liver and the removed and the remnant parts are quantified. Two test exams were selected to simulate this scenario. The liver contour was available and the tumours were contoured manually using an interactive tool. In each case, multiple traces were drawn to specify the cutting surface. Then, the liver was cut with the surface and the resected and remnant volumes were visualized and quantified. These experiments confirmed that the proposed tool provides the level of freedom that is required by this clinical problem. According to the time statistics less than a second was spent for surface interpolation and performing the volume cut, which demonstrates the efficiency of the proposed approach.



Liver segment separation (a) and tumour resection (b) using virtual volume resection

Key thesis points

I. Liver segmentation

Liver segmentation is the basis of computer assisted liver analysis. Since the manual segmentation of the liver is very time consuming, there is a big need for automated techniques. The author developed three algorithms for automated liver segmentation. The related results were published in journal papers [1] and [2].

I.1 Single-phase method for CT images (Section 2.1): The author developed a fully automated liver segmentation technique for portal-phase CT images. The algorithm uses standard image processing concepts and incorporates basic anatomical information about the liver and the surrounding organs. The core of the method is a neighbourhood-connected region-growing that is facilitated by various pre- and post-processing steps, such as the localization of the liver, the separation of liver and heart, the correction of breathing artefact, the removal of IVC, and filling the cavities due to liver veins or lesions. The author evaluated the method using a set of 20 portal-phase CT examinations having ground-truth liver contour. According to the evaluation the proposed approach can accurately segment the liver within short time.

I.2 Multi-phase method for CT images (Section 2.2): The author developed an automated approach for liver segmentation in multi-phase CT images. The algorithm is based on the single-phase one, but it can incorporate the information of more contrast-enhanced phases. The main idea of this technique is to exploit the characteristic contrast uptake of the liver for more precise localization of the organ and to combine the segmentation results belonging to different contrast enhanced phases. The author qualitatively evaluated the algorithm on a set of 19 multi-phase examinations using a questionnaire filled by 5 physicians. The results showed the segmentation was acceptable for clinical use in majority of the cases. The quantitative comparison with the single-phase method demonstrated the multi-phase method performs better than the single-phase one without increasing the running time.

I.3 Model-based method for MR images (Section 2.3): The author developed an automated liver segmentation approach that incorporates probabilistic liver model to increase the accuracy of the intensity-based segmentation techniques presented in prior sections. The model was created by registering 60 manually contoured liver exams. The novelty of the model is that it was partitioned into 8 segments according to the anatomical structure of the liver. The partitioning allows using local intensity statistics in different parts of the liver, which makes the segmentation less sensitive to local intensity differences caused by pathology or artefacts. The author evaluated the algorithm on a set of 8 representative contrast-enhanced MR cases. The results showed the proposed approach can accurately segment the liver in short time despite the significant intensity variation that is characteristic for MR images.

I.4 Quantitative comparison of liver segmentation methods (Section 2.4): The author performed the evaluation of the three algorithms on a large CT dataset including single and dual-phase images. The first two approaches were tested as they were proposed, while the model-based technique was adapted to CT images. The single-phase and the model-based methods were tested for all cases, while the multi-phase algorithm was executed for the dual-phase images only. The comparison of the single-phase and model-based algorithms showed the latter has significantly better overall accuracy. The tests with the dual-phase images demonstrated that the multi-phase and the model-based approaches perform at the same level of accuracy, while the single-phase method proved to be significantly less accurate. The average segmentation time was low for both multi-phase and model-based methods, which indicate these techniques are efficient enough to be used in clinical practice. Since the model-based method requires the portal-phase image only, it has the widest usability.

II. Liver lesion detection

The number of liver cancer cases is increasing in the clinical practice, so the computer assisted detection of liver lesions has recently become an important area. The detection of liver lesions is very challenging task due to the large variety in size, shape, density distribution of liver lesions and the large number of slices to be processed. There is a need for tools that can increase the sensitivity of liver lesion detection without forcing the physician to review many false positives. The author proposed a solution for this problem, which published in a journal paper [3].

II.1. Automated liver lesion detection for contrast-enhanced CT images (Section 3.1): The author developed a novel technique for automated liver lesion detection in contrast-enhanced CT images. The proposed algorithm is based on the segmentation of abnormal regions inside the volume of interest (VOI) and the classification of these regions based on a multi-level shape characterization. The shape description incorporates standard geometric features like asymmetry, size, compactness, and volume. Based on these features a probability is defined for each level of a region that shows the likelihood of the given level to represent a lesion. Using this probability the abnormal regions are classified as lesion or other region, and the contour of each finding is defined.

II.2. Evaluation of automated liver lesion detection (Section 3.2): The author evaluated the method on a set of 30 contrast-enhanced liver CT cases, where all lesions were manually contoured by physician. Manually defined and automatically segmented liver was used as VOI. The algorithm was executed with different sensitivity settings, which allowed FROC analysis of the method. The results showed the algorithm can achieve high detection rate at low false positive per case when the VOI is manually defined. The same level of false positives was achieved at lower detection rate, when the VOI is segmented using automated technique. The detailed analysis of false negatives demonstrated the method can miss small lesions which fade into the lower density boundary of the organ. The average running time of the method was 30s per case, which demonstrates the efficiency of the method.

III. Virtual volume resection

The separation of the anatomical liver segments can facilitate for surgical treatment planning. The automated partitioning of the liver is very challenging because the boundary of the segments is not visible in medical images. There is a need for interactive tools which allow efficient separation of the anatomical liver segments. The author proposed a solution for this problem, which was published in a journal paper [4].

III.1. Volume partitioning using B-spline surfaces (Section 4.1): The author developed a new technique for partitioning of 3D binary objects using smooth surfaces. The method applies B-Spline curve and surface interpolation to fit a smooth surface on the user-defined traces which specify the cutting edge. The proposed volume cutting algorithm creates the multi-resolution triangular representation of B-spline surfaces, which allows computing the intersection of the surface with a scan line very efficiently. The partitioning is based on computing the intersection of the surface with several scan lines, where the direction of the scan lines is defined based on the global orientation of the surface. The cutting edge is propagated to all scan lines which do not intersect the surface.

III.2. Evaluation of virtual volume resection (Section 4.2): The author with a physician performed the evaluation of the proposed tool for liver segment separation. The test set involved 14 CT exams and manually defined liver contour was available for each of them. The liver was partitioned according to a predefined sequence of five cuts and the volume of each segment was measured. The test was repeated three times by the physician with a few weeks of delay, and the variation of segment volumes was computed. The results were compared with a vessel-based segment separation approach. The segment volumes correlated with the other technique as well as the literature, and the intra-operator variability was proved to be low. In addition to these experiments, two case studies on virtual tumour resection confirmed that the tool provides the level of freedom that is required by the clinical application. Less than a second was spent to perform the volume cut, which demonstrates the efficiency of the proposed approach.

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