Using 3D Dense-U-Nets to predict MGMT promoter methylation status in glioblastoma

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https://github.com/MMIV-ML/ELMED219-2021

Team #6

1 Research plan

1.1 A brief background to the field

Glioma is the most common type of malignant brain tumour, with glioblastoma multiforme (GBM) being the principal and most aggressive tumour diagnosed in adults.[1] GBMs belong to astrocytic lineage and correspond to grade IV on the WHO classification. They occur almost exclusively in the brain, but in some cases may affect the brain stem, cerebellum and spinal cord.[2] The symptoms can vary greatly depending on the location and tumour size, but are often a result of increased intracranial pressure. These symptoms may include headaches, neurological deficits, and seizures, with the latter being present in a late stage of the disease. Current treatment options at diagnosis are multimodal and include surgical resection, radiation and chemotherapy, with the latter being the current "gold standard" that can target various genetic mutations.[3]

O6-methylguanine-DNA-methyltransferase (MGMT) is a DNA repair gene. Mutations influencing this gene have implications regarding treatment and prognostics. For example, epigenetic silencing through promoter methylation inhibits normal DNA repair. A 2005 study by Hegi et al.[4] found MGMT promoter methylation to be clinically significant for treatment with the chemotherapeutic agent Temozolomide, concluding that patients with GBM that had a methylated MGMT promoter (thus silencing the transcription of the gene) benefited from treatment with the drug. In their study, the median survival was 21.7 months in the group treated with both radiotherapy and Temozolomide, and 15.3 months in the group treated only with radiotherapy. In the group without MGMT promoter methylation there was an insignificant difference between the treatment groups.[4]

Magnetic resonance imaging (MRI) can provide very detailed medical images of soft tissues. This makes MRI particularly suitable for diagnosing brain tumours like GBM. The signal used for calculating MR images is sensitive to a wide range of influences, for example nuclear mobility, molecular structure, flow and diffusion. Consequently, MRI can provide measures of both structure and function.[5] Four standard MRI modalities are typically applied for diagnosing brain tumour: Fluid attenuated inversion recovery (FLAIR), T2-weighted MRI, T1-weighted MRI, and T1-weighted MRI with gadolinium contrast enhancement, each adding different information useful for diagnosing brain tumours.[6].

The usage of machine learning to classify tumour mutation status based on radiology is quite novel. In a 2019 study, Bangalore Yogananda et al.[7] found that they could predict the IDH mutation status of a brain

tumour based on MRI data with a 97.1 per cent accuracy using deep learning methods. They achieved this using multiparametric brain MRI-data from only 214 patients (94 IDH mutated, 120 IDH wild-type). In that study, the authors designed and trained a Dense-U-Net to classify IDH mutated and IDH wild-type gliomas through voxel segmentation of the tumour. The 3D Dense U-Net model used for IDH-classification looks promising even though they had a relatively small data set available. The 3D Dense U-Net achieved a mean cross-validation testing accuracy of 97.14 per cent using only T2-weighted MRI images in this study.

Deep-learning systems are traditionally very data-hungry (meaning they perform better with more data). Bangalore Yogananda et al.[7] study proves that it is possible to create an accurate deep learning algorithm even with limited patient data. Deep learning has also been applied to other genetic variants. A study published in 2017 demonstrated a 94.9 per cent accuracy for predicting MGMT promoter methylation status.[8] They achieved this using a ResNet50 (50 layer deep neural network) algorithm applied to the preoperative MRI data of 155 patients (66 methylated and 89 non-methylated MGMT promoter tumours). We believe the model would have to be even more accurate before it could be used for clinical applications.

1.2 Objectives and expected impact

Our study proposal is deeply inspired by Bangalore Yogananda et al.[7], and we plan to train the same 3D Dense U-Net model to predict MGMT promoter methylation status in GBM patients from preoperative T2-weighted MRI images. Our main objective is to produce an algorithm that is reliable and accurate in classification of MGMT promoter methylation status in GBMs, using deep learning algorithms on T2-weighted MRI data only.

We are expecting clinicians to be able to use the algorithm in early treatment planning and decision making, regarding GBM patients, when biopsies confirming MGMT promoter methylation status has not yet been obtained. This will benefit the patients by speeding up the early decision making regarding start of treatment (chemotherapy, radiotherapy and surgery), potentially increasing survival rates and reducing the impact of the tumour.

1.3 Material and methods

Deep learning is a form of machine learning where the algorithm – derived from unsupervised learning with large amounts of raw data – creates a neural network to solve a predefined problem. In order for an algorithm to be the best possible, training data has to be used so that the algorithm can detect local features of the input data and create patterns. Validation data are used during the training process, and testing data are used after the training process for validation accuracy of the algorithm.

The neural network in this study will be a 3D Dense-U-Net network. The 3D Dense-U-Net network is capable of precise segmentation of the input image data in the original resolution, without any preprocessing of the input image. Image segmentation is used to part the image into areas with common features and therefore extract information from the input image. This is a part of the neural network in the 3D Dense-U-Net network. In a study by Kolařík et al.[9], this type of network achieved an accuracy of 99.72 per cent on an MRI brain data set, which outperformed results achieved by human experts and other deep learning methods (Table: 1).
As mentioned earlier, deep learning methods have already been used to predict MGMT promoter methylation status from MRI, achieving an accuracy of 94.90 per cent using a residual deep convolutional neural network called ResNet50.[8] We want to see if the 3D Dense U-Net can outperform the ResNet50 network and other

Table 1: This table is part of Table 4 from the study by Kolařík et al.[9] It is a comparison of tested U-Net versions on a brain data set in the training phase versus human experts. The metrics used for performance evaluation were: Pixel accuracy (P.A.), Sørensen-Dice coefficient (Dice c.), intersection over union (I.o.U.), average Hausdorff distance [voxel] (A.H.D. [voxel), and area under receiver operator curve (A.u.R.C.). As mentioned before the 3D Dense-U-Net network outperformed the accuracy achieved by the human experts.

3D Networks					
Metric	Dense-U-Net	Res-U-Net	U-Net	Human	FSL
P.A.	0.99703	0.99662	0.99619	0.99489	0.94289
Dice c.	0.98843	0.98686	0.98514	0.98033	0.79698
I.o.U.	0.97713	0.97407	0.97072	0.96141	0.66248
A.H.D. [voxel]	0.01334	0.01911	0.02427	0.02479	4.58848
A.u.R.C.	0.99439	0.99353	0.99205	0.98325	0.96696

networks previously used to differentiate methylated and non-methylated MGMT promoters in glioblastoma.

Instead of the dual-class segmentation of the tumour in IDH mutated and IDH wild-type, this particular study will classify methylated and non-methylated MGMT promoters in GBM. The two volumes created in the T2-net will correspond to the methylated and the non-methylated MGMT promoter part of the tumour. Dual volume fusion of the two respective volumes combines the two volumes and eliminates false positives to generate a tumour segmentation volume. As in the study by Bangalore Yogananda et al.[7], this study will also use majority voting across voxels to determine the overall MGMT promoter methylation status in the glioblastoma. Figure 1 A visualises the study. In the study, the Dense-U-net network were designed with 7 dense blocks, 3 transition down blocks, 3 transition up blocks, an initial convolution layer, a final convolution layer, followed by an activation layer at the end. Each dense block was made up of 5 layers, and each layer was connected to every other layer in that particular dense block. This is illustrated in figure 1 B.

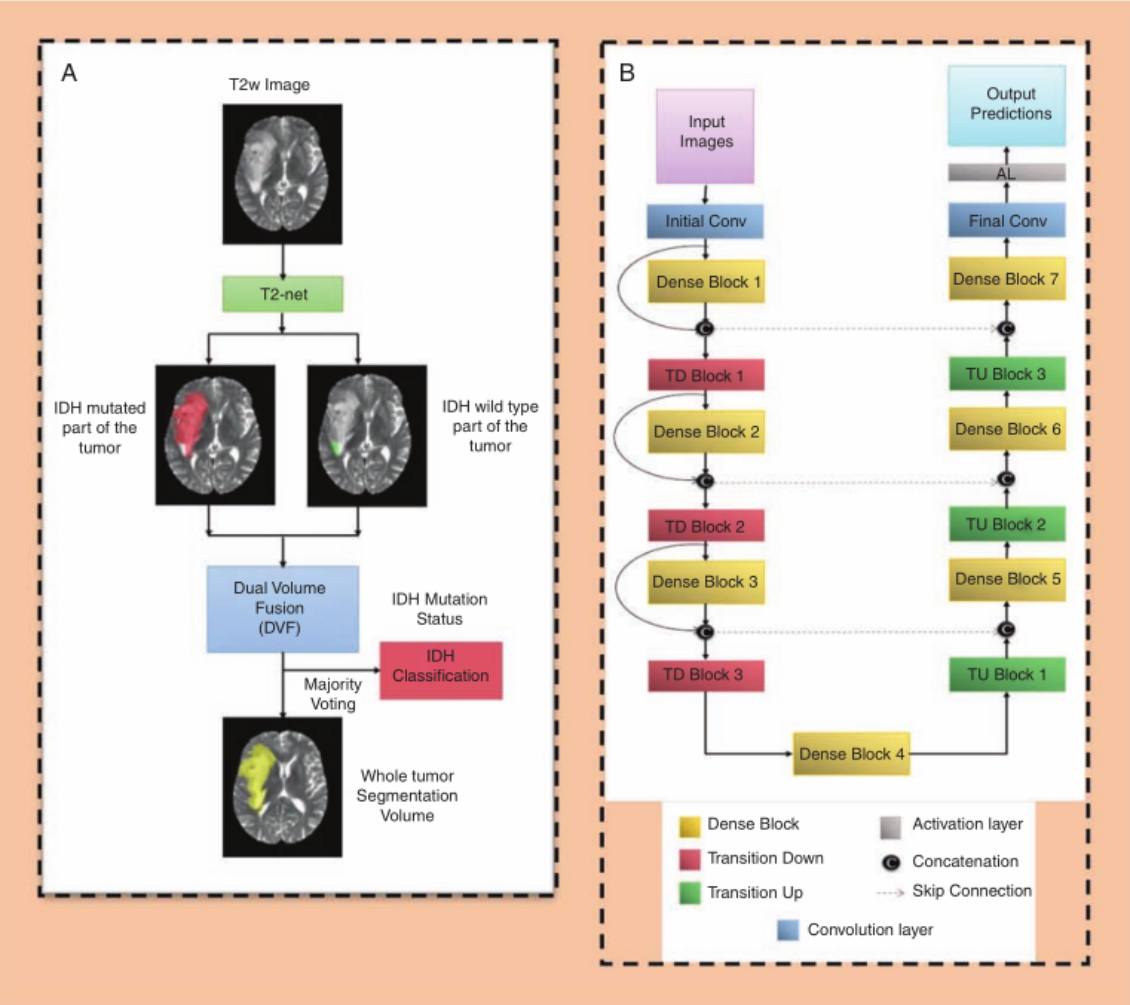

Figure 1: This figure is taken from the study by Bangalore Yogananda et al.[7], fig. 2. Part A is an overview of the IDH classification from T2-weighted image to a whole tumour segmentation volume and classification. Part B is the network architecture for the 3D Dense-U-Net network in the study.

1.4 Evaluation

The data material contains a binary outcome variable for MGMT promoter methylation status that will be used as ground truth for the training set. The MGMT promoter methylation status is based on previously analysed biopsies. The research group will reach out to relevant experts in radiology to create ground truth tumour segmentation. The Sørensen-Dice coefficient will be used to calculate the similarities between ground truth segmentation and network segmentation.

It is possible for a biopsy taken from a heterogeneous tumour to classify tumour status incorrectly. This may affect the validity of the ground truth, but as the method is still considered the golden standard an equal evaluation based on imaging technology is still desirable. The accuracy (percentage of correct predictions divided by the total number of predictions) of MGMT promoter methylation status prediction will be tested on a validation set kept separate from the training set.

2 Data management plan and ethical considerations

The following data management plan is tentative, and subject to change following instructions from the University of Bergen Data Protection Officer and Regional Ethical Committee.

2.1 Description of generated data and code

We will apply for data from the Mid-Norwegian Brain Tumour Registry and Biobank, which contains information on tumour genetics and radiology. Irrelevant information will be stripped from the dataset before any form of analysis takes place, see figure 2. Relevant information will only include MRI data, MGMT promoter methylation data, connected by an anonymous patient identification number. Data augmentation will then be performed to improve the data set, including rotation of images and horizontal and vertical flipping. Data storage and computation will be done using the University of Bergen secure storage system, SAFE (secure access to research data and e-infrastructure).

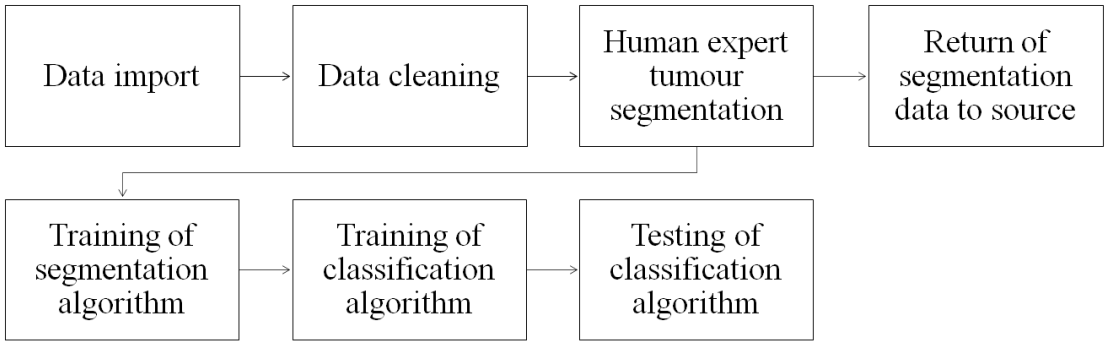

Figure 2: This figure shows the process for data management in the project. Source refers to the Mid-Norwegian Brain Tumour Registry and Biobank.

2.2 Sharing of data and code

The code will be made accessible at GitHub for researchers to use for further research. Relevant data, such as ground truth tumour segmentation by human experts, will be returned to the Mid-Norwegian Brain Tumour Registry and Biobank as part of the agreement. This is done so that the Registry and Biobank can give this information to other researchers for further investigation, should they need it. Any work resulting from this research will be submitted to publication through open access journals to ensure accessibility for all.

2.3 Ethical considerations

This project will have to be approved by regional committees for Medical and Health Research. There are several ethical considerations to take into account which are particularly relevant for the use of medical AI. The project will follow the four principles of AI and ethics proposed by the European Union.[10]

1 - Respect for human autonomy All patients have given their consent to the Mid-Norwegian Brain Tumour Registry and Biobank collecting health data about them as long as anonymity is maintained. The research project will continue to safeguard patient protection and patients have the right to withdraw their consent from the Biobank and Registry at any time. The research project will maintain a human-centric focus on the design of the study, which will hopefully help to open the doors to precision medicine and targeted treatment of GBM in the future.

2 - Prevention of harm First and foremost, we will be using real patient data from the Mid-Norwegian Brain Tumour Registry and Biobank. This is sensitive information regarding patient health status, and can potentially be abused. Thus, access and usage of this information should, and will only be used for carefully planned studies with adequate security. If the algorithm incorrectly labels patients that would otherwise have had biopsies taken, this could lead to clinicians opting out of biopsies, potentially hindering proper evaluation of the patient's tumour. Similarly, if the algorithm is used to replace biopsies, other data that could be available from those biopsies will not be acquired. This would have to be considered before clinical application of the algorithm.

3 - Fairness It is hard to imagine that this algorithm would become discriminatory when it comes to bias, as it only separates GBM on the basis of MGMT promoter methylation. It does not take into account the gender, age, ethnicity or education of the participants. However, seeing as this study will only encompass MRI data from Norwegians, the model might not be valid when it comes to predicting tumours in other groups. It should also be noted that there is a risk that only the patients in countries with high standards of living will be able to afford this technology, as it presupposes access to MRI. Everyone should have access to the benefits of AI.

4 - Explicability Seeing as we plan to use a deep learning algorithm, we also will not be able to fully understand what the computer has done to evaluate the MRI-images. This can hinder the patients right to information as we do not know how the tumour MGMT promoter methylation status was predicted. However, the method can possibly imitate a more invasive test in early stages of examination, provide supplementary information, and help clinicians in making health decisions.

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