STATISTICAL ASYMMETRY-BASED AUTOMATIC BRAIN TUMOR DETECTION FROM 3D MR IMAGES

A Thesis in
Computer Science
by
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Abstract

The detection and accurate segmentation of brain tumors from MR images is an important and necessary step for early diagnosis, optimized treatment, surgical planning, and follow-up assessment. However, it is a tedious and error prone task for the medical professionals to process manually. The performance of existing supervised machine learning techniques for automatic tumor segmentation is time consuming and largely dependent on the type and training samples. Brain tumors are mostly asymmetrical blobs with respect to the mid-sagittal plane (MSP) in the brain, we propose a novel 2D slice asymmetry-based, fast, fully-automatic, and unsupervised framework for brain tumor detection and segmentation from volumetric MR images. This approach detects asymmetrical intensity deviation of brain tissues in 4 stages: (1) automatic MSP extraction, (2) asymmetrical 2D slice extraction for an estimated tumor location, (3) region of interest localization, and (4) 3D tumor volume delineation using a watershed method. The method has been validated on 10 Harvard tumorbase cases with a $67.66\% \pm 7.20\%$ mean Jaccard Coefficient, and an average end-to-end run time of 3.5 minutes per 3D scan.

Furthermore, multiple and small-sized tumors, which are good indicators for potential metastasis or early stage tumor, present substantial challenges to both human and the state of the art automatic brain tumor detection algorithms, that have been overlooked in practice. Thus, we improve our computational framework to solve this challenging problem. The central contributions of our work include (1) a feasible formulation of a 3D blob extraction algorithm directly from volumetric images; (2) an asymmetry-based abnormality detection algorithm for human brain anatomy; and (3) a Bayesian formulation to asymmetry 3D blob analysis by formulating multiple cues as priors and likelihood probabilities. This improved method is validated for brain tumor detection on 20 clinical 3D MR scans from the Hershey dataset with tumors (1 to as many as 15 tumors per 3D scan) of size
3 mm$^3$ to 28079 mm$^3$ in volume. In addition, 5 normal clinical 3D MR scans are evaluated quantitatively to demonstrate that our approach also has the potential for normal/suspicious patient classification. The results show a 87.84 to 95.30% detection rate and an average end-to-end run time of 4 minutes per 3D scan. The goal of this thesis work is to assist medical professionals in automatically evaluating patients’ brain MRI scans that is accurate, robust, and convenient.
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Introduction

Brain tumors vary in size, shape, color, and location (Figure 1.1), which is precisely the reason why automatic tumor segmentation is challenging. While medical professionals are able to hand label the optimal details of each tumor case, this task is incredibly tedious and time-consuming. Therefore, the need for tumors to be automatically detected and segmented remains an unsolved problem in clinical practice.

Detecting small-sized tumors is crucial for early diagnosis and optimized treatment, whereas accurately spotting multiple tumors of varying sizes has different clinical applications. Metastatic brain tumors originating from elsewhere is more than four times as likely to occur than primary brain tumors [1], and the presence of multiple brain tumors implies metastasis. Radiotherapy and chemotherapy with different protocol agents are the choice of treatment in general, while surgery is usually not considered [8]. However, to assess the effectiveness of the treatment for each patient, clinicians must manually search for and measure the presence of multiple tumors from the sequential follow-up scans, comparing volume change of the tumors and looking for possible newly grown masses. Such task becomes increasing tedious for patients with a large number of tumors. Therefore, being able to detect multiple tumors of varying sizes automatically assists in monitoring of patient’s response to treatments.
Figure 1.1. Brain tumors of varying location, size, and shape.
1.1 Related Work

In recent years, there has been brain tumor detection methods that are based on analyzing brain asymmetry [13][38][34][41][3]. Other related unsupervised approaches that utilize brain asymmetry [35] [14] require human interaction to manually select a 2D slice of interest, and the 2D/3D tumor segmentation from such analysis has not been shown to work fully automatically.

Markov Random Fields [24] and Conditional Random Field [20] based machine learning techniques have been applied in tumor segmentation tasks as well. Methods like Discriminative Random Fields [19], Support Vector Random Fields [21], and Pseudo-Conditional Random Field [22] have been shown to offer better performance. Other supervised statistical machine learning approaches include using fractal features [11], alignment features [39], one-class support vector machines [45], Bayesian classifiers [7], tumor localization using diagonal nearest-neighbors [9], segmentation by outliers [31], and high-dimensional features with level-sets [4].

In order to extract features to be used for pixel/voxel classification, standard machine learning methods must first register the input volume. The registration process usually takes hours of time while being a research area of its own [18]. The performance accuracy of the classification and segmentation result depends largely on the training samples and the pre-defined feature sets.

Supervised classification methods for tumor segmentation makes up the majority of recent related work [6][4][9][22][31][21], where a set of training data with multiple modalities (T1, T2, Flair) are used to train a classifier, and the classifier is then evaluated on the test cases to classify voxels [33][16] or regions [6][4] for the tumor class. Different classifiers, learning rules, features, and post-processing demonstrate varying accuracies in automatically segmenting brain tumors. The performance on small (early stage) or multiple tumors (metastasis) have yet to be evaluated qualitatively and quantitatively. Moreover, supervised methods require excessive computation time for both training and inferencing. A detailed comparison of prior work from [6] shows that the total running time can be hours at most 10 or fewer 3D images for evaluation.

Unsupervised algorithms using the bilateral symmetry of the brain have started to emerge in recent years [29][35]. However, unsupervised detection based on
symmetry is still in its early stage as such methods are not yet fully automatic, and the precision and accuracy also has a lot of room for improvement [29][35].

1.2 Problem Statement

Accurate and fast automatic detection of brain tumors from MR images is an important step for computer aided diagnosis (CAD), optimized treatment, and surgical planning. However, the non-uniformity of the tumor location, size, and shape makes it a difficult problem to be automated.

Small and multiple tumor detection also presents substantial computational challenges to the state of the art automatic brain tumor detection algorithms. To the best of our knowledge, there exists no published automatic brain tumor detection algorithm that can accurately (detection rate > 80%) detect small sized brain lesions (radius < 3mm) and multiple tumors (more than 3 per 3D scan) directly from clinical images.

1.3 Contributions

We propose an unsupervised-learning approach to explore potential solutions for this challenging problem. Our contributions are based on unique combinations of a set of key methods and observations.

First, many objects in space present a blob-like shape. We propose a novel, general-purpose and fast 3D blob extraction algorithm using separable 3D Laplacian of Gaussian filters on volumetric images. This algorithm makes it possible to automatically and directly generate a pool of tumor candidates from clinical MR neuroimages.

Second, normal human brains present an approximate bilateral symmetry. It is unlikely (low probability) that brain tumors appear in a bilaterally symmetrical fashion [27]. We have access to algorithms that can reliably extract the midsaggital plane (MSP) from normal and neuroimages, which makes it possible for an automatic detection of asymmetrical blobs in a 3D brain scan. These asymmetrical 3D blobs are candidates of brain tumors.
Third, a Bayesian formulation is a natural and convenient computational framework for this problem, since the likelihood function and the prior probability function can be combined into a multi-constrained, unsupervised system for an effective small and multiple brain tumor detection system.
Data

There are two sets of real world data that we use to evaluate the algorithms developed for this thesis work. The first data set is the publicly available Harvard Tumorbase (http://www.spl.harvard.edu/publications/item/view/1180), which contains 10 cases of meningiomas and low-grade gliomas [17][43]. The second data set is provided to us by the Milton S. Hershey Medical Center, which contains 20 cases from their patient pool, and has not yet been prepared for public release.

The major difference between the two datasets are the characteristics of the tumor types: Harvard tumorbase contains primary brain tumors that are, in general, quite large in size, with no metastasis; the Hershey dataset contains both primary and metastatic diseases with tumor sizes that vary a great deal. Both datasets are converted into ANALYZE format, which is a widely used format to store and share MRI data (http://www.grahamwideman.com/gw/brain/analyze/index.htm). Both datasets come with ground truth labeling by affiliated experts.

2.1 Harvard Tumorbase

The Harvard tumorbase is also called the Brain Tumor Segmentation Database. It was created jointly by the Department of Neurosurgery and the Surgical Planning Laboratory, and the Department of Radiology of the Harvard Medical School. The data contains a total of 10 brain tumor patient MRI scans, all T1 post gadolinium enhanced. The resolution is 256x256x124, with 1.5 mm slice thickness. The individual case information is as followed:
<table>
<thead>
<tr>
<th>Case</th>
<th>Tumor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>meningioma</td>
</tr>
<tr>
<td>2</td>
<td>meningioma</td>
</tr>
<tr>
<td>3</td>
<td>meningioma</td>
</tr>
<tr>
<td>4</td>
<td>low grade glioma</td>
</tr>
<tr>
<td>5</td>
<td>astrocytoma</td>
</tr>
<tr>
<td>6</td>
<td>low grade glioma</td>
</tr>
<tr>
<td>7</td>
<td>astrocytoma</td>
</tr>
<tr>
<td>8</td>
<td>astrocytoma</td>
</tr>
<tr>
<td>9</td>
<td>astrocytoma</td>
</tr>
<tr>
<td>10</td>
<td>low grade glioma</td>
</tr>
</tbody>
</table>

Table 2.1. Harvard tumorbase case information.

Snap shots of the 10 cases are shown in Figures 2.1 to 2.3, and all of the cases can be opened by using 3D Slicer (http://www.slicer.org/), an open-source software package for visualization and image analysis developed by the Surgical Planning Laboratory at the Brigham and Women’s Hospital. For more information of this dataset, please refer to http://www.spl.harvard.edu/publications/item/view/1180.
Figure 2.1. Harvard tumorbse case 1 through 4 in sagittal, coronal, and axial orientation.
Figure 2.2. Harvard tumorbse case 5 through 8 in sagittal, coronal, and axial orientation.
2.2 Hershey Dataset

The 3D Imaging Laboratory of the Hershey Medical Center provided dataset for us to evaluate the performance of this thesis work. There are 20 cases of MRI T1 post gadolinium enhanced images acquired in the Axial plane, all in ANALYZE format. The scanner that was used to acquire all the scans is a Phillips Intera 1.5 Tesla Magnet, with the resolution of 231x185x200 and 1 mm slice thickness. Table 2.2 shows the individual case information.

The more distinct feature of this dataset is that it contains patients with multiple tumors, as well as tumors that are very small in volume, which is contrary to Harvard tumorbases single and mostly large tumors. Figure 2.4 to 2.8 are the snap shots of the 20 cases.
<table>
<thead>
<tr>
<th>Case</th>
<th>Type</th>
<th>Tumor #</th>
<th>Mean</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mets</td>
<td>1</td>
<td>12107±0.00</td>
<td>12107</td>
<td>12107</td>
</tr>
<tr>
<td>2</td>
<td>Primary</td>
<td>1</td>
<td>1448±0.00</td>
<td>1448</td>
<td>1448</td>
</tr>
<tr>
<td>3</td>
<td>Mets</td>
<td>2</td>
<td>10809±10291.23</td>
<td>3532</td>
<td>18086</td>
</tr>
<tr>
<td>4</td>
<td>Mets</td>
<td>4</td>
<td>355.25±276.81</td>
<td>140</td>
<td>732</td>
</tr>
<tr>
<td>5</td>
<td>Mets</td>
<td>11</td>
<td>135.91±241.31</td>
<td>4</td>
<td>625</td>
</tr>
<tr>
<td>6</td>
<td>Primary</td>
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<td>11913±0.00</td>
<td>11913</td>
<td>11913</td>
</tr>
<tr>
<td>7</td>
<td>Mets</td>
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<td>82.31±125.39</td>
<td>3</td>
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</tr>
<tr>
<td>8</td>
<td>Primary</td>
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<td>2262±0.00</td>
<td>2262</td>
<td>2262</td>
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<tr>
<td>9</td>
<td>Mets</td>
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<td>3723±0.00</td>
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<td>2226</td>
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<tr>
<td>12</td>
<td>Primary</td>
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<td>12639</td>
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<td>13</td>
<td>Mets</td>
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<td>22033±0.00</td>
<td>22033</td>
<td>22033</td>
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<td>14</td>
<td>Mets</td>
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<td>150±0.00</td>
<td>150</td>
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<tr>
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<td>Mets</td>
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<td>3617</td>
<td>18041</td>
</tr>
<tr>
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<td>Mets</td>
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<td>25</td>
<td>2145</td>
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<td>533</td>
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<td>572.90±1088.45</td>
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<td>19</td>
<td>Mets</td>
<td>2</td>
<td>179.50±174.66</td>
<td>56</td>
<td>303</td>
</tr>
<tr>
<td>20</td>
<td>Mets</td>
<td>4</td>
<td>487.50±637.16</td>
<td>30</td>
<td>1426</td>
</tr>
</tbody>
</table>

Table 2.2. Hershey tumor dataset information
Figure 2.4. Hershey dataset case 1 through 4 in sagittal, coronal, and axial orientation.
Figure 2.5. Hershey dataset case 5 through 8 in sagittal, coronal, and axial orientation.
Figure 2.6. Hershey dataset case 9 through 12 in sagittal, coronal, and axial orientation.
Figure 2.7. Hershey dataset case 13 through 16 in sagittal, coronal, and axial orientation.
Figure 2.8. Hershey dataset case 17 through 20 in sagittal, coronal, and axial orientation.
Chapter 3

Statistical Asymmetry-based Methods

Human brains are commonly accepted as being symmetrical with respect to the Mid-Sagittal Plane (MSP)\cite{42}. Our proposed method takes advantage of this property by processing the brain through asymmetry comparisons of its structural and pixel intensity distribution. The approach is to formulate the tumor detection problem in a Bayesian framework.

We have developed two asymmetry-based methods to detect and segment brain tumors from 3D MR Images, where the first method is a faster method that analyzes asymmetries among axial slices, and the second method is based on a novel 3-dimensional blob detection algorithm.

Our medical collaborators have verified that brain tumors appear asymmetrically in human brains. Since this work is a symmetry-based method, it depends on the bilateral symmetry analysis of the brain, which requires the localization of the mid-sagittal plane (MSP) that is the reference of symmetry of the brain. The image is then rotated so that the MSP is the up-right central slice of the image in the sagittal plane. Therefore, we apply MSP extraction as our pre-processing step to align the MSP of a volume prior to any operations. The MSP extraction algorithm that this thesis work uses is a recent work developed by an outside collaboration, which is based on quantification of symmetry maximization and cross-correlation of edge features from the input images to achieve fast and accurate MSP extraction results \cite{37}. 
3.1 Method 1: Axial Asymmetry-based Algorithm

We present a novel and unsupervised framework that is based upon an intuitive yet statistically justified observation that tumors are one of the most prominent asymmetrical blobs in the brain. Our asymmetry-based algorithm requires the input to be aligned by its MSP [42]. Because our algorithm is unsupervised and only needs MSP extraction, and not full volumetric registration with an atlas, therefore this greatly reduces the pre-processing time required to completely register a volume from hours to minutes. Our method is fully automatic in that no human interaction is needed for the process. We show in this thesis work that our approach is invariant to different types of tumor satisfying the asymmetrical blob assumption, and that we are able to localize and delineate the tumor without any human interaction.

This algorithm focuses on detecting single tumors, and it is a 3-stage process: 1) locate an axial slice that contains parts of the tumor; 2) localize the 2D shape of the tumor from the extracted slice-of-interest (SOI); 3) and grow the 3D shape of the tumor out bi-directionally.

We formulate the problem using a Bayesian model,

\[
P(Z|S_Z) \propto P(S_Z|Z) \times P(Z)
\]  

(3.1)

We define \( Z \) as the full set of axial-view slices from the neck towards the top of the head, and \( S_Z \) as symmetry evaluation score per axial-view slice, where \( S_Z = \{ S_{Z|L}, S_{Z|R} | Z = 1, ..., z, L = l_1, ..., l_u, R = r_1, ..., r_u \} \). \( P(Z) \) is a prior that models the likelihood of tumor location, and our goal is to extract a 2D slice \( \hat{Z} \) from the volume of interest (VOI) that contains part of the tumor, found as the MAP estimate (maximum a posteriori) \( \hat{Z} \) obtained by maximizing the posterior likelihood \( P(Z|S_Z) \).
3.1.1 Slice of Interest (SOI) Extraction

The brain is split into 2 halves by the MSP of $S_Z$, where $S_{L|Z}$ and $S_{R|Z}$ are the left and right halves, respectively. $S_{L|Z}$ and $S_{R|Z}$ are then further equally partitioned perpendicular to the MSP into $u$ pieces for the consideration of spatial information.

We compute an asymmetry score using Earth-Mover Distance [36][26] for each pair of $S_{L|Z}$ and $S_{R|Z}$ that is equally partitioned into $u$ pieces ($u = 3$ in our experiment). The Earth-Mover Distance between two normalized histograms $H(A)$ and $H(B)$ is denoted here as $\Phi( H(A), H(B) )$. The normalized 3-dimensional histogram (x,y location and the intensity level at each pixel) of each partitioned piece are denoted as $H_3(S_{l|i}|Z)$ and $H_3(S_{r|i}|Z)$. To determine how asymmetrically distributed are the intensity values of $S_z$ with its piece-wise spatial information, each pair of partitions’ EMD asymmetry scores are summed to form the likelihood probability:

$$P(S_Z|Z) = \sum_{i=1}^{u} \Phi( H_3(S_{l|i}|Z), H_3(S_{r|i}|Z) )$$

(3.2)

We obtain the likelihood probability from each slice $S_z$, which we can plot and treat as a 1D signal (Figure 3.1b). We wish to locate the most asymmetrical slice. However, this signal can be noisy due to different parts of the brain (especially the neck region and the scalp top) having different densities, leading to intensity variation, therefore we must apply a prior $P(Z)$ that models the likelihood of tumor location. We found that an Inverse-Gamma distribution resembles the prior likelihood of tumor location well (Figure 3.1a) as its probability gradually increases from (neck to head) then decreased toward the end (scalp top). We denote Inverse-Gamma as $f(Z; \alpha, \beta)$, and it is defined as:

$$P(Z) = f(Z; \alpha, \beta) = \frac{\beta^\alpha}{\Gamma(\alpha)}(1/Z)^{\alpha+1}e^{-\beta/Z}$$

(3.3)

The Inverse-Gamma prior (Eq. 3.3) is combined with the likelihood (Eq. 3.2) to form the Bayesian posterior probability $P(Z|S_Z)$.

After $P(Z|S_Z)$ is computed (Figure 3.1c), any posterior probability that is outside of $3\sigma$ is reduced to the mean of the entire posterior probability and its $S_{Z-2}$, $S_{Z-1}$, $S_{Z+1}$, and $S_{Z+2}$ neighbors as a measure to remove outliers. The processed
Figure 3.1. The complete process of Slice of Interest $E[S]$ extraction on sample case 2. A: the inverse Gamma prior; b: spatially-constrained EMD asymmetry distance for $S_Z$; c: posterior probability $P(Z|S_Z)$; d: $P(Z|S_Z)$ filtered by Gaussian low-pass filter with $\sigma = 3$; d: the most asymmetrical slice $E[S]$ extracted as the maxima of $P(Z|S_Z)$ posterior probability $P(Z|S_Z)$ is convolved by a 1D Gaussian filter $N(\mu = 0, \sigma^2 = 3)$ with horizontal size of 9 (spans 4 slices before and after the current position) for all observations to be weighted by their neighboring information as well as filtering out any high frequency noise (Figure 3.1d). Finally, we can take the maximum of this signal to be our $\hat{Z}$ and proceed to segment the tumor’s 2D shape. We denote the convolution of $f$ and $g$ as $f \ast g$, and by setting the parameters $Z = 1 : n, \mu = 0,$
and $\sigma = 3$, we are able to find the tumor slice (Figure 3.1e):

$$\hat{Z} = \max_Z \{ P(Z|S_Z) \ast N(\mu, \sigma) \} \quad (3.4)$$

### 3.1.2 Stage 2: Blob Feature Extraction with Asymmetry Processing

From the extracted SOI, we proceed to extract the tumor’s 2D shape with a state of the art blob detector. We use Center-Surround Distribution Distance (CSDD) [5] as our blob and interest region detector, because it is insensitive to geometric deformation. CSDD is based on comparing the cumulative distributions of intensity and texture of an extracted region and its surrounding circular background.

$\hat{Z}$ (Figure 3.2a) is first smoothed with a Gaussian low-pass filter, where $N(\mu = 0, \sigma^2 = 2)$ to get rid of possible noise, then CSDD blob features [5] are extracted from the filtered $E[S]$ (Figure 3.2b). We denote the extracted blob features as $\vec{B}$ with each single blob feature denoted as $B_i$. To eliminate all the false positives blobs that do not surround an actual tumor, we compute the EMD [26] of the intensity distribution 1D histogram (only intensity information) from the areas enclosed by each blob $B_i$ and its corresponding MSP-reflected area $Ref(B_i)$, and retain the blobs with the highest $x\%$ EMD score ($5\%$ is used for our experiment here), denoted as $\vec{B}^*$, in which blobs with higher EMD score imply the enclosed structure is more asymmetrical (Figure 3.2c).

$$\vec{B}^* = \max \{ \Phi( H_1(B_i), H_1(Ref(B_i)) ), \frac{5N}{100} \} \quad (3.5)$$

We define and compute the tumor-likelihood score $P(B_j^*)$ of each blob $B_j^*$ of $\vec{B}^*$ by weighting the EMD asymmetry score of $B_j^*$ with its blob strength $S(B_j^*)$, which is the EMD measure of how distinctive is the foreground and background intensity of blob $B_j^*$. Then, we divide the weighted asymmetry score by its foreground intensity variance $Var[I(B_j^*)]$, because the non-tumor false positives such as part of the scalp and surrounding tissues may yield high intensity variance, whereas the tumor tissue in an area remains of uniform intensity.
\[ P(B_{*j}) = \frac{S(B_{*j}) \Phi(H_1(B_{*j}), H_1(Ref(B_{*j})))}{Var[I(B_{*j})]} \] (3.6)

The K-means clustering [15] algorithm with \( k = 2 \) is then used to cluster \( P(\vec{B}^*) \) into two groups \( \vec{B}^*_{k=1} \) and \( \vec{B}^*_{k=2} \) for automatic thresholding on tumor likelihood, and the estimated tumor blobs \( E[\vec{B}^*] \) can be retained by keeping the cluster that yields the highest likelihood (Figure 3.2d, e).

\[ E[\vec{B}^*] = \max \{ \text{avg}(\vec{B}^*_{k=1}), \text{avg}(\vec{B}^*_{k=2}) \} \] (3.7)

It is possible that \( E[\vec{B}^*] \) can have blobs at spur and false positive locations instead of one connected component. In these cases, we use a heuristic approach to remove outlier blobs by keeping the connected components of a group of overlapping blobs (overlapping as in enclosed foreground pixels) with the highest EMD asymmetry score \( \Phi(H_1(B_{*j}), H_1(Ref(B_{*j}))) \). To obtain the final rough 2D location and shape of the tumor from \( E[\vec{B}^*] \), we segment the combined contour of the blobs \( E[\vec{B}^*] \), which yields the rough 2D shape of the tumor (Figure 3.2f).

### 3.1.3 Stage 3: 3D Tumor Delineation by IFT Watershed

The previous steps give us the approximate location of the tumor and a rough shape of this tumor within the SOI. The next step is the precise delineation of the tumor and this is performed for the whole 3D image.

The approach we use in this work uses a markers-controlled watershed algorithm, placing object and background seeds within the SOI and letting the watershed [10][30] grow the regions in 3D. However, there are many different algorithms for watershed and their segmentation results are not the same [2]. In this work, we use the IFT-watershed [28] which is based on the Image Foresting Transform [28]. IFT is a general tool for designing image processing operators based on connectivity, reducing image processing problems into an optimum path forest problem in a graph derived from the image. We chose the IFT-watershed method because it is fast [28] and implements the watershed in such a way that resolves the “tie zones” by dividing them in a balanced manner between the seeds. Further information about the details and evaluation of the IFT-watershed can be found in [2] and [28].
However, the IFT-watershed algorithm requires an initialization by placing some object and background seeds, so we developed a way to automatically place these seeds using the result from the blobs extraction stage. In our case, the term “object” below refers to the tumor, and the background refers to everything else.

The result from the blob extraction is a 2D binary mask (where we have zero for background and one for object), shown in Figure 3.3b. To generate the object seeds, we apply the erosion morphological operator on this mask using a circular structuring element with radius adaptive to the input mask. This morphological operation is performed in 2D within the SOI. The result is shown in Figure 3.3c. The background seeds are generated in a similar way by applying the dilation operator instead of erosion but then computing the complement of the image (inverting values 0 for 1 and vice-versa), resulting in the image shown in Figure 3.3d.

In essence, we create a region of uncertainty around the borders of the mask within the SOI. By definition, the internal seed voxels are already considered to be tumor voxels, and the background seeds are non-tumor voxels. The unmarked voxels are the region of uncertainty which will be resolved by the IFT-Watershed.

Although the seed generation is performed only in one slice (SOI), we let the watershed grow to the rest of the 3D image. Figure 3.3e-g shows the resulting segmentation after the IFT-Watershed.

### 3.1.4 Experimental Results

We tested our algorithm on the 10-case Harvard tumor data set. Because the algorithm assumes the brain contains a single brain tumor, the Harvard tumor data is more suitable to be used as the evaluation set for this algorithm since all 10 cases contain just single primary brain tumor.

For the results of our first algorithm, we visually verified the outputs of MSP alignment (pre-processing) and find the symmetry planes were successfully extracted for all 10 cases, which is critical to the success of our symmetry based algorithm. Stage 1 (SOI extraction) located correct slices for 8 out of 10 cases, where stage 2 (2D localization) located the correct tumor location in all 8 of 8. Stage 3 (IFT-Watershed) was able to segment the 3D shape of the tumor in all 8 cases, however 2 segmentations were not as good due to complicated tumor tissue.
Overall, our stage 2 and stage 3 generated solid results based on the slice that was extracted from stage 1.

Quantitative results are calculated using Jaccard Coefficient, where the True Positives (TP) are identified as the overlap between the manually segmented ground truth tumor labels and the machine generated tumor labels. It is a measure that is commonly used in the field of 3D segmentation quantitative analysis.

Jaccard Coefficient is defined as:

\[
JC = \frac{TP}{FP + FN + TP}
\]  

(3.8)

Our algorithm achieves a mean Jaccard Coefficient of 73.28% ± 7.44% and a median of 77.8% from the cases that produced outputs (excluding cases 5 and 8), and overall Jaccard Coefficient of 67.66% ± 7.20. We also visually inspected the output of each intermediate stage and labeled the result as either Match or Mismatch to indicate whether or not the tumor was successfully located. To further demonstrate the robustness of the blob localization (stage 2) asymmetry processing, we manually selected a tumor slice when stage 1 failed to locate one (cases 5 and 8) and ran stage 2. Table 3.1 shows the complete quantitative results where bold letters indicate a manually selected tumor slice in the case of failed stage 1. Figure 3.4 shows the sample results from cases 1, 6, and 7. A complete set of results can be found in the appendix.

Compared to 2 other unsupervised and symmetry-based methods [29][35], our proposed method is able to work fully automatically without any user intervention, and is able to generate 3D volumetric segmentations. We also achieve a much higher accuracy than what was reported in [35] (highest segmentation score being 71.15%, as compared to our highest at 93.99%), with very fast mean run time of around 4 minutes per 3D MR scan, which is very fast comparing to recent publications in both supervised and unsupervised related work.

To generate the complete run-time result (Table 3.2), the algorithm was implemented in Matlab and ran on an Intel core-duo machine at 1.83 Ghz with 2 Gb of memory.
### Post MSP Extraction 3-Stage Result for 10 Harvard Cases

<table>
<thead>
<tr>
<th>Case #</th>
<th>Stg 1</th>
<th>Stg 2</th>
<th>Stg 3</th>
<th>Jcrd Coeff (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>In</td>
<td>Auto</td>
<td>Success</td>
<td>93.99</td>
</tr>
<tr>
<td>2</td>
<td>In</td>
<td>Auto</td>
<td>Success</td>
<td>88.07</td>
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<tr>
<td>3</td>
<td>In</td>
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<td>73.92</td>
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<tr>
<td>4</td>
<td>In</td>
<td>Auto</td>
<td>Success</td>
<td>72.61</td>
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<tr>
<td>5</td>
<td>Out</td>
<td>Manual</td>
<td>Success</td>
<td>57.31</td>
</tr>
<tr>
<td>6</td>
<td>In</td>
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<td>Success</td>
<td>81.68</td>
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<td>7</td>
<td>In</td>
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<td>8</td>
<td>Out</td>
<td>Manual</td>
<td>Success</td>
<td>32.93</td>
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<td>9</td>
<td>In</td>
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<td>Success</td>
<td>31.74</td>
</tr>
<tr>
<td>10</td>
<td>In</td>
<td>Auto</td>
<td>Success</td>
<td>54.10</td>
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<tr>
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<tbody>
<tr>
<td>median</td>
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<td></td>
<td>73.27</td>
</tr>
<tr>
<td>mean</td>
<td></td>
<td></td>
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<td>67.66±7.20</td>
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**Table 3.1.** Axial asymmetry-based 3-stage result for 10 Harvard cases.

### Post MSP Extraction 3-Stage Run Time for 10 Harvard Cases

<table>
<thead>
<tr>
<th>Case #</th>
<th>Stg 1 (s)</th>
<th>Stg 2 (s)</th>
<th>Stg 3 (s)</th>
<th>Total (s)</th>
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<td>76.34</td>
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<td>3</td>
<td>114.24</td>
<td>81.03</td>
<td>42.61</td>
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<td>4</td>
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<td>79.23</td>
<td>38.01</td>
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<td>5</td>
<td>106.54</td>
<td>62.21</td>
<td>23.09</td>
<td>191.84</td>
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<tr>
<td>6</td>
<td>98.02</td>
<td>65.12</td>
<td>42.35</td>
<td>205.49</td>
</tr>
<tr>
<td>7</td>
<td>113.25</td>
<td>79.21</td>
<td>38.55</td>
<td>231.01</td>
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<td>8</td>
<td>94.43</td>
<td>51.17</td>
<td>36.91</td>
<td>182.51</td>
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<tr>
<td>9</td>
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<td>69.49</td>
<td>35.29</td>
<td>199.33</td>
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<tr>
<td>10</td>
<td>106.41</td>
<td>73.88</td>
<td>44.78</td>
<td>225.07</td>
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</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>105.16±2.31</td>
<td>68.62±3.70</td>
<td>38.50±1.96</td>
<td>212.28±6.07</td>
</tr>
</tbody>
</table>

**Table 3.2.** Axial asymmetry-based 3-stage run time for 10 Harvard cases.
Figure 3.2. Blob feature extraction process on sample case 2. A: the slice of interest \( E[S] \); b: extracted CSDD blob features \( \vec{B} \); c: the top 55\% most asymmetrical \( \vec{B} \) and the extracted MSP, where the whiter the outline represents the higher asymmetrical score; d: result of k-means clustering with y axis as the tumor-likelihood \( P(\vec{B}^*_j) \) for each blob \( \vec{B}^*_j \); e: retaining the cluster that yields the higher mean \( P(\vec{B}^*_j) \) gives us the true positive tumor blobs \( E[\vec{B}^*] \); f: the final 2D rough tumor shape.
Figure 3.3. IFT-Watershed segmentation process and result on sample case 2.
Figure 3.4. Sample results for case 1, 6 and 7.
3.2 Method 2: Asymmetrical 3D Blob-based Algorithm

The first algorithm was able to detect a single brain tumor from MRI 3D scans. However, there are situations when a patient may have multiple, very small brain tumors. Multiple, small-sized tumors, though a good indicator for early stage tumor or potential metastasis, are often overlooked as a research area since they present substantial computational challenges to the state of the art automatic brain tumor detection algorithms.

Therefore, we propose a second algorithm to approach such problems. The central contributions of our work include (1) localize brain tumors using a 3D blob extraction algorithm based on separable 3D Laplacian of Gaussian filters on volumetric images; (2) an abnormality detection algorithm for approximately bilateral symmetrical anatomical structures (human brain); and (3) a Bayesian formulation to combine multiple constraints for effective small and multiple 3D blob detection by asymmetry.

We once again formulate our tumor detection problem in a Bayesian framework. We denote $B$ as a tumorous 3D blob, and $D_B$ as its 3 observed features: blob detection response ($B_r$), blob shape ($B_s$), and blob asymmetry score ($B_a$). The Bayesian formulation is:

$$P(B|D_B) \propto P(D_B|B) \times P(B)$$

(3.9)

The posterior probability $P(B|D_B)$ - how likely a given 3D blob is considered as a tumor, is calculated by multiplying the likelihood function $P(D_B|B)$ of each 3D blob by the prior $P(B)$, both normalized to $[0, 1]$ and summing to 1 separately. Our prior probability $P(B)$ is a binary map of the volume where 1s represent the brain voxels and 0s represent the non-brain voxels, segmented automatically using FSL [40][12]. We define the log-likelihood function $P(D_B|B)$, that we are trying to maximize as follows:

$$P(D_B|B) \propto \log(B_r) + \log(B_a) - \log(B_s)$$

(3.10)

The 3D blob detection response $B_r$ for each detected blob is obtained using a
separable 3D Laplacian of Gaussian (LoG) filter, which is described in detail in Section 3.2.1; the shape parameter $B_s$ represents the non-compactness of a 3D blob, and is explained in Section 3.2.2; the bilateral asymmetry score $B_a$ is calculated using Earth-Mover’s Distance (EMD) [36][26] in Section 3.2.3. Once the posterior probability $P(B|D_B)$ is computed from the 3 features and the brain prior, we are able to segment the precise 3D volume of each tumor using a watershed method called IFT-watershed [2]. Figure 3.5 illustrates the entire process of this method.

MSP extraction [37] as a pre-processing step is also required to be applied to all evaluation images, in order for the algorithm to utilize the underlying brain symmetry property.

Figure 3.5. The entire process of asymmetrical 3D blob-based algorithm.
3.2.1 3D Laplacian of Gaussian (LoG) filtering

The shape of tumors are usually blobby [32], therefore we propose to use blob
detection to locate initial volumes of interest. A method of 3D blob extraction
has been introduced by Ying and Parvin in 2002 [44], using convex hull of elliptic features designed specifically for volumetric images of multicellular systems.
In our work, based on Lindeberg’s scale space-theory [25], we use the Laplacian
of Gaussian as a general purpose 3D blob detector, using its 1D separable form
for optimized performance and deriving the appropriate scale-space normalizing
factor.

We define an isotropic Gaussian function in 3 dimensions as:

\[
g(x, y, z) \equiv g_{xyz} = \frac{1}{\sigma^3(2\pi)^{3/2}} \exp\left(-\frac{(x^2 + y^2 + z^2)}{2\sigma^2}\right)
\]  

(3.11)

The isotropic Laplacian of Gaussian (LoG) in 3 dimensions takes the following
form:

\[
\Delta g(x, y, z) \equiv \Delta g_{xyz} = \frac{\partial^2 g_{xyz}}{\partial x^2} + \frac{\partial^2 g_{xyz}}{\partial y^2} + \frac{\partial^2 g_{xyz}}{\partial z^2}
\]  

(3.12)

From Eq. 3.12, it shows that the 3 dimensional LoG is composed of separate
1D LoG functions in each dimension x, y, and z, where the 1D LoG in the x-axis
is given by:

\[
\frac{d^2}{dx^2} g(x) \equiv \Delta g_x = \frac{x^2 - \sigma^2}{\sigma^5\sqrt{2\pi}} \exp\left(-\frac{x^2}{2\sigma^2}\right)
\]  

(3.13)

We can construct 3D LoG kernels $\Delta g_{xyz}$ according to Eq. 3.12 with different
scales ($\sigma$), and filter a given 3D volumetric image $f$ by $\Delta g$ to extract 3D blobs
different scales. However, convolution in 3D will require $n^3$ multiplications per
voxel for a $n \times n \times n$ 3D LoG kernel, which is very expensive and time consuming.
Therefore, we attempt to decompose the 3D convolution into sums of separate 1D
convolutions.

Since the Gaussian spatial filter is separable, the 3D Gaussian spatial filter can
also be constructed by convolving three 1D Gaussian spatial filters. We define $g_x$
as the 1 dimensional Gaussian filter along the x axis, and $f \otimes g$ as the convolution
of function $f$ by $g$, thus
Given the separation property of the Gaussian filters in conjunction with Eq. 3.12, we can derive the separable 3D LoG filtering of 3D volumetric image $f$ as the sum of separate convolutions between 1D Gaussian filters and 1D Laplacian of Gaussian filters:

$$g_{xyz} = g_x \otimes g_y \otimes g_z$$

(3.14)

$$h = \left[ (f \otimes \Delta g_x) \otimes g_y \otimes g_z \right] + \left[ (f \otimes \Delta g_y) \otimes g_x \otimes g_z \right] + \left[ (f \otimes \Delta g_z) \otimes g_x \otimes g_y \right]$$

(3.15)

Where $h$ is the resulting LoG filtered volumetric image of $f$. Eq. 3.15 shows that the 3D LoG filtering can be decomposed and separated into 9 1D convolutions. This significantly reduces the multiplications per voxel of 3D LoG from $n^3$ down to just $9n$, which enables general purpose 3D blob detection using LoG in 3D volumetric data feasible.

Each detected 3D blob’s central radius is determined by the scale parameter $\sigma$. To find the radius that corresponds to a given scale, we calculate the zero-crossing of the 3D isotropic LoG in polar coordinates:

$$\Delta g_{xyz} = \frac{1}{\sigma^5 2\pi \sqrt{2\pi}} \left( \frac{r^2}{\sigma^2} - 3 \right) \exp\left( -\frac{r^2}{2\sigma^2} \right)$$

(3.16)

Therefore, each detected blob would have its radius $R$ as $(\frac{r^2}{\sigma^2} - 3) = 0 \Rightarrow r \equiv R = \sqrt{3} \sigma$. Furthermore, since we are detecting 3D blobs at different scales, the 3D LoG detection responses must be comparable across different scales. Since the LoG function sums to 0, where the center region sums to -1, the normalizing factor $c(\sigma)$ can be found by integrating over the center region of the 3D LoG and setting equal to -1. We solve the integration using spherical polar coordinates:

$$c(\sigma) \ast \int_{r=0}^{R} \int_{\theta=0}^{2\pi} \int_{\phi=0}^{\pi} \Delta g_{xyz} \ r^2 \sin(\phi) \ d\phi \ d\theta \ dr = -1$$

(3.17)

The normalizing factor is found to be $c(\sigma) = \exp(\frac{3}{2})\sigma^2/3 \sqrt{\frac{6}{\pi}}$, thus it is in proportion to $\sigma^2$, and the different scales of 3D LoG detection responses computed
by Eq. 3.15 can be compared equally by multiplying with a normalizing weight of $\sigma^2$.

Finally, non-maximum suppression across scales is applied to the normalized 3D LoG detection responses to eliminate the weak interest points. The responses of the remaining 3D blobs represents $B_r$ from Eq. 3.10, and is shown in Figure 3.6B.

### 3.2.2 Affine Adaptation and Shape Pruning

Due to the fact that blood vessels, brain linings, ventricles, or the skull plates may also be picked up by the 3D LoG detector, we may discard those 3D blobs by removing blobs with more elongated shapes. 3D affine adaptation of the detected blobs is applied to determine the 3D elliptical shape of all the detected 3D blobs, and the ones with highly elliptical shapes are considered as false positives.

For every 3D blob detected, we find the overall gradient direction from its enclosed boundary by finding its structure tensor, or the second moment matrix in 3 dimensional space:

$$M = \begin{bmatrix} I_x^2 & I_xI_y & I_xI_z \\ I_xI_y & I_y^2 & I_yI_z \\ I_xI_z & I_yI_z & I_z^2 \end{bmatrix}$$

(3.18)

where $I_x$, $I_y$, and $I_z$ denotes the gradient information along one of the three dimensions x, y, or z. Eigenvalue decomposition is then applied to the structure tensor matrix $M$, and we can obtain eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and eigenvectors ($\vec{u}_1, \vec{u}_2, \vec{u}_3$) from the decomposition. The eigenvalues represent the 3D elliptical shape of each 3D blob, whereas the eigenvectors give the rotational information in 3D.

Because the ventricles, skull plates, and the arteries may be picked up as 3D blobs having elongated shapes, we can discard such 3D blobs as false positives according to their shape parameter. The affine adapted shape parameter $B_s$ from Eq. 3.10 is the ratio between the 3D blob’s longest and shortest axis:
Figure 3.6. The intermediate and final results for sample case#17 in 2D view.

\[ B_s = \frac{\max(\lambda_1, \lambda_2, \lambda_3)}{\min(\lambda_1, \lambda_2, \lambda_3)} \]  

(3.19)

Therefore, the shape feature \( B_s \) serves as a penalty factor where the higher the value, the less likely such blob would be a tumor blob. Figure 3.6c shows the shape
pruning result on sample Hershey case 17.

3.2.3 Bilateral Symmetry-based Pruning

We compare each 3D blob to its bilaterally symmetrical location with respect to the MSP, using Earth-Mover distance to compare the two intensity distributions. Earth-Mover distance (EMD) was introduced by Rubner et al in the context of image retrieval [36]. Here, we use EMD as a metric to compare how similar a 3D blob’s enclosed intensity distribution \( I(B) \) is to its reflectional symmetrical location \( I(ref(B)) \).

Note that since both \( I(B) \) and \( I(ref(B)) \) are 1D distributions, applying Mallow’s distance in 1D is equivalent to EMD [23]. Using Mallow’s distance allows the computation to run in linear time [5]. Therefore, the asymmetry score \( B_a \) of a given 3D blob \( B \) is the sum of the cumulative absolute differences between \( I(B) \) and \( I(ref(B)) \), where Mallow’s distance \( M(x, y) \) between cumulative distributions \( x \) and \( y \) can be defined as

\[
M(x, y) = \frac{1}{n} \sum_{i=1}^{n} |x_i - y_i| \tag{3.20}
\]

In our case of comparing 2 intensity distributions, \( n \) from Eq. 3.20 equals 256 as there are 256 total grey-scale intensity levels in our images. Figure 3.6d shows the result after applying the 3D affine adaptation and asymmetry processing, which shows the drastic reduction of false positives from an average of roughly 24,000 to 7 per volume. Figure 3.6e shows the final result on applying the prior (non-skull area) that produces the final detection result on sample Hershey case 17.
3.2.4 Experiments and Results

We validate our 3D blob-based method to detect the size and location of tumors from the Hershey dataset containing 20 clinical 3D brain MR images. Each image is automatically segmented for its brain-only region (skull-stripping) using FSL tools [40][12] and is normalized and used as $P(B)$ for our Bayesian framework in Eq. 3.9.

There is a total of 85 distinct tumors from the 20 ground truth-labeled clinical cases. The approximate volume of the tumors range from 3 mm$^3$ to 28079 mm$^3$ (Table 2.2), with both homogeneous and heterogeneous necrotic cores.

We apply the 3D LoG detection algorithm (section 3.2.1) to the 3D images under a discrete set of scales consisting of 9 half-octave samples, where the $\sigma$ value ranges from 1 to 14 and the actual radius $\sqrt{3}\sigma$ is rounded to the nearest integer, such that we are able to detect tumors as small as 1 and as large as 24 or more voxels in radius. Non-maximum suppression is done over a 5x5x5 neighborhood across scales.

We threshold the resulting computed posterior probabilities $P(B|DB)$ of a tumor blob at 6 decision tolerance levels for analysis and comparison, shown in Figure 3.8.

We define “detection rate” as detected/total, which corresponds to recall rate. We evaluate our algorithm on the Hershey dataset that contains 20 clinical cases using detection rate, and analyze the result using precision and recall rates. In addition, we also evaluate this algorithm on 5 normal cases. For the 5 normal cases, total final blobs detected are used as a metric to compare against the 20 pathological cases. We qualitatively consider a True Positive ($T_p$) as an extracted region that overlaps the vast majority of a tumor volume, a False Positive ($F_p$) as an extracted region that consists of little to none of any part of the tumor volume, and a False Negative ($F_n$) as a tumor region that isn’t part of any extracted blobs. Precision is defined as $T_p/(T_p + F_p)$ and recall is $T_p/(T_p + F_n)$.

The performance of our multi-stage false-positives pruning process is shown in Figure 3.7. The plot shows that pruning stages are able to reduce false positives from extremely high initial numbers (~24,275) down to single digits.

The performance of detection rates from the 6 decision thresholds is shown in Figure 3.8. The plot shows that high recall rates can be obtained from the highest
3 tolerance levels, with recall rates from 87.8% to 95.3%. Table 3.3 shows the quantitative results across the 3 parameter settings.

**Figure 3.7.** Per stage pruning performance on the 20 Hershey cases.

We show the end-to-end run time of our complete method in Table 3.6. The table shows that our algorithm is able to finish running entirely with mean run time of 15.90 minutes, using a Windows Vista 64-bit machine running on an Intel Core i7 920 2.67 GHz with 6.00 GB of RAM. Figure 3.6e and Figure 3.9 shows the final result of a sample case using our algorithm (case#17) with medium decision tolerance, where all 5 tumors are correctly detected.

For nearly all cases, the final detected 3D blob outputs with affine adapted ellipses already represent a good estimate of detected brain tumor volumes, as shown in Figure 3.9b. For more precise segmentation purposes, we show that our detected blobs can act as automatic initialization regions for many state of the art
segmentation methods. To demonstrate this point, we apply a watershed method (IFT-Watershed [28]) on all 20 cases. With the detected 3D blobs localizing each tumor, we erode each blob by half the size, using the remaining voxels as foreground seeds, and similarly we apply dilation using the complementary voxels as background seeds for watershed to segment the tumor volumes. Table 3.5 shows the complete 3d segmentation result for the 20 cases, and Figure 3.9 shows the visualization of the 3d segmentation result for 3 sample cases (11, 15, and 17).

Moreover, Table 3.4 shows a reduced average number of final blobs detected from all 5 normal brain MR images, specifically using the low tolerance level (0.2) where the final blobs yield an average of less than 1 per case, which is significantly different from the average of 7.10 final blobs of the pathological cases in Table 3.3.

**Figure 3.8.** The precision-recall curve, low to high tolerance from left to right.
<table>
<thead>
<tr>
<th>Tolerance</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case#</td>
<td>Tp</td>
<td>Fp</td>
<td>Tp</td>
</tr>
<tr>
<td>1</td>
<td>1/1</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td>2</td>
<td>1/1</td>
<td>3</td>
<td>1/1</td>
</tr>
<tr>
<td>3</td>
<td>1/2</td>
<td>2</td>
<td>2/2</td>
</tr>
<tr>
<td>4</td>
<td>4/5</td>
<td>2</td>
<td>4/5</td>
</tr>
<tr>
<td>5</td>
<td>9/11</td>
<td>6</td>
<td>9/11</td>
</tr>
<tr>
<td>6</td>
<td>1/1</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td>7</td>
<td>12/15</td>
<td>10</td>
<td>14/15</td>
</tr>
<tr>
<td>8</td>
<td>1/1</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td>9</td>
<td>1/1</td>
<td>6</td>
<td>1/1</td>
</tr>
<tr>
<td>10</td>
<td>4/5</td>
<td>2</td>
<td>5/5</td>
</tr>
<tr>
<td>11</td>
<td>8/8</td>
<td>6</td>
<td>8/8</td>
</tr>
<tr>
<td>12</td>
<td>1/1</td>
<td>4</td>
<td>1/1</td>
</tr>
<tr>
<td>13</td>
<td>1/1</td>
<td>2</td>
<td>1/1</td>
</tr>
<tr>
<td>14</td>
<td>1/1</td>
<td>9</td>
<td>1/1</td>
</tr>
<tr>
<td>15</td>
<td>2/2</td>
<td>3</td>
<td>2/2</td>
</tr>
<tr>
<td>16</td>
<td>4/8</td>
<td>1</td>
<td>6/8</td>
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<tr>
<td>17</td>
<td>5/5</td>
<td>3</td>
<td>5/5</td>
</tr>
<tr>
<td>18</td>
<td>6/10</td>
<td>3</td>
<td>6/10</td>
</tr>
<tr>
<td>19</td>
<td>2/2</td>
<td>0</td>
<td>2/2</td>
</tr>
<tr>
<td>20</td>
<td>3/4</td>
<td>6</td>
<td>4/4</td>
</tr>
<tr>
<td>Total</td>
<td>68/85</td>
<td>74</td>
<td>75/85</td>
</tr>
<tr>
<td>Avg Recall</td>
<td>87.84±3.91%</td>
<td>94.51±2.51%</td>
<td>95.30±2.44%</td>
</tr>
<tr>
<td>Avg Precision</td>
<td>46.17±5.24%</td>
<td>35.71±5.41%</td>
<td>26.63±3.98%</td>
</tr>
<tr>
<td>Avg TP volume (mm³)</td>
<td>362.18±1717.04</td>
<td>333.06±1637.77</td>
<td>324.63±1617.21</td>
</tr>
<tr>
<td>Avg FN volume (mm³)</td>
<td>48.54±87.01</td>
<td>46.08±80.49</td>
<td>61.78±90.67</td>
</tr>
<tr>
<td>Tp : Fp</td>
<td>1 : 1.09</td>
<td>1 : 1.83</td>
<td>1 : 2.71</td>
</tr>
<tr>
<td>Avg Final Blobs</td>
<td>7.1±1.13</td>
<td>10.30±1.35</td>
<td>15.10±1.56</td>
</tr>
</tbody>
</table>

Table 3.3. Asymmetrical 3D Blob-based method detection result on 3 tolerance levels.
<table>
<thead>
<tr>
<th>Normal</th>
<th>3 Tolerance Level Results (Fp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case</td>
<td>Low</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Avg Final Blobs</td>
<td>0.80±0.20</td>
</tr>
</tbody>
</table>

**Table 3.4.** Asymmetrical 3D Blob-based method detection result for normal brains.

<table>
<thead>
<tr>
<th>Case #</th>
<th>Jaccard Coefficient (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>87.07</td>
</tr>
<tr>
<td>2</td>
<td>86.99</td>
</tr>
<tr>
<td>3</td>
<td>31.16</td>
</tr>
<tr>
<td>4</td>
<td>71.96</td>
</tr>
<tr>
<td>5</td>
<td>80.31</td>
</tr>
<tr>
<td>6</td>
<td>72.69</td>
</tr>
<tr>
<td>7</td>
<td>40.62</td>
</tr>
<tr>
<td>8</td>
<td>5.28</td>
</tr>
<tr>
<td>9</td>
<td>89.86</td>
</tr>
<tr>
<td>10</td>
<td>51.87</td>
</tr>
<tr>
<td>11</td>
<td>85.60</td>
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<tr>
<td>12</td>
<td>92.95</td>
</tr>
<tr>
<td>13</td>
<td>32.91</td>
</tr>
<tr>
<td>14</td>
<td>72.78</td>
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<tr>
<td>15</td>
<td>90.33</td>
</tr>
<tr>
<td>16</td>
<td>45.98</td>
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<tr>
<td>17</td>
<td>84.96</td>
</tr>
<tr>
<td>18</td>
<td>56.63</td>
</tr>
<tr>
<td>19</td>
<td>75.06</td>
</tr>
<tr>
<td>20</td>
<td>18.46</td>
</tr>
<tr>
<td>Median</td>
<td>72.74</td>
</tr>
<tr>
<td>Mean</td>
<td>63.67 ± 26.57</td>
</tr>
</tbody>
</table>

**Table 3.5.** The 3D segmentation results from using the True Positives of Medium tolerance.
Table 3.6. Asymmetrical 3D Blob-based method runtime result.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Run Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSP</td>
<td>0.44 ± 0.03</td>
</tr>
<tr>
<td>3D LoG</td>
<td>3.03 ± 0.17</td>
</tr>
<tr>
<td>3D Affine</td>
<td>6.60 ± 0.46</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>5.58 ± 0.53</td>
</tr>
<tr>
<td>File I/O</td>
<td>0.25 ± 0.01</td>
</tr>
<tr>
<td>Total</td>
<td>15.90 ± 1.01</td>
</tr>
</tbody>
</table>
Figure 3.9. The 3D segmentation results of case 15, 11, and 17.
Discussion

From the two methods proposed in this thesis, it is apparent that a thresholding parameter is needed for the false positive elimination process, and this threshold is currently set manually. Towards more automated threshold setting, it is our assumption that the tumor blobs are separable against the non-tumor blobs in a 3D feature space with axes as blob response score, shape score, and asymmetry score. Figure 4.1 shows that the tumor blobs (red) seem to be separable from the non-tumor blobs (blue) in the 3D feature space, which prompts the possibility of using a supervised method for classifying the pruned blob results, in order to improve the false positive elimination.

It would be intuitive to use a decision tree as the choice of classifier for this work, given that both our methods are pruning in a hierarchical fashion with binary class label (tumor/non-tumor). However, further experiments will need to be conducted to evaluate the effectiveness of using decision trees as the model to classify the resulting blobs for reducing false positives.

Furthermore, if the skull removal stage is move forward, there would be less blobs for the affine adaptation pruning, as well as the subsequent asymmetry pruning. As a result, the total run time greatly improves while the accuracy remains similar as Table 3.3. Table 4.1 shows that the total run time improved from 16 minutes down to around 4 minutes per case on average.
Figure 4.1. The detected 3d blobs from the 20 Hershey cases in feature space.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Run Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSP</td>
<td>0.44 ± 0.03</td>
</tr>
<tr>
<td>3D LoG</td>
<td>3.03 ± 0.17</td>
</tr>
<tr>
<td>3D Affine</td>
<td>0.26 ± 0.12</td>
</tr>
<tr>
<td>Asymmetry</td>
<td>0.08 ± 0.04</td>
</tr>
<tr>
<td>File I/O</td>
<td>0.12 ± 0.07</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3.93 ± 0.43</strong></td>
</tr>
</tbody>
</table>

Table 4.1. Asymmetrical 3D Blob-based method runtime result, with skull removal immediately after 3D blob detection.
Conclusion

We have presented two fully 3D automatic brain tumor detection methods developed under a Bayesian framework and operating on clinical MR scans. Both approaches are developed within a novel unsupervised statistical asymmetry-based, automatic tumor segmentation framework. Moreover, the second approach is based on a general-purpose and novel 3D blob detector. The 1D separable filtering of 3D LoG speeds up the 3D blob detection tremendously for real world applications. Our asymmetry-based and blob-like (affine adaptation) based pruning proves to be effective in reducing the number of potential tumors from about 24,000 down to single digits (Figure 3.6). We have shown through experiments that the method is fully automatic, unsupervised and sensitive to multiple small tumors.

The 87.84 to 95.30% detection (recall) rates show the potential value of this methodology for future clinical usage. In computer aided diagnosis, low false negatives is more important than low false positives, which is reflected in our high recall rates. With human expert intervention, less than 3 false positives (Table 3.3) need to be eliminated for each true positive detection. We have achieved an initial average end-to-end run time of 15.90±1.01 minutes per volume (Table 3.5), and an improved average end-to-end run time of 3.93±0.43 minutes per volume by applying the skull removal immediately after the 3D LoG detection (Table 4.1), which is at least one order of magnitude faster than previous methods.

Our future work will focus on developing robust methods to further reduce the false positive rate in order to improve the precision score, as well as optimizing the algorithm to achieve a faster run time.
Appendix A

Axial Asymmetry-based Algorithm

Results

There are 10 figures and tables showing our 3D tumor segmentation results. The format is as followed:

Row 1: Results from stage 1 and 2. The first image is the automatically extracted Slice of Interest (SOI), and the rest of the images display the intermediate results for stage 2 in sequential order.

Table: 3D segmentation output (stage 3) in 3 orientations and 3D view.

Accuracy is calculated as Jaccard Coefficient \( \frac{TP}{FP + FN + TP} \), where TP is True Positive, FP is False Positive, and FN is False Negative.
Figure A.1. Harvard Case 1: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 1</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td><img src="image1" alt="Axial Input" /></td>
<td><img src="image2" alt="Axial Ground Truth" /></td>
<td><img src="image3" alt="Axial Result" /></td>
</tr>
<tr>
<td>Coronal</td>
<td><img src="image4" alt="Coronal Input" /></td>
<td><img src="image5" alt="Coronal Ground Truth" /></td>
<td><img src="image6" alt="Coronal Result" /></td>
</tr>
<tr>
<td>Sagittal</td>
<td><img src="image7" alt="Sagittal Input" /></td>
<td><img src="image8" alt="Sagittal Ground Truth" /></td>
<td><img src="image9" alt="Sagittal Result" /></td>
</tr>
<tr>
<td>3-D</td>
<td><img src="image10" alt="3-D Input" /></td>
<td><img src="image11" alt="3-D Ground Truth" /></td>
<td><img src="image12" alt="3-D Result" /></td>
</tr>
</tbody>
</table>

Table A.1. Harvard Case 1: 3D watershed segmentation stage 3 outputs. Accuracy: 93.99%
**Figure A.2.** Harvard Case 2: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 2</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Axial</strong></td>
<td><img src="image1" alt="Axial Input" /></td>
<td><img src="image2" alt="Axial Ground Truth" /></td>
<td><img src="image3" alt="Axial Result" /></td>
</tr>
<tr>
<td><strong>Coronal</strong></td>
<td><img src="image4" alt="Coronal Input" /></td>
<td><img src="image5" alt="Coronal Ground Truth" /></td>
<td><img src="image6" alt="Coronal Result" /></td>
</tr>
<tr>
<td><strong>Sagittal</strong></td>
<td><img src="image7" alt="Sagittal Input" /></td>
<td><img src="image8" alt="Sagittal Ground Truth" /></td>
<td><img src="image9" alt="Sagittal Result" /></td>
</tr>
<tr>
<td><strong>3-D</strong></td>
<td>n/a</td>
<td><img src="image10" alt="3-D Ground Truth" /></td>
<td><img src="image11" alt="3-D Result" /></td>
</tr>
</tbody>
</table>

**Table A.2.** Harvard Case 2: 3D watershed segmentation stage 3 outputs. Accuracy: 88.07%
Figure A.3. Harvard Case 3: 2D Asymmetry-based stage 1 and 2 outputs.

Table A.3. Harvard Case 3: 3D watershed segmentation stage 3 outputs. Accuracy: 73.92%
Figure A.4. Harvard Case 4: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 4</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
</tr>
</thead>
<tbody>
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<td>Axial</td>
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<td><img src="image2" alt="Image" /></td>
<td><img src="image3" alt="Image" /></td>
</tr>
<tr>
<td>Coronal</td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td>Sagittal</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
<td><img src="image9" alt="Image" /></td>
</tr>
<tr>
<td>3-D</td>
<td>n/a</td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
</tr>
</tbody>
</table>

Table A.4. Harvard Case 4: 3D watershed segmentation stage 3 outputs. Accuracy: 72.61%
Figure A.5. Harvard Case 5: 2D Asymmetry-based stage 1 and 2 outputs.

Table A.5. Harvard Case 5: 3D watershed segmentation stage 3 outputs. Accuracy: 57.31% (Slice selected manually)
Figure A.6. Harvard Case 6: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 5</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
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<td><img src="image1" alt="Axial" /></td>
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<td><img src="image3" alt="Axial" /></td>
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<td><img src="image3" alt="Sagittal" /></td>
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<tr>
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<td><img src="image1" alt="3-D" /></td>
<td><img src="image2" alt="3-D" /></td>
<td><img src="image3" alt="3-D" /></td>
</tr>
</tbody>
</table>

Table A.6. Harvard Case 6: 3D watershed segmentation stage 3 outputs. Accuracy: 81.68%
Figure A.7. Harvard Case 7: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 6</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
</tr>
</thead>
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<tr>
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<td><img src="image" alt="Axial Ground Truth" /></td>
<td><img src="image" alt="Axial Result" /></td>
</tr>
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<td><img src="image" alt="Coronal Input" /></td>
<td><img src="image" alt="Coronal Ground Truth" /></td>
<td><img src="image" alt="Coronal Result" /></td>
</tr>
<tr>
<td>Sagittal</td>
<td><img src="image" alt="Sagittal Input" /></td>
<td><img src="image" alt="Sagittal Ground Truth" /></td>
<td><img src="image" alt="Sagittal Result" /></td>
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<td>3-D</td>
<td>n/a</td>
<td><img src="image" alt="3D Input" /></td>
<td><img src="image" alt="3D Result" /></td>
</tr>
</tbody>
</table>

Table A.7. Harvard Case 7: 3D watershed segmentation stage 3 outputs. Accuracy: 90.11%
**Figure A.8.** Harvard Case 8: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 1</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
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<td><img src="image" alt="Axial Ground Truth" /></td>
<td><img src="image" alt="Axial Result" /></td>
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</tr>
<tr>
<td>Sagittal</td>
<td><img src="image" alt="Sagittal Input" /></td>
<td><img src="image" alt="Sagittal Ground Truth" /></td>
<td><img src="image" alt="Sagittal Result" /></td>
</tr>
<tr>
<td>3-D</td>
<td>n/a</td>
<td><img src="image" alt="3-D Result" /></td>
<td><img src="image" alt="3-D Result" /></td>
</tr>
</tbody>
</table>

**Table A.8.** Harvard Case 8: 3D watershed segmentation stage 3 outputs. Accuracy: 32.93% (Slice selected manually)
**Figure A.9.** Harvard Case 9: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 7</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td><img src="image1" alt="Axial Input" /></td>
<td><img src="image2" alt="Axial Ground Truth" /></td>
<td><img src="image3" alt="Axial Result" /></td>
</tr>
<tr>
<td>Coronal</td>
<td><img src="image4" alt="Coronal Input" /></td>
<td><img src="image5" alt="Coronal Ground Truth" /></td>
<td><img src="image6" alt="Coronal Result" /></td>
</tr>
<tr>
<td>Sagittal</td>
<td><img src="image7" alt="Sagittal Input" /></td>
<td><img src="image8" alt="Sagittal Ground Truth" /></td>
<td><img src="image9" alt="Sagittal Result" /></td>
</tr>
<tr>
<td>3-D</td>
<td>n/a</td>
<td><img src="image10" alt="3-D Ground Truth" /></td>
<td><img src="image11" alt="3-D Result" /></td>
</tr>
</tbody>
</table>

**Table A.9.** Harvard Case 9: 3D watershed segmentation stage 3 outputs. Accuracy: 31.74%
Figure A.10. Harvard Case 10: 2D Asymmetry-based stage 1 and 2 outputs.

<table>
<thead>
<tr>
<th>Case # 8</th>
<th>Input</th>
<th>Ground Truth</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axial</td>
<td><img src="image" alt="Axial Input" /></td>
<td><img src="image" alt="Axial Ground Truth" /></td>
<td><img src="image" alt="Axial Result" /></td>
</tr>
<tr>
<td>Coronal</td>
<td><img src="image" alt="Coronal Input" /></td>
<td><img src="image" alt="Coronal Ground Truth" /></td>
<td><img src="image" alt="Coronal Result" /></td>
</tr>
<tr>
<td>Sagittal</td>
<td><img src="image" alt="Sagittal Input" /></td>
<td><img src="image" alt="Sagittal Ground Truth" /></td>
<td><img src="image" alt="Sagittal Result" /></td>
</tr>
<tr>
<td>3-D</td>
<td>n/a</td>
<td><img src="image" alt="3-D Ground Truth" /></td>
<td><img src="image" alt="3-D Result" /></td>
</tr>
</tbody>
</table>

Table A.10. Harvard Case 10: 3D watershed segmentation stage 3 outputs. Accuracy: 54.10%
Appendix B

Asymmetrical 3D Blob-based Algorithm Results

There are 28 figures showing our asymmetrical 3D blob-based detection results for the 20 Hershey cases using the medium tolerance level.

The ellipsoids on the images are the affine adapted blob detection results, representing the central cut-slice of the 3D sphere.

The True Positives are marked in green, False Positives are marked in yellow, and the False Negatives are marked in red.
Figure B.1. Hershey Case 1: TP: 1/1, FP: 2, FN: 0.
Figure B.2. Hershey Case 2: TP: 1/1, FP: 9, FN: 0.
**Figure B.3.** Hershey Case 3: TP: 2/2, FP: 6, FN: 0.
Figure B.4. Hershey Case 4: TP: 4/5, FP: 2, FN: 1.
Figure B.5. Hershey Case 5: part 1.
Figure B.6. Hershey Case 5: part 2 – TP: 9/11, FP: 8, FN: 2.
**Figure B.7.** Hershey Case 6: TP: 1/1, FP: 5, FN: 0.
Figure B.8. Hershey Case 7: part 1.

True Positives:
Figure B.9. Hershey Case 7: part 2.
Figure B.10. Hershey Case 7: part 3 – TP: 14/15, FP: 15, FN: 1.
Figure B.11. Hershey Case 8: TP: 1/1, FP: 5, FN: 0.
Figure B.12. Hershey Case 9: TP: 1/1, FP: 10, FN: 0.
Figure B.13. Hershey Case 10: TP: 5/5, FP: 7, FN: 0.
Figure B.14. Hershey Case 11: part 1.
Figure B.15. Hershey Case 11: part 2 – TP: 8/8, FP: 6, FN: 0.
Figure B.16. Hershey Case 12: TP: 1/1, FP: 5, FN: 0.
Figure B.17. Hershey Case 13: TP: 1/1, FP: 6, FN: 0.
Figure B.18. Hershey Case 14: part 1.
Figure B.19. Hershey Case 14: part 2 – TP: 1/1, FP: 15, FN: 0.
Figure B.20. Hershey Case 15: TP: 2/2, FP: 8, FN: 0.
Figure B.21. Hershey Case 16: part 1.
**Figure B.22.** Hershey Case 16: part 2 – TP: 6/8, FP: 5, FN: 2.
Figure B.23. Hershey Case 17: TP: 5/5, FP: 6, FN: 0.
Figure B.24. Hershey Case 18: part 1.
Figure B.26. Hershey Case 19: TP: 2/2, FP: 0, FN: 0.
Figure B.27. Hershey Case 20: part 1.
Figure B.28. Hershey Case 20: part 2 - TP: 4/4, FP: 12, FN: 0.
Bibliography


