ÓBUDAI EGYETEM

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(PHD) THESIS

ABSTRACT

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Automatic Detection and Segmentation of Brain Tumors in Multispectral MRI Records

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Contents

Preface

Cancers of the brain and the central nervous system result in over two hundred thousand deaths annually worldwide [Patel et al., 2019]. A significant part of these could be prevented with early diagnosis. The need for automated procedures that efficiently, quickly, and reliably pre-screen images and recommend cases suspected to be abnormal to physicians has become increasingly evident due to the sheer volume of image data produced by medical imaging equipment today.

The automated detection and segmentation of brain tumors in MRI data has been a current research topic during the last three decades [Gordillo et al., 2013]. The Brain Tumor Segmentation Challenges (BraTS) organized annually since 2012 have intensified the research work in this field, providing standardized training, testing data, and uniform assessment frameworks [Menze et al., 2015, Bakas et al., 2017].

Understanding the prognosis of brain tumors is crucial for patient management. Factors such as tumor type, grade, and early detection play significant roles. The World Health Organization classifies brain tumors into different grades, each with its own prognosis and treatment approach.

The volume of MRI images produced by medical imaging devices is constantly increasing, while the specialist capacity to analyze the images is limited. Therefore, there is an urgent need to develop automated segmentation methods that provide high quality results with reduced computational requirements.

The aim of this study was to propose a solution for brain tumor segmentation that delivers high-quality results while reducing computational requirements. Furthermore, my objective was to investigate how preprocessing methods can contribute to enhancing the efficiency of segmentation, as well as to analyze the performance and functionality of classifiers under various approaches. Additionally, I aimed to explore the role and potential of post-processing techniques in refining segmentation results and improving their accuracy.

To do this, I implemented a classification using ensemble learning [Gordillo et al., 2013], aided by a number of image processing methods designed to process MRI images likely to contain focal lesions. In addition, I propose a U-net [Ronneberger et al., 2015] based approach with the aim of producing higher quality segmentation using state-of-the-art machine learning techniques.

The first thesis group addresses important issues of MRI data preprocessing. It investigates and recommends the most suitable histogram normalization method for high-quality brain MRI segmentation with and without focal lesions. It proposed a feature generation and selection scheme to reduce the number of features required for segmentation without compromising quality. It explores the effect of spectral resolution on segmentation accuracy and recommends a reduction in storage space for MRI data representation. Finally, it introduces an atlas-based [Yang et al., 2019, Cabezas et al., 2011] data enhancement technique that improved segmentation accuracy for tumor volumes.

The second thesis group compares ensemble learning and deep learning methods [Pereira et al., 2016, Fernando and Tsokos, 2023, Yu et al., 2021] for brain tumor segmentation, highlighting the superior performance of deep learning methods. The study analyzes the accuracy and efficiency of various classifiers, showcasing the notable capabilities of deep learning in capturing complex patterns and spatial relationships within medical images. Unlike traditional handcrafted feature-based approaches, deep learning methods demonstrate a high degree of adaptability and scalability. The substantial improvement in segmentation accuracy highlight deep learning methods as a promising avenue for enhancing the efficiency and reliability of brain tumor analysis.

The third thesis group formulates a two-stage post-processing method and incorporates a secondary U-net convolutional neural network [Ronneberger et al., 2015] for refining and enhancing brain tumor segmentation accuracy. By leveraging classical machine learning-based and structural post-processing techniques, the study achieves significantly higher levels of accuracy and reliability in the segmentation results. This refined segmentation output serves as a valuable foundation for subsequent analyzes and clinical applications, ensuring accurate information is obtained for diagnosis and treatment planning. The integrated approach of classical machine learning and deep learning methods has proven its effectiveness in improving the quality of segmentation of brain tumors, ultimately benefiting both clinicians and researchers in the field of neuroimaging.

Background of Research

The research team at the Sapientia University, which I joined in 2017, elaborated an ensemble learning based solution for the brain tumor segmentation problem [Szilágyi et al., 2018], that stands at the foundations of my doctoral research work. Preliminary works of the team were presented in [Szilágyi et al., 2015a, Szilágyi et al., 2015b, Kapás et al., 2016, Kapás et al., 2018]. The flowchart of the procedure can be found in Figure 1.

Segmentation is achieved by classifying the pixels, which is per-

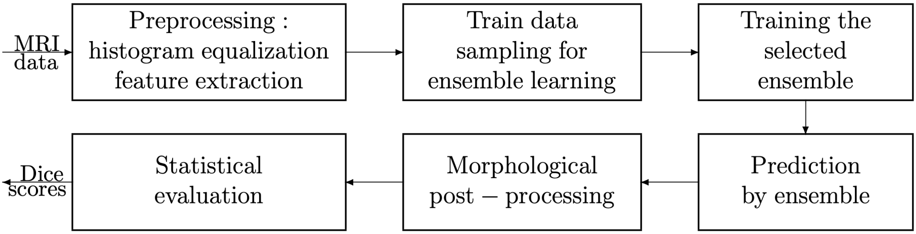

Figure 1: Block diagram of the initial brain tumor segmentation procedure.

formed by an ensemble (forest) of binary decision trees. Before classification, the MRI data is fed to preprocessing steps, aiming to make the raw MRI data suitable for classification. The necessary and possible steps of *preprocessing*, listed in order of execution are the following:

1. The intensity values of pixels in different MRI scans are not on the same scale, causing the same tissue types to appear differently in various scans. Hence, we incorporate histogram normalization during preprocessing, aligning the histograms of intensity values on each data channel separately. This step was implemented in the initial procedure through a context-dependent linear transformation.

2. Among the multi-spectral MRI data available at BraTS, not every pixel has measured intensity values on each data channel; in some cases, a zero value indicates missing data. To compensate for missing data, we primarily use the average intensity values of the 26 pixels that are direct spatial neighbours of the given pixel, or if this is not available, we use the average intensity value of the entire data channel for that particular scan.

3. Methods employing classical machine learning perform better in high-dimensional data spaces. However, it can also be said that not every possible detail of a voxel or the cubic millimeter of brain tissue it represents can be found in the four measured data channels provided by T1, T2, T1c, and FLAIR. Therefore, our initial procedure generated 100 additional features, thus using feature vectors with a total of 104 elements for training and testing.

Segmentation is performed by classifying the pixels using supervised machine learning techniques. The initial segmentation framework deployed an ensemble of binary decision trees (BDT) to accomplish the classification. A BDT of unlimited depth can describe any hierarchy of crisp (non-fuzzy) two-way decisions [Akers, 1978]. Further on, a BDT can perfectly learn the classification of any training data set if there is no contradiction in the data. The decision trees of the initial segmentation procedure learned to separate positive and negative pixels from the feature vectors of equal sized sets of randomly selected pixels.

Post-processing represents a posterior relabeling scheme, which in the initial segmentation framework involved an unsupervised technique based on a simple morphological criterion. The input data of the post-processing step consisted in the labels provided by the BDT ensemble to all pixels in the test volume. For each pixel, the number of neighbours marked as positive within a predefined neighbourhood and the total number of neighbours were determined. The final label of a pixel became a tumor if and only if the proportion of positive neighbours exceeded the empirically determined threshold (1/3).

Proposed solutions

The vast majority of the papers published during my PhD studies optimized the operation of the brain tumor segmentation procedure used as a starting point, each paper focusing on a particular step in the processing. Each of these papers deals with the complete segmentation procedure, proposes some alternative solutions to the focused processing unit, and establishes the best performing version.

Paper [GyA4] identifies the histogram normalization method that best supports segmentation, comparing the simple linear transformation with the most commonly used method in the literature, the piecewise linear transformation [Nyúl et al., 2000] of László Nyúl, taking into account the possible parameters of both. Based on tests conducted on MRI scans with and without focal lesions, I determined that the piecewise linear transformation performs the best, and I have made suggestions for appropriate parameterization of the algorithm.

Paper [GyA1] introduced a feature selection procedure aimed at reducing the computational and memory requirements of the segmentation process without significantly diminishing the quality of the results. The proposed method performs the entire training and testing cycle iteratively using a gradually smaller set of features. During each iteration, I remove the least used features and those contributing to the worst decisions. The original feature set was successfully reduced to one-eighth of its original size, while the decrease in the average Dice score characterizing the final segmentation result remained below 0.3%.

Paper [GyA5] examined the impact of spectral resolution (color depth) of MRI data on the quality of segmentation. During histogram normalization, I had the opportunity to generate feature values with any number of bits in resolution. I investigated how the segmentation accuracy of MRI images with and without focal lesions changes in the 2-10 bit color depth range. Results show that classical machine learning methods can achieve their maximum segmentation accuracy using a 6-bit color depth, while any additional bits are largely redundant. Based on this observation, it is possible to reduce the memory space used for storing feature data without affecting segmentation accuracy. The [GyA2] paper is an early version of [GyA5] with fewer test cases, but similar results.

Paper [GyA3] proposed a multi-atlas based solution for enhancing the quality of MRI data. For a given learning task, I first aligned the complete MRI volumes using rigid registration, then considering only the pixels belonging to normal tissue types, I determined the local average and standard deviation of the intensity values of normal pixels, separately for each data channel. Subsequently, I modified the intensity values of every pixel in the learning and test dataset according to how much the local intensity differed from the local average value of normal intensities, how many times the difference is larger than the variance, and what is the sign of the difference. I used these modified intensity values for training and testing. Depending on the size of the atlas, I achieved an improvement of about 0.5-1% in the average Dice score indicators characterizing the quality of segmentation.

Papers [GyA10] and [GyA7] investigate the possible replacement of the BDT ensemble with other classical machine learning algorithms, in the role of the decision making unit used for segmentation. Both in case of testing with MRI records containing LGG and HGG tumors, I achieved the best segmentation accuracy with the random

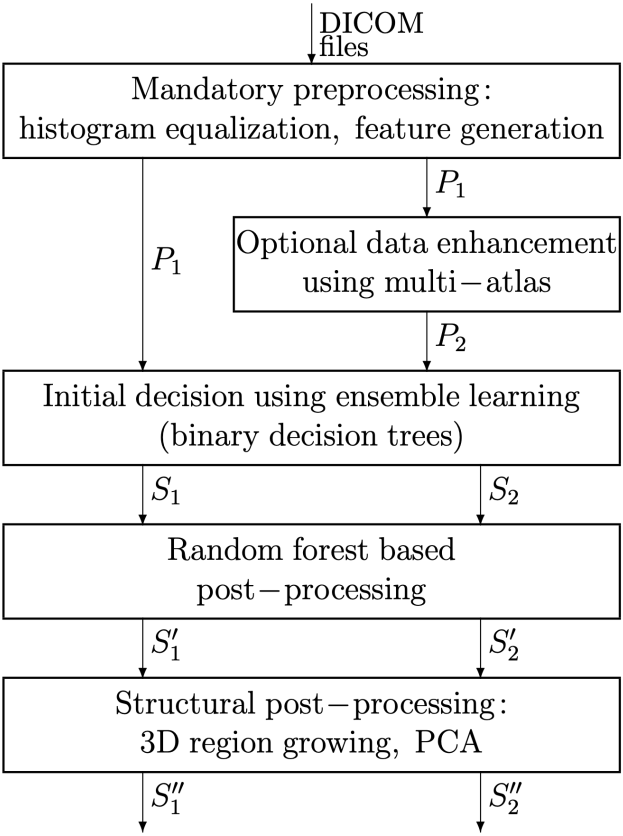

Figure 2: The input DICOM files are transformed into two variants of preprocessed data (P_1 and P_2). The intermediary segmentation results produced by the ensemble of binary decision trees (S_1 and S_2) are fine tuned in two post-processing steps to achieve high-quality segmentation (S_1'' and S_2'')

forest classifier.

Paper [GyA12], proposed an intelligent post-processing algorithm instead of the initially used morphological criterion, which re-evaluates the initially determined label of each pixel based on morphological features extracted from labels found in its predefined spatial neighbourhood. The proposed algorithm uses a random forest for decision-making. Compared to the simple morphological criterion, an improvement of up to 1% can be achieved in the final accuracy of the segmentation.

Paper [GyA11] introduced a structural post-processing operation. In the output of the initial segmentation, I first use spatial region growing to identify the contiguous regions classified as positive. I discard the very small positive regions and, for the others, I determine their three principal axes and corresponding sizes through principal component analysis. Using an empirically established criterion, the very flat positive regions (those with a small size in the third relevant dimension) are relabeled as negative, while the rest are definitively classified as positive.

Paper [GyA6] integrates all previously mentioned modifications simultaneously into the initial procedure, and a detailed evaluation process is carried out using various datasets. The flowchart of the modified procedure is shown in Figure 2. The modified procedure is competitive in terms of segmentation accuracy and efficiency with the best performing algorithms found in the literature.

During the later phase of my doctoral studies, I proposed a brain tumor segmentation procedure that incorporates U-net architectures [Ronneberger et al., 2015]. Paper [GyA8] introduced a U-net cascade system, where two U-net networks of identical type and size perform the classification and post-processing. The flowchart of the

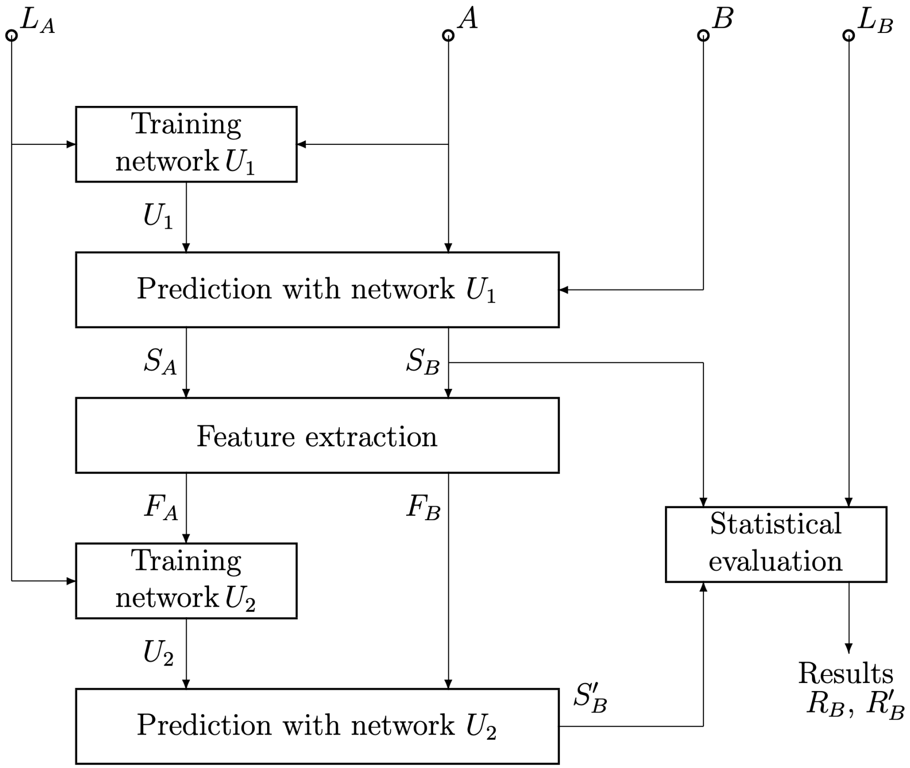

Figure 3: Block diagram of the proposed two-stage segmentation process. The first U-net U_1 produces initial segmentation results, while the second U-net U_2 performs a post-processing based on neighbourhood features extracted from the labels provided by U_1. A and B represent the set of pixels used for training and testing, respectively, while L_A are L_B stand for the corresponding ground truth labels.

proposed procedure can be found in Figure 3. The first U-net performs a primary segmentation on the MRI data, applying spatial convolution. It receives as input all four data channels of a multi-spectral MRI scan at once and outputs the estimated probability of each pixel belonging to the positive regions. From the output, I calculate four morphological features similarly to those described in paper [GyA12], and I provide the spatial distribution of these features as the input to the second U-net network, which performs the post-processing and outputs the final estimated classification of each pixel. The segmentation accuracy achieved surpasses the results of my previous solution by an average of 1%. Paper [GyA9] involves an adaptive local histogram equalization algorithm (CLAHE) as a preprocessing step before the U-net cascade, which further improves the segmentation accuracy.

New scientific results

Thesis group I. – Results concerning the preprocessing of MRI data

Thesis 1.1

I have accomplished an investigation regarding the most suitable histogram normalization method that would support high-quality segmentation of brain MRI records, both with and without focal lesions. I have formulated new recommendations for the use of the best performing algorithm, originally published by Nyúl *et al* [Nyúl et al., 2000], which yields 0.5-3.0% improvement of average Dice similarity coefficients in comparison with previously published scenarios.

Relevant own publication pertaining to this thesis: [GyA4].

Thesis 1.2

I have proposed a feature generation and selection scheme to support the segmentation of brain tumors from multispectral MRI records, to establish an optimal sized handcrafted feature vector that enables classical machine learning based methods to achieve high-quality segmentation. The proposed method can significantly reduce the number of necessary features, and consequently the computational load of training and testing, without any loss in terms of the segmentation quality.

Relevant own publication pertaining to this thesis: [GyA1].

Thesis 1.3

As a spin-off of the histogram normalization study, I have investigated the effect of spectral resolution used when storing the preprocessed data, upon the achievable segmentation quality. The evaluation using MRI data with and without focal lesions revealed that 6-bit spectral resolution is sufficient for classical machine learning based classifiers to obtain the best segmentation quality they are capable of. This way we may significantly reduce the necessary storage space, taking into consideration that the MRI devices produce data at 16-bit resolution.

Relevant own publications pertaining to this thesis: [GyA2], [GyA5].

Thesis 1.4

I have proposed an atlas-based data enhancement technique relying on the statistical analysis of pixels from the training dataset that belong to healthy tissues. Locally extracted means and variances are used to update the pixel intensities in all volumes of the training and testing datasets, before proceeding to the classification. The proposed method caused up to 1% improvement of average Dice scores in case of both HGG and LGG records.

Relevant own publications pertaining to this thesis: [GyA3], [GyA6].

Thesis group II. – Results concerning the classification of pixels

Thesis 2

I conducted a thorough analysis of commonly employed classifiers, including both classical machine learning and deep learning approaches, to determine their performance in relation to the brain tumor segmentation task and the dataset at hand. The findings revealed that deep learning methods operate more effectively, showcasing superior performance in the context of the designated task and dataset.

Relevant own publications pertaining to this thesis: [GyA6], [GyA7], [GyA8], [GyA9], [GyA10].

Thesis group III. – Results concerning the post-processing of segmentation outputs

Thesis 3.1

I have proposed a two-stage post-processing for the classical machine learning based segmentation methods. The first stage consists of a random forest that predicts the label of pixels based on morphological features extracted from the initial decision. The second stage, relying on spatial region growing and principal component analysis, establishes the size and shape of contiguous ranges of lesions, and provides final decision based on the identified structures. The proposed method improved the final segmentation outcome of HGG and LGG records by 0.5-1.0% and 0.5-0.8%, respectively, compared to the baseline morphological method.

Relevant own publications pertaining to this thesis: [GyA11], [GyA12].

Thesis 3.2

I have developed a novel approach involving the incorporation of a secondary U-net convolutional neural network for post-processing. This method refines the results obtained from the initial segmentation process and enhances the overall segmentation accuracy.

Relevant own publications pertaining to this thesis: [GyA8], [GyA9].

Practical Applicability of the Results

The results offer numerous potential applications in medical practice and scientific research. The developed segmentation methods can contribute to faster and more accurate diagnosis of brain tumors, reducing the workload of physicians and improving the quality of patient care. Automatic segmentation allows for tracking changes in the size and shape of the tumor during treatment, providing important information about the effectiveness of the therapy. Moreover, the new methods and algorithms developed during the research can be applied to the processing of other medical imaging data as well, contributing to the further advancement of machine learning and deep learning methods, thereby supporting research and development activities. Additionally, the developed procedures and achieved results can be utilized in education within the fields of medical imaging and machine learning, helping to expand the practical knowledge of students and to acquire modern technological skills.

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