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KNOWLEDGE BASED MEASUREMENT OF ENHANCING BRAIN TISSUE IN ANISOTROPIC MR IMAGERY

by

ERIC LEACH B.S. University of Central Florida, 2007

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in the School of Electrical Engineering and Computer Science in the College of Engineering and Computer Science at the University of Central Florida Orlando, Florida

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Major Professor: Mubarak Shah

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ABSTRACT

Medical Image Analysis has emerged as an important field in the computer vision community. In this thesis, two important issues in medical imaging are addressed and a solution for each is derived and synergistically combined as one coherent system. Firstly, a novel approach is proposed for High Resolution Volume (HRV) construction by combining different frequency components at multiple levels, which are separated by using a multi-resolution pyramid structure. Current clinical imaging protocols make use of multiple orthogonal low resolution scans to measure the size of the tumor. The highly anisotropic data result in difficulty and even errors in tumor assessment. In previous approaches, simple interpolation has been used to construct HRVs from multiple low resolution volumes (LRVs), which fail when large interplane spacing is present. In our approach, Laplacian pyramids containing band-pass contents are first computed from registered LRVs. The Laplacian images are expanded in their low resolution axes separately and then fused at each level. A Gaussian pyramid is recovered from the fused Laplacian pyramid, where a volume at the bottom level of the Gaussian pyramid is the constructed HRV. The effectiveness of the proposed approach is validated by using simulated images. The method has also been applied to real clinical data and promising experimental results are demonstrated.

Secondly, a new knowledge-based framework to automatically quantify the volume of enhancing tissue in brain MR images is proposed. Our approach provides an objective and consistent way to evaluate disease progression and assess the treatment plan. In our approach, enhanced regions are first located by comparing the difference between the aligned set of preand post-contrast T1 MR images. Since some normal tissues may also become enhanced by the administration of Gd-DTPA, using the intensity difference alone may not be able to distinguish normal tissue from the tumor. Thus, we propose a new knowledge-based method employing knowledge of anatomical structures from a probabilistic brain atlas and the prior distribution of brain tumor to identify the real enhancing tissue. Our approach has two main advantages. i) The results are invariant to the image contrast change due to the usage of the probabilistic knowledge-based framework. ii) Using the segmented regions instead of independent pixels facilitates an approach that is much less sensitive to small registration errors and image noise. The obtained results are compared to the ground truth for validation and it is shown that the proposed method can achieve accurate and consistent measurements.

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LIST OF ACRONYMS

HRV	High Resolution Volume
LRV	Low Resolution Volume
MIA	Medical Image Analysis
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
T1	Pre-contrast MR Image
T1E	Post-contrast MR Image

CHAPTER ONE: INTRODUCTION

Medical Image Analysis

Medical Image Analysis has become a large community within the computer vision world. Extracting knowledge from medical images brings forth difficulty and interesting new problems such as dealing with noise, artifacts, and partial volume effects in images [1]. Analyzing these images manually can be difficult and time consuming, especially when attempting to quantify structures within the image. In particular, neuroimaging plays an important role in the evaluation of patients with brain neoplasms. Often, MRI is the modality of choice in this setting, and its usage is most important in establishing the initial diagnosis in these patients. Additionally, MRI is invaluable to the assessment of therapeutic response and post-treatment follow up. Standard MR examinations typically include pre- and post-contrast T1-weighted sequences as well as other imaging sequences such as proton-density, FLAIR, and T2-weighted images. An example of a T1 post contrast MR image is shown in Figure 1.

Central nervous system (CNS) neoplasms can exhibit a varied appearance. Most of these "enhance" following the administration of MR contrast agent, and only enhancing neoplasms will be included in the scope of this thesis. In such cases, a reduction in the volume of enhancing tissue concomitant with therapy is often regarded as a positive response, and vice versa.

Unfortunately, direct computation of enhancing volume is currently time consuming, labor intensive, and may be imprecise. It requires the manual tracing and segmentation of areas of enhancement typically extending over multiple images. Because of the direct computation of enhancing tissue volume can be impractical for usage in clinical practice, substitute methods are utilized. One such substitute is the method of performing bi-directional measurements wherein long and short-axis enhancing margins are recorded, which is the most commonly used method by radiologists in clinical routines. However, the practice of providing bi-directional measurements for tumor follow-up has significant limitations. First, tumors may possess characteristics that decrease the usefulness of such measurements. For example, some tumors may contain large proportions of cystic or necrotic material with only a relatively small peripheral component of viable enhancing tumor. Bi-directional measurements which include the necrotic or cystic portion may not accurately assess the volume of tumor present.

Furthermore, in order to lessen the mass effect of these neoplasms, necrotic or cystic components may be evacuated surgically. In this situation, the viable portion of the tumor remains unaltered, yet bi-directional measurements change giving a false picture of improvement. Secondly, tumors may be irregular in shape creating ambiguity as to where measurements should be taken and selecting sites for measurement can be subjective. Significantly different measurements may be given for the same tumor by different radiologists. Thirdly, tumors may be multi-focal and the measurement of individual foci can become arbitrary and difficult to report. These factors may decrease the correlation between bi-directional measurements can be tedious, and the necessity of reviewing previous scans in order to understand how the neoplasm was measured in the past is time-consuming for physicians.

Although faster MR scanners with high resolution in all dimensions are being equipped in some hospitals, the images captured in the past cannot be reproduced using the new machines. The low resolution significantly limits the precision of tumor measurement, where large variance between scans from different orientations is known to occur. It may even consequently affect the evaluation of the tumor treatment plan.

Problem Statement

Magnetic Resonance Imaging (MRI), which has become the main imaging modality used for brain tumor assessment, provides an excellent view of the internal structures of the brain in a non-invasive manner. The development of ultra fast acquisition techniques has made the application of MRI in clinical use even more convenient. However, increased image resolution shares a direct trade off with (expensive) image acquisition time. While in-plane resolution of these scans is normally high, distance between slices is often large, rendering low inter-slice resolution. Even when time is not an issue, most scanners are by design incapable of sampling with high resolution in the inter-slice direction. In practice, the inter-slice spacing is commonly 4 to even 16 times of the in-plane spacing.



Figure 1: T1 post-contrast MR image with large enhancing tissue present

Our work is motivated by the observation that current clinical imaging protocols make use of multiple low resolution volumes (LRVs) to measure the size of brain neoplasms as shown in Figure 2. This limits the precision of tumor measurement, where significant variance between scans from different orientations is known to occur. Furthermore, a large inter-slice distance degrades the volume measurement accuracy and it may consequently affect the evaluation of the tumor treatment plan. Our work deals with improving the accuracy of tumor measurement by constructing volumetric MR images with high resolution in each direction from three orthogonal scans known as the axial, sagittal, and coronal orientations. With a high resolution volume (HRV) constructed from the LRVs, tumor measurement can be reported in a much more effective and accurate manner.

Magnetic Resonance (MR) imaging is commonly used to visualize enhancing tissue for diagnosis. Initially, a T1 MR image is captured, then, Gd-DTPA (Gadolinium) contrast is administered to the subject and another T1 image (referred to as the T1E in this paper) is captured to show enhanced tissue. There are many ways in which the brain neoplasms are treated. However, it is difficult to measure the success of any particular method in an objective and consistent way. Accurate and reproducible quantification of these pathologies can greatly assist doctors in treatment planning and evaluating the response to therapy.

After the T1 pre-contrast (T1) image is captured, Gd-DTPA (Gadolinium) contrast is administered to the subject and another T1 image (referred to as the T1E in this paper) is captured to show enhanced tissue. Determination of enhancing tissues requires accurate delineation of tumor boundaries. The pre- and post-contrast T1 MR images are the primary visual cue to assisting radiologists in building a treatment plan. Currently, enhancing tissue is measured using bi-directional (longitudinal and horizontal) measurements taken separately in 2D slices. Doctors use these enhancing tissue measurements in the T1E as an indication to the size



Figure 2: Example of low resolution imaging. Sample slices are extracted from LRVs scanned in the axial view (1st row), sagittal view (2nd row), and coronal view (3rd row). It can be seen that each scan has a high in-plane resolution, but a very low out-of-plane resolution.

of the tumor. It is time-intensive and tedious to manually calculate the volume. It is also common to find large variance among intra- and inter-operator interpretation of tumor delineation, yielding results which are often not reproducible [1]. This can greatly affect the evaluation of treatment plans. Thus, an automated system for quantifying the brain neoplasm volume would allow physicians to better assess the efficacy of treatment and save physicians valuable time.

System Overview

To achieve our goal, there are two main technical challenges to be addressed. One is to improve the measurement accuracy by reducing the influence of the large inter-slice distance in the low resolution scans. The other main challenge is to accurately label the enhancing tissues by differentiating them from normal tissue. In this section, we present a novel multi-resolution algorithm for constructing a HRV from rigidly aligned LRVs of a single patient. The LRVs are first compactly represented by using Laplacian pyramids, which are fused after expanding the Laplacian images at each level to the same size as the other Laplacians at that level.

A Gaussian pyramid is then recovered from the fused Laplacian pyramid and the volume obtained at the bottom level is the constructed HRV. The multi-resolution pyramid structure separates different frequency components at each level of the pyramid. In this way, the combination of different LRVs is carried out in coarse-to-fine fashion which deals with the challenges of large inter-slice spacing. The proposed method is applied to facilitate improved consistency and accuracy in tumor measurement.

After constructing the HRV, a new probabilistic framework is proposed to automatically determine the true enhancing tissue by considering the anatomical knowledge from an aligned probabilistic brain atlas and the prior distribution of tumor in the brain. The false enhancing tissues can be successfully removed and the true enhancing regions are then correctly measured. We validate the method by using both simulated and real clinical brain MR images containing enhanced tumor.

In the proposed framework, identification of enhancing tissue from MR brain images is a key operation, which is a very challenging task due to two factors. One is that the intensity representation of the data may not allow a clear delimitation of the different tissue types present in an MRI, because of partial volume effect, image noise and intensity non-uniformities caused by magnetic field inhomogeneities. The other more important factor is that besides the enhancing tissue to be assessed, some other normal tissues will also be enhanced due to the administration of Gd-DTPA. This means that the enhancing tissue cannot be identified using only the image information. These difficult problems will be solved in the proposed framework using novel computer vision techniques.

Organization of the Thesis

This section describes the layout and organization of the thesis. In chapter two, a review of related literature is presented to show recent works in volume reconstruction and tumor measurement methods. Chapter three explains a framework for reconstructing a high resolution volume from multiple orthogonal low resolution views. Then, in chapter four, a new knowledge based tumor measurement system is presented. Finally, in chapter five, a summary of the contributions in this thesis are discussed including a section on future work.

CHAPTER TWO: LITERATURE REVIEW

With the advent of computer technology and recent advances in computer vision, researchers have been able to achieve considerable progress in Medical Image applications. In this chapter, a literature review of related work is presented. Previous works in volume reconstruction are presented in the next section, followed by a discussion on past and current tumor measurement methods.

Volume Reconstruction

Only a few works have been reported on the reconstruction of a HRV from multiple LRVs. Tamez-Pena et al. [9] studied the problem of MRI isotropic resolution reconstruction from two orthogonal scans. In their work, two LRVs are rigidly aligned first, and then a HRV is interpolated from them.

Recently, Rousseau et al. [10] and Jiang et al. [11] achieved high resolution fetal brain MRI imaging by interpolating non-rigidly aligned LRVs. However, these works have only addressed the cases where the ratio of in-plane to inter-slice spacing was small. But in practice, much larger spacing is often found in clinical routines. A large inter-slice distance may cause interpolation techniques to fail and the constructed image could be significantly blurred with visible artifacts introduced.

Tumor Measurement Methods

Previous efforts for brain tumor measurement have taken many forms, but have remained largely experimental work. In [18] and [19] for example, fuzzy rules were applied to make initial classification decisions, and then clustering was used to classify the remaining pixels. Liu et al. [4] proposed to register the T1E and T1 images to reveal the enhancing regions by finding their differences. However, they have difficulty in distinguishing false positives from true enhancing tissues, since some normal tissues, such as the choroid plexus and superior sagittal sinus regions, are often enhanced by the administration of Gd-DTPA. Besides using local image information, incorporation of a priori knowledge has been proven to be able to make more intelligent and robust classification and segmentation systems.

More explicit knowledge has been used in the form of frames [20] or tissue models as in [21] and [22]. Clark et al. [2], for example, developed a system by combining knowledge based techniques and multispectral analysis (in the form of unsupervised fuzzy clustering) to extract tumor from transaxial MR images over a period of time during which the tumor is treated. However, the system only processes 2D slices, which does not exploit the benefits of 3D imaging. In addition, the expert knowledge used in the system is limited to the image contrast of tumor. However, the labeling may not be precise since other parts of the image, such as the choroid plexus and dura mater, can be found in the same intensity range, making them indistinguishable. Additionally, when MR images are scanned, several parameters can affect the intensities of tissues, which may produce different intensities for the same tissue and make it difficult to specify a tissue using an exact intensity value. Other knowledge like global position within the brain and position relative to neighboring brain structures is not considered in the system. To further exploit a priori knowledge, atlas-based segmentation techniques have been developed.

Due to the relatively invariant structures in the brain, an atlas can be constructed for the whole brain. In the atlas based methods, segmentation of the image is converted to performing a non-rigid registration of the image to a labeled atlas. The image is segmented by the labels associated with the atlas mapped according to the resulting non-rigid transformation [32]. Together with local image feature based segmentation methods, atlas based segmentation techniques have been used for automated segmentation of brain tumor. Kikinis et al. [15,30,31] developed a system for automatic brain tumor segmentation by iteratively assigning labels to tissue types using statistical classification and registering a digital anatomic atlas to the patient data. A pre-segmented image is used in their work as the atlas. However, these simple atlases may not be able to deal with the variance between different subjects and the accuracy of segmentation could be affected.

The advanced use of spatial information to aid in classification is facilitated by the construction of the probabilistic atlas [3,28,29]. In this type of atlas, information regarding the statistical properties of anatomical structures is stored in a space in which coordinates have anatomical meaning as opposed to the somewhat arbitrary coordinates in a raw image, which are dependent on the position, orientation, and shape of a subject's head in the MR scanner. Bullitt and Gerig et al. [3,26,27] applied a probabilistic atlas to brain tumor segmentation. Their method relies on the information provided by the (non-enhancing) T1 and T2 image channels, the use of a registered probabilistic brain atlas as a spatial prior, and the use of shape prior. Besides the tumor, edema can also be extracted using their method. However, the use of a probabilistic atlas built from brains of healthy people [7] may lead to underestimation of the volume of tumor in that the deformation caused by presence of tumor is not encoded in the atlas and some part of the

tumor might be mislabeled as normal brain structures. The samples of normal tissues are first obtained by finding regions with high probability above a certain confidence level. Statistical properties of the normal tissues are then computed using these samples to detect tumors. However, tumor tissue and edema could be included in the drawn samples, which may cause the algorithm to fail. Furthermore, the approach is based on the assumption that all of the normal tissues can be represented using the obtained samples, which may not always be the case.

Efforts have been made to model the deformation of atlases caused by the presence of large space-occupying tumors. Besides the work of Prastawa et al. [23], Cuadra et al. [24] proposed a method for atlas-based segmentation of pathological MR brain images using a model of lesion growth. The brain atlas deformation is compensated based on a priori model of lesion growth that assumes radial expansion of the lesion from its starting point. The common steps of these algorithms can be described as such: First, an affine registration brings the atlas and the patient into global correspondences. The pose and scale difference is handled in this step. Then, a synthetic tumor is put into the brain atlas, which provides a template for the lesion. The last step is the non-deformation of the seeded atlas. Some methods have been developed for modeling the non-rigid deformation of atlas with the presence of tumor [23-25]. After the deformation compensation, the accuracy of segmentation should be improved.

However, several difficulties exist in this kind of deformed atlas based tumor segmentation system. In order to compute the deformation of brain atlas, an estimate or presegmentation of the tumor (and edema) is needed, which makes automatic segmentation an extremely challenging task. The difficulty might be solved by iterating the tumor segmentation and atlas deformation process but it is very inefficient. In addition, the non-rigid deformation of brain atlas is highly computationally complex with a lot of parameters to be well tuned. It is necessary for the whole brain to be segmented in order to precisely extract the tumor. Another major difficulty that would prohibit this kind of method from being used in clinical practice is that those methods can only handle single tumor cases. For multi-foci tumor patient cases, which are often observed, the deformation of atlas caused by presence of tumor becomes intractable to model and compute.

To deal with the above mentioned problems, in this paper, we propose a new framework to quantify enhancing brain tissue by utilizing T1 and T1E MR image characteristics combined with prior medical knowledge. Our method follows from the fact that radiologists determine the enhancing tissue by analyzing both T1 and T1E images and by applying their expert medical knowledge at the same time. The brain atlas is used to remove false enhancing in the ventricles and in other regions, such as the dura sinus, where tumor is not normally found. Here, a system to automatically measure the positive enhancements is presented and validated. In the following chapter, a novel method for high resolution volume construction is presented to increase the accuracy of tumor measurement.

CHAPTER THREE: IMPROVING ANISOTROPIC RESOLUTION

Low resolution imagery is a common limitation in clinical practice as described in the previous chapters. In the following sections, a novel method for improving low resolution MR images is presented. After a registration phase, a multi-resolution pyramid structure is implemented to separate the different frequency components of the image at each level of the pyramid. In this way, the combination of different LRVs is carried out in coarse-to-fine fashion which deals with the challenges of large inter-slice spacing. Thus, the proposed method facilitates improved consistency and accuracy in measurement of enhanced tissue.

Registration

To effectively utilize the information contained in each low resolution scan, the LRVs are fused to produce a single HRV. In order to combine the LRVs for constructing HRV, orthogonal MRI scans are first registered so that corresponding locations in each volume may be correctly aligned. We first align the three LRVs using a two-pass registration algorithm. Then the registered volumes are fused with a new pyramid reconstruction algorithm. We start with the acquisition of a three orthogonal 3D MR volume set from a single subject. Before the images can be merged, they must be registered so they can share the same coordinate space. Registration is an important step to align the orthogonal MRI scans so that corresponding locations in each volume can share the same coordinate space.

A lot of research has been done in the area of medical image registration as described in [12]. Due to the low resolution, however, it is not trivial to register the orthogonally scanned volumes. We thus propose a two-pass strategy to align the LRVs. In the first pass, initial

registration is obtained by selecting one of the views (axial view selected in our work) as the reference and registering the other two low resolution volumes to it. After registration, a HRV is constructed using the proposed construction method, which will be presented in the following section. In the second pass, all of the three LRVs are registered to the constructed HRV to achieve a more accurate registration. Finally, the HRV is constructed again from the aligned LRVs by using our multi-resolution construction method.

In our work, brain MR images are investigated. So it is reasonable to assume there should not be deformations between the LRVs of a single subject under the same machine. However, a small amount of translation and rotation can be expected due to involuntary motion from the patient. Thus, a rigid transformation based registration is well suited to correct these differences. The images are aligned when the mutual information between the images is maximized, which can be achieved by adjusting the transformation parameters iteratively along the gradient ascent direction of the error metric. The registration method was implemented using the Insight ToolKit (ITK) [13].

Since a change in contrast between the views is quite possible, contrast adjustment is applied before the construction phase. Again, one of the views is selected as the reference view and the contrast of the other two views are adjusted by minimizing the mean square error at the intersection points.



Figure 3: Laplacian pyramids are computed for axial, sagittal, and coronal views (from left to right). The top level images in the three views have the same size and can be combined directly.



Figure 4: Fusing the Laplacian images at each level and computing the fused Gaussian pyramid from the fused Laplacian pyramid.

Fusion and Gaussian Pyramids



Figure 5: (a) A slice from the simulated input LRV in the axial view. Slices from the HRVs constructed using (b) Gaussian interpolation and (c) the proposed multi-resolution construction, respectively. (d) Slice from the ground truth.



Figure 6: 2 dimensional visualization of the spacing between known data points

Due to the large out-of-plane distance, constructing a HRV using interpolation techniques can lead to low quality images. Figure 5(b) shows a slice of the reconstructed volume using Gaussian kernel based interpolation, which is significantly blurred as compared to the ground truth. The problem is caused by the large inter-slice distance in the LRVs, which is illustrated in 2D as shown in Figure 6. The known in-plane high resolution columns and rows from two orthogonal scans are displayed in blue and red colors, respectively. The intensity values of the pixels inside the region need to be interpolated using the known red and blue pixels intensities. For example, the intensity of pixel p can be obtained by linear combination of the values of the four known pixels as shown in Figure 6 where the intensities of pixels far away from the high resolution planes are difficult to interpolate. Thus, results from direct interpolation are usually not good. If more known pixels are involved in the interpolation, the reconstructed image may become over-smoothed and blurred. More sophisticated techniques, like spline or kernel based interpolation, can be applied, but these methods have the similar difficulties. The result shown in Figure 5(b) is obtained by using the Gaussian interpolation, which is significantly blurred.

To deal with this problem, a new multi-resolution algorithm using pyramid structure is proposed in this paper. The main idea is to reduce the number of unknown pixels at each level so the pixel intensities can be easily computed. By using the pyramid structure, this is nicely handled without explicitly selecting any neighborhood. The proposed structure is presented the next section.

Multi-Resolution Construction

Recall that each LRV has an axis along which the resolution is much lower than in the plane perpendicular to that axis. This large inter-slice distance is problematic for direct intensity interpolation schemes. Instead of constructing the HRV in one step, we propose a multiresolution method to increase the resolution of the volume gradually by fusing the LRVs at different levels of the pyramid until the required resolution is achieved. A Gaussian pyramid for each LRV is first computed [14], which consists of set of volumes { $G_l \mid l = 0, 1, ..., n-1$ }, where G_0 is the original volume and

$$G_{l} = REDUCE(G_{l-1}). \tag{1}$$

The *REDUCE* operation is defined as Gaussian filtering followed by down-sampling by a factor of 2. At each level, however, we only apply a 2*D REDUCE* operation to each high resolution plane until the volumes at the top level of all the Gaussian pyramids have the same dimensions as shown in Figure 3. With the Gaussian pyramid, a Laplacian pyramid can be easily computed by subtracting the expanded higher level Gaussian image from the current level image,

$$L_{l} = G_{l} - EXPAND(G_{l+1}) \quad and \quad L_{n} = G_{n}.$$
(2)

The operation *EXPAND* is defined as up-sampling the image by a factor of 2 followed by Gaussian filtering in 2D. The top level Gaussian image and the Laplacian pyramid are saved. A Laplacian pyramid essentially consists of multiple edge-like copies of original image with different levels of blurring. At the top level of Laplacian pyramid, each LRV is reduced to an isotropic volume, where each dimension has the same low resolution as shown in the top left side of Figure 3. This produces a 3D Gaussian pyramid for each LRV. At the same time, a 3D Laplacian pyramid is also computed for each LRV by applying the operation.

The Laplacian pyramids are fused separately by taking average at each level as shown in Figure 4. Since the Laplacian images at lower levels in each pyramid have different sizes, a 1*D EXPAND* operation is used to expand these images along the low resolution axis, so that all the Laplacian images from the same level will have equal size. With the fused Laplacian pyramid, we can easily compute the fused Gaussian pyramid according to

$$G_{l} = L_{l} + EXPAND(G_{l+1}) \quad and \quad G_{n} = L_{n}.$$
(3)

At this point, the LRVs can be easily fused by taking their average at each voxel. The fused volume is expanded using the *3D EXPAND* operation, where the size of each dimension is doubled as shown in the right side of Figure 4. The higher resolution Gaussian image is then obtained by adding the Laplacian image back into the expanded image as in (3).

The image obtained at the bottom level of the Gaussian pyramid is the final constructed HRV, which is obtained by combining the three orthogonal scans through all the levels. The proposed new multi-resolution construction method provides a natural way to fuse the LRVs at different levels. There is no explicit interpolation needed. Thus, it effectively solves the difficulty of the direct interpolation based methods as we mentioned earlier.

Summary of the Reconstruction Algorithm

The proposed multi-resolution construction algorithm is summarized in the figure below:

ALGORITHM: Reconstruction of High Resolution Volume

INPUT: Three LRVs scanned orthogonally in the axial, sagittal, and coronal orientations.

- Align the LRVs using rigid registration.

- Adjust image contrast of the aligned LRVs.

- Compute Gaussian and Laplacian pyramids of the LRVs using (1) and (2).

- Fuse the top level Laplacian images by taking the average.

WHILE{The bottom level of the pyramids is not achieved} DO

- Move down to next level of the pyramids.

- Expand the reconstructed Gaussian image from previous level in 3D to the current level.
- Expand the Laplacian images along the low resolution axis so that they have the same

size and combine them by taking the average.

- Fuse the Laplacian images by taking average.
- Compute the Gaussian image at this level of the Gaussian pyramid using (3).

ENDWHILE

OUTPUT: The constructed HRV (Bottom level image of the Gaussian pyramid).

Figure 7: Reconstruction algorithm.

Volume Measurement

The reason why the proposed method is able to solve the problem caused by large interslice distance and outperforms other direct interpolation based methods can be two-fold. Firstly, the image information fusion is done at multiple levels in a coarse-to-fine fashion. In the proposed approach, image resolution becomes higher and higher from top to bottom levels in the pyramid, but the Gaussian filter remains the same. The effect is equivalent to varying filter bandwidth without changing the image resolution. At a higher level, the Gaussian filter has larger bandwidth, while it decreases as we move down to a lower level. So, the bandwidth is adaptively changing during the construction process. In addition, the step-by-step expansion makes the reconstruction continuous and smooth, which prevents interpolation artifacts from occurring.

Secondly, the Laplacian pyramid used in our method can be viewed as the output of a set of band pass filters applied to the original image. Thus, LRVs are in fact decomposed into multiple frequency components and fused separately at each level. Adding these fused Laplacian images into the expanded volumes for recovering Gaussian pyramid can enhance the image sharpness. So, our method is able to get better results. This is not the case in other direct interpolation based methods where parameters must be explicitly set. Therefore, although Gaussian filtering is used in the *EXPAND* operation of computing the pyramids, our method is quite different from the Gaussian kernel based interpolation.

Results

In this section, we first validate the method by using artificially created low resolution data from high resolution volumes. Then, we demonstrate an application on real clinical brain MR images containing tumor.



Figure 8: (a) The plot of PSNR values of the constructed HRVs using direct Gaussian interpolation and our multi-resolution method against the ground truth. (b) Tumor volume difference to the ground truth for the constructed HRVs (blue) and the LRVs in each view.



Figure 9: HRV construction results using (1st Row) cubic spline interpolation and (2nd row) the proposed multi-resolution method for real clinical data shown. The slices were selected far from the high resolution planes in the original LRVs.

Simulated Data Sets

The proposed method was first validated using simulated data. Ten sets of MR volumes containing brain tumors were used in the validation [15]. The dimensions of each volume are 256x256x124 with voxel size of 0.9375x0.9375x1.5mm³. LRVs were extracted from the high resolution data in the axial, sagittal, and coronal orientations. In each view, the high resolution planes are not altered, but the out-of-plane resolution is decreased by a factor of 4, i.e., a high resolution plane is sampled every four slices from the original high resolution volume. To simulate real data, the sampled volumes are also randomly rotated 5 to 15 degrees along each axis similar to what may be found in practice.

We first evaluate the quality of the reconstructed HRV by comparing it against the ground truth (the original high resolution volume). The peak signal-to-noise ratio (PSNR) is used for quality assessment. For comparison, we also include a HRV obtained by using direct Gaussian interpolation from the three LRVs in our evaluation. The validation results are shown in Figure 8(a). It can be seen that the HRVs reconstructed using the proposed approach have very high PSNR values and these values are much higher than those of the direct interpolation approach.

One of the main motivations of our work is to improve the measurement precision of brain tumors, so the validation is also conducted on tumor measurement. For objectivity and consistency, the measurement was performed by using a user-guided segmentation tool implemented in ITK-SNAP [16] with parameter values and initialization fixed equally for all images. Figure 8(b) shows the differences between the ground truth and the tumor measurement results of the constructed HRV as well as the three LRVs. In most cases, the measurement based on the constructed HRVs is very close to the ground truth. More over, it is clear that the measurement based on the LRVs has large variance, which results in ambiguity for tumor assessment and diagnosis.

Application to Clinical Data

Our method was also tested on 8 clinical MRI datasets, where each LRV consists of 30 high resolution planes with 512x512 pixels. The in-plane resolution is 0.45×0.45 mm², while the ratio between in-plane and inter-plane spacing is very large (1:16). Other interpolation algorithms perform very poorly on these datasets. For example, cubic spline was used and the results are shown in the first row of Figure 9. It can be seen that the images are very blurring

with obvious artifacts. However, we are able to construct HRVs with much higher quality using the proposed multi-resolution method. Sample slices from our constructed HRV are shown in the second row of Figure 9. The large inter-slice distance results in some blurring because so much information has been lost during the imaging sampling process. Compared to the original LRVs shown in Figure 5, radiologists confirm that the reconstructed HRVs provide a more accurate and consistent way for measuring tumor tissue size. In the following chapter, a novel approach for knowledge based measurement of enhancing tissue is described.

CHAPTER FOUR: KNOWLEDGE BASED MEASUREMENT

In the previous chapter, we described a method for the construction of a HRV from orthogonal low resolution volumes. Here, we present a novel framework for the quantification of enhancing tissue volume in brain MR scans. A registration and segmentation phase is given, followed by a section which describes a new knowledge based decision method based on a probabilistic model. Finally, results for multiple cases are presented and analyzed.



Registration of Pre- and Post-Contrast MR Images

Figure 10: Example of registration before and after

The proposed scheme begins with processing the acquired T1 and T1E 3D MR volume sets from a single subject. All of the enhancing regions are detected by comparing the T1 and T1E images. The two image channels are aligned to each other and segmentation is performed on the T1E channel. The mean shift segmentation algorithm [6] is used to divide the image into small regions according to local intensity distribution.

Using the regions created by the T1E segmentation, the mean intensity difference of each region is compared between the T1E and T1 images. Regions with the low differences are discarded and only enhanced regions remain. Registration is necessary to align the T1 and T1E MR images so that corresponding locations in each image can be directly compared. Explanatory reviews of medical image registration are presented in [1] and [17].

A small amount of translation, rotation, and shear are possible between the two scans of a subject, because they are captured at different times. Thus, an affine transformation based registration is well suited to correct these differences. A distance metric which utilizes a mutual information based scheme by [5] is used. The combination of these two has been shown to have high robustness in multi-modality image registration. The images are well aligned when the mutual information between the images is maximized, which can be achieved by adjusting the transformation parameters iteratively along the gradient ascent direction. Thus, the transformation parameter, α^* , is determined by,

$$\alpha^* = \arg \max_{\alpha} I(\alpha) \,. \tag{4}$$

The mutual information $I(\alpha)$ is estimated as,

$$I(\alpha) = \sum_{f,r} p(f,r) \log_2 \frac{p(f,r)}{p(f)p(r)},$$
(5)

where f and r are the intensities of the floating image F and the reference image R, respectively. An example of the registration of pre- and post-contrast MR slices is shown in Figure 10.

Segmentation of Brain MR Images



Figure 11: Example of mean shift segmentation and initial detection of enhancing regions.

Segmentation of images has been widely exploited in many problems, but is still an active area of research [2,4,6]. In our work, we note that the tumor is often arbitrarily shaped so no assumptions are made about its form. The segmentation method used for automatic tumor delineation should respond well to arbitrary shapes and accurately separate the regions. The non-parametric mean shift segmentation method [6] was used in our system and the results are shown in the middle of the figure above.

Mean shift estimates the density gradient in a search window of bandwidth h and iteratively shifts toward the maximum increase in the density gradient. This process is repeated for an arbitrary set of points and the end points for each (modes) define the clusters for which remaining pixels are assigned to. The main parameter for the mean shift segmentation is the search bandwidth. Optimal bandwidth selection for the mean shift procedure is based on the method described in [6]. The estimate of the pdf is given by,

$$\hat{f}_{k(x)} = \frac{1}{n_x h^d} \sum_{x_i \in S_{h(x)}} k(x_i - x),$$
(6)

then, differentiating the pdf estimate, we find,

$$\nabla f_{k(x)}^{'} = \frac{1}{n_x h^d} \sum_{x_i \in S_{h(x)}} (x_i - x) k'(x_i - x) , \qquad (7)$$

where K is the uniform kernel. From here we can find the mean shift vector given by,

$$M_{h} = \frac{1}{n_{x}} \sum_{x_{i} \in S_{h(x)}} (x_{i} - x), \qquad (8)$$

where n_x is the number of samples in S with bandwidth h.

Determination Enhancing Tissue

After image segmentation, the mean of each region from the T1E image is compared to the T1 image (see Figure 11). This process reveals the regions which are brighter (enhanced) in the T1E, but not in the T1. Note that in the posterior right side of Figure 11 right, a cyst that was bright in both the T1 and T1E is correctly marked as non-enhancing tissue. If only the intensity values were used in the T1E, the cyst as well as other regions would be indistinguishable from the enhancing tissue.

A threshold learned by prior training on previous subjects is used to eliminate nonenhancing regions and the enhancing regions are detected. However, this does not fully isolate true enhancement from other non-tumor enhancements as we can see in Figure 11 right. A robust post-processing method subsequent to the segmentation is necessary to achieve accurate results.

Expert Anatomical Knowledge



Figure 12: Probabilistic Brain Atlas from the International Consortium for Brain Mapping (ICBM). (left) The single subject T1 template, (middle) the corresponding CSF, and (right) non-CSF probability map.

It is commonly observed that not only the tumor, but other tissues can be enhanced by the administration of Gd-DTPA, as shown in Figure 11 right. In the ventricles, for example, there will normally be enhancing due to the choroid plexus that should not be included in tumor labeling. In fact, several other parts of the brain included in the cerebral spinal fluid (CSF) are often enhanced by the contrast, such as the superior sagittal sinus region where blood can become enhanced. Also contained within the CSF, the vertical linear region in the middle of axial slices, i.e. the falx cerebri, can also become enhanced.

These negative detections cannot be excluded from the detection results using only the intensity information from the MR images. When viewing the T1 and T1E MR images, however, radiologists are able to interpret whether true enhancing tissue exists by utilizing their expert knowledge concomitant with the intensity information of the images. The expert knowledge consists of two parts, the anatomical knowledge of the brain structures and the prior knowledge of distribution probability of tumor in the brain. In other words, the expert knowledge can help to

answer two questions: What is the anatomical structure? And, what is the likelihood of observing enhancing tissue in this structure?

In order to remove the false enhancement from the initial detection results, we propose a new knowledge based method. The anatomical knowledge used in our method is modeled through a probabilistic brain atlas. By aligning the atlas to the subject, the tissue type at each location in the subject's brain can be predicted as shown in Figure 12. The prior knowledge of observing tumor in a specific structure is also given in a probabilistic form, obtained from radiologist's summaries of hundreds of cases.

Probabilistic Model

The probability that a pixel belongs to true enhancing tissue is given by $p(e_s = true)$, which can be simplified to say $p(e_s)$, where s is the pixel location in the region S. Using the prior knowledge, the probability $p(e_s)$ can be computed as a marginal probability distribution. For convenience, we start by computing the probability that a pixel (or voxel) corresponds to enhancing tissue, determined by,

$$p(e_s) = \sum_{t \in T} p(e_s \mid t_s) p(t_s), \qquad (9)$$

where t_s is the tissue type at location s. The anatomical structure information $p(t_s)$ is provided by the atlas, and $p(e_s | t_s)$ is the likelihood of observing enhancing tissue inside the tissue type t_s . In our work, three tissue types are obtained from the atlas, which includes CSF, gray matter, and white matter. Since the gray matter and white matter have similar likelihoods, they are combined and denoted as \overline{CSF} . So the tissue type set T is defined as $\{CSF, \overline{CSF}\}$ and we have,

$$p(e_s) = p(e_s \mid t_s = CSF) p(t_s = CSF) + p(e_s \mid t_s = \overline{CSF}) p(t_s = \overline{CSF}),$$
(10)

where non-CSF regions have low probability to be CSF.

Since our probabilistic decision method is applied to the image after region segmentation, the mean probability of each enhanced region is used to determine whether the region is true enhancing tissue. This approach has two advantages. Firstly, using the segmented regions instead of independent pixels makes the method much less sensitive to small registration errors. Secondly, it helps preserve regions where voxels of the tumor are close to or protruding into high probability CSF regions.

For a specified possibly enhancing tissue region $E_s = \{e_s \mid s \in S\}$, where S denotes the set of all the voxels in the region,

$$p(E_{s}) = \sum_{s \in S} p(e_{s}) = \sum_{s \in S} \sum_{t \in T} p(e_{s} \mid t_{s}) p(t_{s}).$$
(11)

The probabilistic brain atlas provided by ICBM [7] was used in our work. The averages of 452 subject's T1-weighted scans were combined to produce a probabilistic value for each tissue type to occur at each voxel. In order for the atlas probabilities to be applied to the subject data, the atlas must be registered to the subject data. A T1 template previously aligned to the atlas is provided together with the atlas. Thus, the atlas can be aligned with the subject's image by registering the template image.

The subject's pre-contrast T1 image is used in registration to prevent errors in the system due to the enhancements of the T1E image. Since a global transformation will not provide an accurate registration to the subject due to the deformation that the tumor and edema may have caused, a non-rigid registration procedure based on a level sets framework [8] is used to bring the image of the subject and the brain atlas into local alignment (see Figure 13 middle). The likelihoods of observing enhancing tissue in *CSF* and \overline{CSF} are set to 0.05 and 0.95, respectively. It was discovered through experiments that the likelihood parameters were not sensitive to their values and varying them by ± 0.03 did not have distinguishable effects.

<u>Results</u>



Figure 13: (left) Initial detection of enhanced regions shown in red. (middle) The T1 template associated with the atlas non-rigidly registered to the subject image. (right). The final detected enhancing tissue determined using our knowledge-based method.

Our method was tested on MR images consisting of 512 x 512 pixels with pixel spacing 0.45×0.45 mm² data with a field of view of 23.0cm² at a resolution of a 320 x 224 and was reconstructed as 512 x 512 pixel images. Slices in the volume had thickness between 4.0-5.0mm

Table 1: Enhancing tissue val	idation for 7 experiments	using the ground truth	provided by radiologists.
U	1	0 0	

Patient ID	1	2	3	4	5	6	7
Precision	96.70%	92.11%	91.74%	98.22%	91.41%	89.46%	96.50%
False Negative	3.31%	7.89%	8.26%	1.78%	8.59%	10.54%	3.50%
False Positive	6.82%	4.46%	8.07%	6.15%	2.09%	4.91%	8.26%



Figure 14: (left) The post-contrast T1E slice, (middle) initial detection of enhancing tissue with dura falx wrongly included (near the bottom of the image), (right) and after atlas is applied, the false enhancement is removed.

and 2.0-2.5mm inter-plane spacing. Software was developed in the open source form based in part on the National Library of Medicine Insight Toolkit (ITK) [13]. Validation is presented using standard performance metrics. For validation, the enhancing tissue labeling results were compared to the ground truth which was manually calculated by radiologists. Percentage of overlapping, false positive rate, and false negative rate are computed.

Figure 14 demonstrates the ability of the atlas to assist in removing false enhancement. Note in Figure 15 how the enhancing tissue region near the border of the CSF region is not



eliminated because the regions are measured for their enhancement as opposed to a pixel by

Figure 15: The results of the enhancing tissue labeling in consecutive MR slices in the axial view. Row 1 shows three consecutive T1 slices. Row 2 shows initial detection of enhancing tissue in the corresponding T1E images. Row 3 shows the final labeling of enhancing tissue after applying a knowledge-based decision.

pixel comparison. The atlas has a skull stripped version to improve registration and a mask is created from the subject's brain to remove extra-cranial regions from the results. Due to the large inter-slice spacing commonly used in practice, we found no advantage in using 3D segmentation. In fact, processing time can be reduced significantly by segmenting in the 2D plane without a reduction in accuracy. However, our method can be directly extended to 3D for segmenting higher resolution cases.

The quantitative validation results of the volumetric analysis are shown in Table 1. *Precision* is computed as the number of pixels (or voxels) in the labeled tumor that overlaps with the ground truth divided by the size of ground truth. *False positive* includes the percentage of labeled pixels which were incorrectly marked as tumor. *False negative* is defined as the percentage of pixels not labeled, but present in the ground truth. Overall, it can be seen that the system slightly underestimated the size of the tumor consistently, but the percentage of overlapping is very high. Particularly, when used for evaluating tumor treatment plan, the proposed automatic measurement method can provide objective and consistent information for doctors to make decision.

CHAPTER FIVE: CONCLUSIONS AND FUTURE WORK

<u>Summary</u>

In this thesis we presented a synergistic system composed of two main functions. Firstly, we presented a novel method to enhance image resolution by using a multi-resolution pyramid structure to combine orthogonally scanned LRVs. Different frequency components are separated at each level of the pyramid and fused separately. Combination of different LRVs in this coarse-to-fine fashion solves the problem caused by large inter-slice spacing. The proposed method is applied to improving consistency and accuracy of tumor measurement. We validate the method by using both simulated and clinical brain MR images containing tumor and promising experimental results have been demonstrated. The proposed method provides doctors a better way to accurately determine tumor size and they could benefit immediately from this work.

In the second portion of this thesis we presented a new knowledge based framework to determine enhancing brain tissue volume. While most previous methods require manual removal of non-tumor segmentations and would fail to provide reliable results where false enhancement exists, our method provides an automatic and consistent way to measure enhancing brain tissue by utilizing the knowledge of anatomical structures and prior distribution of tumor. Radiologists currently rely on crude bi-directional measurements that can not accurately detect changes in size of tumor due to the irregular shape of brain tumors. Our method measures the enhancing tissue in both T1 and T1E MR images and has been validated using several data sets with excellent results. Using this method, tumor volume can be measured over time to assess the efficacy of treatment and assist in treatment planning.

Future Work

In our future work, we will investigate extending the proposed method to measure the volume of edema surrounding the tumor. In spite of the previous works discussed, a widely accepted enhancing tissue volume tracking system has not been implemented, and could provide immediate clinical assistance to the medical field.

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