Precision medicine and quantitative imaging in glioblastoma

ELMED219 (Artificial Intelligence and Computational Medicine), January 3-28, 2022

https://github.com/MMIV-ML/ELMED219-2022

Team #6

1 Introduction: A brief background to the field

1.1 Brain tumor: Glioblastoma multiforme

Brain tumor is a severe form of cancer and is caused by uncontrolled multiplication of cells leading to abnormal growth of brain tissue. When brain tumors increases rapidly in size, it provides pressure on the brain resulting in abnormal neurological symptoms. Brain tumors are classified as either primary brain tumors or metastatic. The most common type of primary brain tumor is glioblastoma multiforme (GBM), which we will focus on during this project. Glioblastoma multiforme is the most aggressive primary malignant brain tumor in adults. Treatment of glioblastomas consists of chemotherapy, radiotherapy and/or surgery, and the choice of treatment is an important clinical decision based on tumor presence, location, and type. Early and correct diagnosis is fundamental to optimize the treatment. However, there is a lack of effective treatment and there is also inability to preform complete surgical tumor resection. In addition, poor drug delivery contributes to bad prognosis [7]. One of the major challenges in treatment development and response is the Blood Brain Barrier (BBB). With the use of MRI one can detect treatment responses clear with for example shrinkage of the tumor. However, an ineffective drug cannot be distinguished from a drug that simply just do not cross the BBB [7]. This makes it hard to find effective treatment options.

Glioblastoma is considered as a heterogeneous tumor type with intratumoral spatial variation in cellularity and areas of necrosis [7]. Which makes it difficult to resect, and in some cases, inoperable. It exists both high-grade (HG) gliomas, like glioblastoma multiforme (GBM), and low-grade (LG) gliomas, such as oligodendrogliomas or astrocytomas. They are mainly located in the cerebral hemispheres, with a median survival time of 15 months after diagnosis [6].

Biological variables and imaging-derived biomarkers can hopefully help us map out and explain to a certain extent all these observed variations in glioblastoma patients. MGMT promotor methylation status, 1p/19q deletion and IDH1 gene mutation status is among these promising markers that when combined with supervised classification, can be used as imaging biomarkers. In addition to certain host variables such as age and gender [6].

It is most definitely an oversimplification to look at glioblastoma as a single disease. Using molecular subtyping and biomarkers to divide GBM into subgroups is and has been attempted [19]. However, there is no clear distinction between the subgroups, and it is still difficult, expensive and time-consuming in routine clinical practice to differentiate the subtypes of glioblastomas.

Surgical resection of the glioblastoma is the first step in treatment. However, this is not always possible and it is especially difficult when the tumor is located in parts of the brain that controls language and movement. Radiation is the next step of treatment and is often combined with chemotherapy (temozolomide). Radiation has the purpose of damaging the DNA of tumor cells and inhibiting mitosis. Finding the perfect time and dose for the radiation treatment is a specialist job. If we could use machine learning to do this task, it would save both time and rule out human errors.

In this project, our goal is to use machine learning techniques to process MRI images of glioblastoma. The processing firstly includes segmentation and classification of tumors, then further usage of this information and also machine learning to predict radiation dose. With this project we want to outline a method for prediction of patient-specific radiation dose through usage of machine learning. The overall purpose of the project is to achieve better treatment and extended life expectancy for each patient with glioblastoma.

1.2 MRI: Magnetic Resonance Imaging and PET: Positron Emission Tomography

MRI is an important imaging modality and is considered as a standard technique in tumor detection, segmentation and classification. High quality imaging modalities are needed in order to get a clear overview of the entire glioblastoma and also surrounding organs at risk, for instance the eyes. Today's technology offers different imaging variants based on which cancer type the patient have. Some of the most used imaging methods are MRI (magnetic resonance imaging), PET (positron emission tomography) and CT (computer tomography), or also a combination of these.

Briefly explained, the MRI concept is to take advantages of the protons in the body and their magnetic charge [8]. By applying an external magnetic field the protons within the body will get a so-called spin. When different gradient-fields are applied and switched off, the protons will fall back into their initial position and send out a signal which by Fourier transform can be converted into readable signals [8]. In the end this will lead to a picture of the body, with better quality wherever there is a high density of protons. Since the MRI is dependent on the protons, some parts of the body is easier to scan than others. The brain for instance consists of fat, water and other proton-rich elements which means that MRI is a good choice when it comes to scanning of the brain.

The MRI scan alone may though not be sufficient in order to declare the extent of the tumor. Often the MRI is combined with the PET scan to get a better picture of where the tumor is located. While the MRI scan will show the contrasts in tissue, the PET scan will have lower resolution on the body contours, but will on the other hand light up the tumor and can also light up potential metastasis around the main tumor [13].

Before a PET scan the patient is injected with a contrast medium which contains a radioactive isotope. The different parts in the body will take up different amounts of the contrast liquid, and this is what is taken advantage of in the scan. The radioactive isotope will send out gammas for the detector around the patient to detect. Due to the time of detection of the gammas, and where they are detected, it is possible to create an image of the patient where the area of the tumor will "light up". The most common contrast medium is FDG, short for Fluorodeoxyglucose, but when imaging the brain, another contrast medium has shown to be more useful [13]. This medium is called 11C-methyl-methionine [13]. This tracer is taken up by glioma-cells but have a lower uptake in cerebral tissue around the tumor [13]. The delineation of the tumor will therefore be easier, and especially if this is combined with MRI.

See figure 1 for MRI images of a glioblastoma.

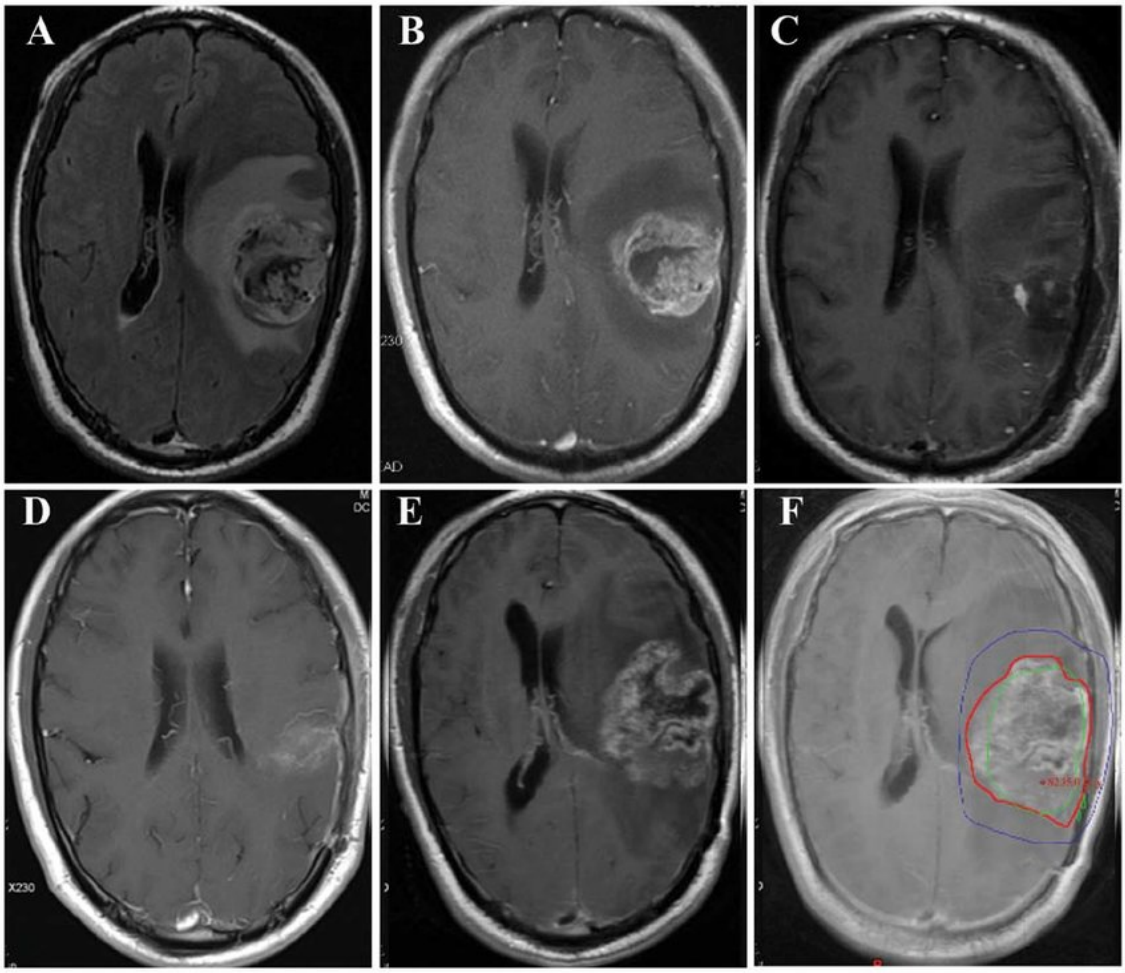

Figure 1: MRI scan images of glioblastoma multiforme (Image taken from [20])

See figure 2 for a PET scan image of a glioblastoma together with a MRI image.

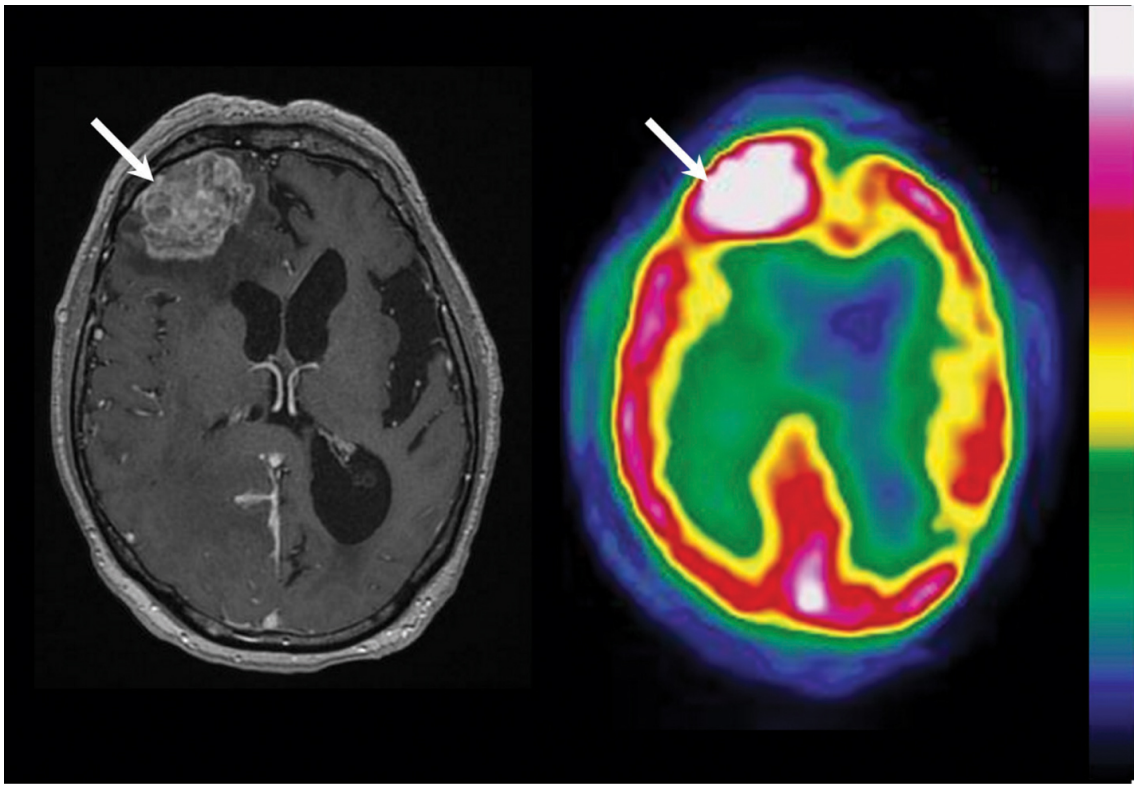

Figure 2: Images of a glioblastoma. On the left hand side - a MRI scan, on the right hand side - a PET scan. (Image taken from [13])

1.3 Machine learning

Modern machine learning techniques have been developed and applied to simplify the use of brain images and to enhance the obtained information. The machine learning techniques have led to development of both semiautomatic and fully automatic brain tumor diagnosis. However, the clinical application of these methods is limited, primarily because of the lack of connection between clinicians and researchers.

1.4 Imaging-derived biomarkers for glioblastoma

All glioblastoma tumors presents similar or overlapping phenotypes, although every glioblastoma mutiforme tumors differs in both representation and progression. Histological profiling is used to expose the phenotypes, but it presents a challenge as it require resection or biopsy of the brain tissue. This is problematic due to the sensitive nature of the brain. Therefore, non-invasive diagnostic measures is beneficial if they are able to identify and differentiate glioblastoma tumors.

Biomarkers is a potentially non-invasive diagnostic tool, that focuses on molecular markers beyond the phenotypic differences that are described through biopsy or resection of brain tissue. Glioblastoma multiforme microvesicles may be useful to detect microenviroments that are hospitable to tumor growth. Therefore the serum that the microvesicles is in should be further studied in order to provide highly valuable diagnostic information from non-invasive methods. Microfluidic chips can be used to detect microvesicles in the bloodstream, and therefore be used as a diagnostic tool for gliblastoma multiforme tumors. Regular measures of biomarkers is also useful to detect recurrence of cancer, and then provide quick identification with subsequent quick treatment. Through treatment measures of biomarkers will also give an indication on whether the treatment, radiotherapy, chemotherapy or both, is working or not [4].

2 Objectives and expected impact

Images from MRI and/or PET scan needs to thoroughly studied before deciding treatment of patients with glioblastoma. If radiotherapy is considered as the optimal treatment, the MRI pictures are necessary during the whole treatment time. That includes the basics in the planning of radiation angles. Therefore the images are a central part in the development of predicting a patient-specific radiation dose.

2.1 Material and methods

The goal of this project is to use machine learning, more precisely supervised deep learning, to predict patient-specific radiation dose in glioblastoma. We will use supervised learning, where our model is trained on data with available output variables, and the model is trained to match the relation between the different input variables and the output variables [9]. We will use the datasets "The Cancer Genome Atlas Glioblastoma Multiforme" (TCGA-GBM), "Genomic Data Commons" (GDC) and "The Cancer Imaging Archive" (TCIA) as input data to our deep learning model. TCGA contains demographic, clinical, patholofigal and/or genomic data, GDC contains clinical, genetic and pathological data, while TCIA contains radiological data. Clinical and genomic data from GDC can be matched to patient identifiers of images in TCIA. Radiology images stored in TCIA is also identified with a Patient ID, identical to the Patient ID of the same subject for data in TCGA. By matching the Patient ID, it is possible to generate datasets that combine radiological images with the corresponding patient information, even though this is stored in different datasets [3]. After analyzing the MRI images and other features from the dataset, we want our model to be able to predict the optimal radiation dose for each individual patient.

There are several benefits using machine learning in medicine. Some benefits are the machine learning's ability to "increase the speed and efficiency of manually labor-intensive tasks, standardize output where subjective or human error is a significant factor, or potentially improve accuracy where results are definitive" [9]. It is important to choose a good machine learning model with the right features and hyperparameters, which will be discussed later.

Different machine learning techniques can be used in brain tumor diagnosis, treatment stratification and prediction. Brain tumor diagnosis is roughly divided into three parts; detection (detecting presence or absence of tumors from MRI images), segmentation (localizing and isolating different tumor tissues inside the MRI images) and classification (for example classification of abnormal MRI images as malignant or benign tumors) [1].

Segmentation is important to change the MRI images to be more significant and easier to analyse in our machine learning model [1]. Manually performed segmentation must be performed by a neuroradiologist, and is a difficult and time-consuming task [15]. Many different machine learning methods (and deep learning methods) and techniques are developed for brain tumor segmentation based on MRI images, which can lead to a more effective therapy progress and more precise therapy. One option, which we will use in our project, is the U-Net; a convolutional network architecture for fast and precise segmentation of images. See figure 3 for graphically description of how the U-Net works, and [16] and [18] for more details.

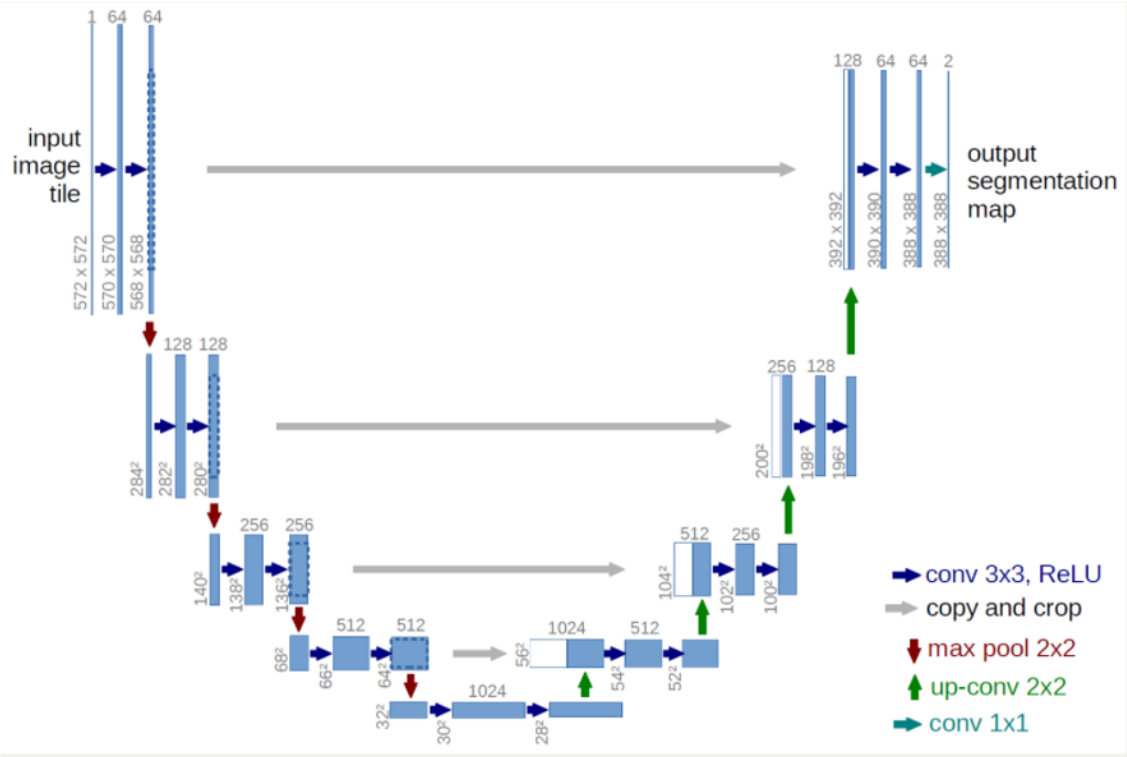

Figure 3: "Architecture (example for 32x32 pixels in the lowest resolution). Each blue box corresponds to a multi-channel feature map. The number of channels is denoted on top of the box. The x-y-size is provided at the lower left edge of the box. White boxes represent copied feature maps. The arrows denote the different operations". The figure and its description is created by the Computer Vision Group, Dept. of Computer Science, University of Freiburg [18].

"Classification is the process for assigning the input features to different classes or categories. Feature extraction and selection are very important for particularly brain tumor classification" [1]. Classification is an important operation which divides the MRI images into smaller subgroups, and thus helps to prepare the data for the prediction. Various machine learning methods are developed for brain tumor classification through MRI images. What method to use depends on what "output" you want to generate – what properties you want your data to have for the machine learning model for prediction. Exactly how we want to classify the MRI-images in our project and thus which machine learning model we will use for classification, requires further investigation. It may be worthwhile to train our model for prediction on data that is classified in different ways with different methods, and then evaluate the model to check which classifications contribute to a better or worse model. However, if we for example decide to use a classifier to distinguish between metastatic and primary brain tumors on MRI-images (which is most likely relevant for radiation dose and we thus will want to implement), this can be done using PNN (probabilistic neural network), incorporating LSFT (non-linear least squares features transformation), as in the study "Improving brain tumor characterization on MRI by probabilistic neural networks and non-linear transformation of textural features" [10]. Gradually, when we choose which other classifications that will increase the accuracy of the predictions of radiation dose in our project, we will have to make similar assessments for which classification models to use.

Before building the deep learning method for prediction of patient-specific radiation dose in glioblastoma, the data needs to be prepared. Our project is inspired of the study "Deep learning method for prediction of patient-specific dose distribution in breast cancer" described in [2] by Ahn, S.H. et al. In the study, CT images and a database of VMAT plans for left-sided breast cancer patients were used as training and

validation datasets to a deep learning model, with the goal of predicting patient-specific dose distribution in breast cancer [2]. Our goal is to largely follow the procedure in this study, but to a greater extent based on MRI images, features in the TCGA/TCIA dataset [3], and radiation doses used on these previous patients from the dataset. As in the previous mentioned study, our network will be based on Keras, an open-source software library in Python, which you can learn more about on Github [12]. For the dose prediction, we will use the model DpNet: dose prediction deep neural network. The DpNet performs a down- and up-sampling path, which can use different combinations of convolution layers for the sampling paths [2]. When machine learning models are being trained, there is a risk that the model can become overfitted – the model fits too well with training data, but does not generalize. To avoid overfitting, it is possible to add batch normalization [5]. We can also use an optimizer, which is an algorithm that finds the value of the weights that minimizes the error when mapping inputs (features from the data) to outputs (predictions). One option is to use the Adam optimizer [11].

The DpNet model is as mentioned going to be trained on TCGA/TCIA data. After the model is trained, it is being validated on a separate dataset, containing the same data information as the training data. Figure 4 shows how DpNet is being trained, validated and used for dose prediction.

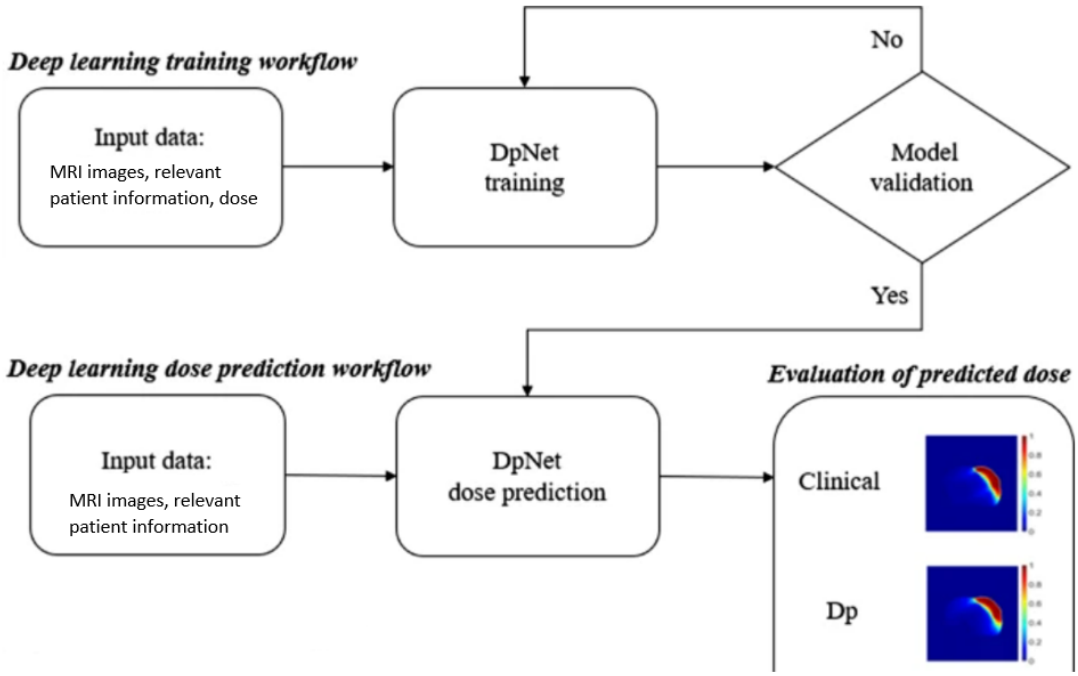

Figure 4: Flowchart for DP: deep learning dose prediction, modified figure 2 from [2].

2.2 Evaluation

Our goal is to predict a radiation dose best suited to a specific patient. Absolute dose error between the actual dose a patient (from validation data) received and the predicted dose the model suggests for the same patient can therefore give a good indication of the generalizability of our model. Absolute dose error can be calculated using the following equation from [2] .

Percentage of absolute error = $|\frac{Clinicaldose - Predicteddose}{Clinicaldose}| * 100\%$

Mean squared error can also be used in calculating the difference between actual (clinical) dose and predicted dose. MSE is a loss function that measures the accuracy of our DpNet machine learning model,

which means how accurately the model predicts the expected outcome i.e. the truth [17]. MSE is calculated using the following equation from [2] :

$$\text{MSE} = \frac{1}{n}\sum_{i=1}^{n}(D_p^i - D_c^i)^2$$

References

[1] Abd-Ellah MK, Awad AI, Khalaf AAM, Hamed HFA. A review on brain tumor diagnosis from MRI images: Practical implications, key achievements, and lessons learned. Magnetic Resonance Imaging. 2019;61:300-318. Accesed 19/01/2022 https://www.sciencedirect.com/science/article/pii/S0730725X18304302

[2] Ahn SH, Kim E, Kim C, Cheon W, Kim M, Lee SB et al. Deep learning method for prediction of patient-specific dose distribution in breast cancer. Radiation Oncology. 2021;16. Accessed 19/01/2022 https://ro-journal.biomedcentral.com/articles/10.1186/s13014-021-01864-9?fbclid=IwAR0l8fDU2kUd-jAj-pDf0kR_if35uf-aN3wKUaFK8D7m7BInRL7MAG-yFrQ

[3] Aldape K, Brindle KM, Chesler L et al. Challenges to curing primary brain tumours. Nat Rev Clin Oncol 2019;16:509–520. https://doi.org/10.1038/s41571-019-0177-5

[4] Aldape K, Brindle KM, Chesler L, Chopra R et al. Challenges to curing primary brain tumours. Nat Rev Clin Oncol . 2019 Aug;16(8):509-520. https://pubmed.ncbi.nlm.nih.gov/30733593/

[5] Analytics India Magazine. Hands-On Guide To Implement Batch Normalization in Deep Learning Models [online]. [published 25/07/2020, accessed 19/01/2022] https://analyticsindiamag.com/hands-on-guide-to-implement-batch-normalization-in-deep-learning-models/

[6] Baid U, Rane SU, Talbar S, Gupta S, Thakur MH, Moiyadi A, Mahajan A. Overall Survival Prediction in Glioblastoma With Radiomic Features Using Machine Learning. 2020.https://www.frontiersin.org/articles/10.3389/fncom.2020.00061/full

[7] Chaddad A, Tanougast C. Extracted magnetic resonance texture features discriminate between phenotypes and are associated with overall survival in glioblastoma multiforme patients. 2016; 54, 1707-1718. https://link.springer.com/article/10.1007%2Fs11517-016-1461-5

[8] Cox I.J, Crossey M.M.E, Grover V.P.B, McPhail M.J.W, Taylor-Robinson S.D and Tognarelli J.M. Magnetic Resonance Imaging: Principles and Techniques: Lessons for Clinicians. PMC. 2015; 5(3): 246–255. DOI: 10.1016/j.jceh.2015.08.001

[9] Field M, Hardcastle J, Jameson M, Aherne N, Holloway L. Machine learning applications in radiation oncology. Physics and Imaging in Radiation Oncology. 2021;19:13-24. Accesed 19/01/2022 https://www.sciencedirect.com/science/article/pii/S2405631621000300

[10] Georgiadis P, Cavouras D, Kalatzis I, Daskalakis A, Kagadis GC, Sifaki K, Malamas M, Nikiforidis G, Solomou E. Improving brain tumor characterization on MRI by probabilistic neural networks and non-linear transformation of textural features. Comput Methods Programs Biomed. 2008;89(1):24-32. Accessed 19/01/2022 https://www.sciencedirect.com/science/article/pii/S0169260707002404

[11] Gupta A. A Comprehensive Guide on Deep Learning Optimizers. Analytics Vidhya. 2021. Accessed 19/01/2022 https://www.analyticsvidhya.com/blog/2021/10/a-comprehensive-guide-on-deep-learning-optimizers/

[12] Keras: Deep Learning for humans. Accessed 19/01/2022 https://github.com/keras-team/keras

[13] Langen K., Verger A. Glioblastome: PET Imaging in Glioblastoma: Use in Clinical Practice. 1. Brisbane: Codon publications; 2017. Hentet: 21.01.2022. Tilgjengelig fra: ttps://www.ncbi.nlm.ni.gov/books/NBK470000/chapter21.r01

[14] Louis DN, Perry A, Reifenberger G et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803–820. https://doi.org/10.1007/s00401-016-1545-1

[15] Ranjbarzadeh R, Kasgari BA, Ghoushchi JS et al. Brain tumor segmentation based on deep learning and an attention mechanism using MRI multi-modalities brain images. Scientific Reports. 2021;11. Accessed 19/01/2022 https://www.nature.com/articles/s41598-021-90428-8#citeas

[16] Ronneberger O, Fischer P, Brox T. U-Net: Convolutional Networks for Biomedical Image Segmentation. Medical Image Computing and Computer-Assisted Intervention (MICCAI). 2015;9351:234-241. Accessed 19/01/2022 https://link.springer.com/chapter/10.1007%2F978-3-319-24574-4_28

[17] Seif G. Understanding the 3 most common loss functions for Machine Learning Regression. 2019. Accessed 19/01/2022 https://towardsdatascience.com/understanding-the-3-most-common-loss-functions-for-machine-learning-regressio

[18] Uni Freiburg. Pattern Recognition and Image Processing [online]. Freiburg: [2015; accessed 19/01/2022] Available from: https://lmb.informatik.uni-freiburg.de/people/ronneber/u-net/

[19] Verhaak RGW, Hoadley KA, Purdom E, Wang V, Qi Y….Hayes, DN. Integrated Genomic Analysis Identifies Clinically Relevant Subtypes of Glioblastoma Characterized by Abnormalities in PDGFRA, IDH1, EGFR, and NF1. 2010; 17 (1). 98-110. https://www.sciencedirect.com/science/article/pii/S1535610809004322?via%3Dihub

[20] Zhou, Xiaofeng and Liao, Xiaofang and Zhang, Bicheng and He, Huijuan and Shui, Yongjie and Xu, Wenhong and Jiang, Chaogen and Shen, Li and Wei, Qichun, year = 2016, month = 06, pages = , title = Recurrence patterns in patients with high-grade glioma following temozolomide-based chemoradiotherapy, volume = 5, journal = Molecular and Clinical Oncology, doi = 10.3892/mco.2016.936

3 Data management plan and ethical considerations

3.1 Description of generated data and code

The objective of the project is to predict patient-specific radiation dose based on MRI images and patient information. By using deep learning instead of traditional machine learning models, the computer itself will learn useful representations and features from the raw data. Thus, we don't have to do the manual, and hard, work of designing features from the data. This is called feature learning [1].

We will be using the different datasets mentioned in 2.1 to train our model. By combining these datasets we will train our model using MRI images and personal data about the patient. The personal data, or features, of the patients consist of age, gender, if they are dead or alive, race and ethnicity. If the patient is dead, information about how long the patient survived after being diagnosed is also available.

As mentioned earlier, the goal of this project is to predict a patient-specific treatment based on MRI images and patient information, therefore we would also need to get access to the patients treatment history to be able to make a model that would be able to predict a treatment. To make a good model, we would need information about which treatment each patient got, if it was chemotherapy, radiation or surgery, and the survival time after the treatment started and other features. Together with the patient features, MRI images and their treatment history we think a good model could be made to predict a patient-specific treatment with good result.

3.2 Sharing of data and code

All generated code in this project will be made available to the public through GitHub. By doing this, others can fork the project to modify the code as they please. The data used to train the model are already available to the public through the National Cancer Institute GDC Data Portal [2].

3.3 Ethical considerations

In June 2021 the World Health Organization published a guideline on Ethics Governance of Artificial Intelligence for Health [6]. This is a product of deliberation between experts in ethics, digital technology, law, human rights and more. Even though new technology can help to improve diagnosis, treatment etc, they must put ethics and human rights at the heart of the design. They have outlined six principles for the ethical use of AI in health, which we will ensure is maintained throughout our project. These six ethical principles are listed in table 1. WHO's guidelines creates a framework for the general use of artificial intelligence in health, but we also need to consider the demands i the Norwegian context. All research project in this field require approval of the Regional Committee for Medical and Health Research Ethics in advance. This includes all research with humans, biological material from humans and/or personal health information. Studies defined as experimental studies and pilot studies, such as our study, must also be approved by the Regional Committee for Medical and Health Research Ethics.

Principle	Description
Protect autonomy	Health decisions shall not be made entirely by machines, humans should be able to override them. Health AI also requires the pasient's consent and dataprotection.
Promote human safety	AI tools shall be continuously monitored by developers to control their quality
Ensure transparency	Information about the AI tools shall be published and available to doctors and researchers so they can know how the AI makes its decisions.
Foster accountability	If the AI makes a wrong decision or something else goes wrong with the AI, there shall be possible to determine who is responsible.
Ensure equity	The AI tools shall be available in multiple langugages so that everyone has the the same opportunity to access and use the tools. The tools must also be trained on diverse sets of data.
Promote AI that is sustainable	Developers shall always be able to update their tools, and only tools that can be updated or repaired shall be used.

Table 1: WHO's six ethical principals for health AI, available from [5]

References

[1] An overview of deep learning in medical imaging focusing on MRI. Accessed on 20/01/2022.
https://www.sciencedirect.com/science/article/pii/S0939388918301181

[2] National Cancer Institute GDC Data Portal. Accessed on 02/01/2022.
https://portal.gdc.cancer.gov/repository?facetTab=cases&filters=%7B%22op%22%3A%22and%22%2C%22content%22%3A%5B%7B%22content%22%3A%7B%22field%22%3A%22cases.demographic.days_to_death%22%2C%22value%22%3A%5B%22365%22%5D%7D%2C%22op%22%3A%22%3E%3D%22%7D%2C%7B%22content%22%3A%7B%22field%22%3A%22cases.diagnoses.age_at_diagnosis%22%2C%22value%22%3A%5B7305%5D%7D%2C%22op%22%3A%22%3E%3D%22%7D%2C%7B%22op%22%3A%22in%22%2C%22content%22%3A%7B%22field%22%3A%22cases.project.project_id%22%2C%22value%22%3A%5B%22TCGA-GBM%22%5D%7D%7D%5D%7D&searchTableTab=cases

[3] The TCGA-GBM data collection. Accessed on 02/01/2022.
https://wiki.cancerimagingarchive.net/display/Public/TCGA-GBM

[4] Vollmer S, Mateen BA, Bohner G et al. Machine learning and artificial intelligence research for patient benefit: 20 critical questions on transparency, replicability, ethics, and effectiveness. BMJ 2020;368:l6927.
https://www.bmj.com/content/368/bmj.l6927

[5] Wetsman N. WHO outlines principles for ethics in health AI. 2021. Accessed on 20/01/2022.
https://www.theverge.com/2021/6/30/22557119/who-ethics-ai-healthcare?fbclid=IwAR3ooC42IfARSIiIwkuXouiynanq-P-kNjCVkbbZyCEB4mEhxqh1vHWPEM0

[6] World Health Organization. Ethics and governance of artificial intelligence for health. Accessed on 20/01/2022.
https://www.who.int/publications/i/item/9789240029200