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Structural and functional tracking in longitudinal magnetic resonance imaging of glioblastoma

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Preface

This thesis is submitted in partial fulfillment of the requirements for the degree of *Philosophiae Doctor* at the University of Oslo. The research presented here was conducted at the University of Oslo and at Oslo University Hospital, under the supervision of Kyrre E. Emblem and professor Eirik Malinen.

This work was supported by the European Research Council ERC through grant 758657, the Norwegian Research Council through grant 261984 and the South-Eastern Norway Regional Health Authority through grant 2017073.

The thesis is a collection of three papers, presented in chronological order of writing. The common theme to them is structural and functional tracking of magnetic resonance imaging data of Glioblastoma with the objective to improve the diagnostic and prognostic accuracy of the disease. The papers are preceded by an introductory, aims and background chapter that relate them to each other and provides background information and motivation for the work.

The first paper is joint work with Oliver M. Geier, Ingrid Digernes, Elies Fuster-Garcia, Grethe Løvland, Einar Vik-Mo, Torstein R. Meling and Kyrre E. Emblem, the second paper joint work with Elies Fuster-Garcia, Siri F. Svensson, Christopher Larsson, Jonas Vardal, Atle Bjørnerud and Kyrre E. Emblem, and the third paper joint work with Elies Fuster-Garcia, Jingpeng Li, Atle Bjørnerud, Christopher Larsson, Siri F. Svensson and Kyrre E. Emblem. I am the first and corresponding author of the first and third paper, and second author of the second paper.

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I acknowledge my main supervisor Kyrre E. Emblem for kickstarting my journey into research. This has not only involved extensive project and grant writing prior to my time at Oslo University Hospital, but also substantial efforts to assure clinically relevant results and to improve my academic writing.

Associate professor Elies Fuster-Garcia offered much of his time at Oslo University Hospital to teach me medical physics as a fresh doctoral candidate and has been an invaluable resource for bridging the gap between computational methods and clinical research, both theoretical and practical, throughout my entire research period. Siri F. Svensson, that started her doctoral period at about the same time as me and in the same research group, has been a great partner to share experiences and challenges.

Through professor Atle Bjørnerud and his computational radiology and artificial intelligence research group additional collaborators were formed that have been valuable in shaping the technical aspect of my work, enabling me to gain practical experience in hardware and software systems and maintenance for research, and generally keeping me motivated as a doctoral candidate. Some of them were the doctoral candidates Jingpeng Li, Jon Andre Ottesen and Lidia Luque, software engineers Jon Nesvold and Martin Rørvang.

✶ Ivar Thokle Hovden

Oslo, December 2022

List of papers

1. Hovden, I.T., Geier, O.M., Digernes, I., Fuster-Garcia, E., Løvland, G., Vik-Mo, E., Meling, T.R., Emblem, K.E., 2020. The impact of EPI-based distortion correction of dynamic susceptibility contrast MRI on cerebral blood volume estimation in patients with glioblastoma. *European Journal of Radiology* 132, 109278.
<https://doi.org/10.1016/j.ejrad.2020.109278>
2. Fuster-Garcia, E., Thokle Hovden, I., Fløgstad Svensson, S., Larsson, C., Vardal, J., Bjørnerud, A., Emblem, K.E., 2022. Quantification of Tissue Compression Identifies High-Grade Glioma Patients with Reduced Survival. *Cancers* 14, 1725.
<https://doi.org/10.3390/cancers14071725>
3. Thokle Hovden, I., Fuster-Garcia, E., Li, J., Bjørnerud, A., Larsson, C., Fløgstad Svensson, S., Emblem, K.E., 2022. A Parametric Evaluation of Deformable Image Registration Methods for Assessing Glioblastoma Growth. *Medical Physics* (submitted and in review).

Other related articles

1. Gu, X., Eklund, A., 2019. Evaluation of Six Phase Encoding Based Susceptibility Distortion Correction Methods for Diffusion MRI. *Frontiers in Neuroinformatics* 13.
<https://doi.org/10.3389/fninf.2019.00076> (acknowledgements in software)
2. Fløgstad Svensson, S., Fuster-Garcia, E., Latysheva, A., Fraser-Green, J., Nordhøy, W., Isam Darwish, O., Thokle Hovden, I., Holm, S., Vik-Mo, E.O., Sinkus, R., Eeg Emblem, K., 2022. Decreased tissue stiffness in glioblastoma by MR elastography is associated with increased cerebral blood flow. *European Journal of Radiology* 147, 110136.
<https://doi.org/10.1016/j.ejrad.2021.110136>

Other communications

Table 1: Other written communications (i.e. essays, conference abstracts and posters that are part of the doctoral fellowship).

Year	Title	Type
2018	Internet of Heads	MNSES9100 essay
2019	Hovden, I.T., Digernes, I., Emblem, K.E.. Susceptibility Distortion Correction for Registration of Perfusion and Anatomical MRI	ISMRM 2019 abstract
2019	Optimizing Artificial Neural Network Hyperparameters and Architecture	IN9400 review
2019	Echo Planar Imaging (EPI) Distortion Correction for Accurate Coregistration of Perfusion and Anatomical MRI	NMFM 2019 abstract and poster
2019	Hovden, I.T., Digernes, I., Geier, O.M., Digernes, Løvland, G., Vik-Mo, E., Meling, T.R., Emblem, K.E. How does magnetic susceptibility distortion impact EPI-based perfusion MRI?	ESNR 2019 & GeiloWS 2020 abstract and poster
2019	Hovden, I.T., Geier, O.M., Digernes, I., Fuster- Garcia, E., Løvland, G., Vik-Mo, E., Meling, T.R., Emblem, K.E. Increased cerebral blood volume in cortical and subcortical brain regions in Glioblastoma patients after EPI distortion correction	ISMRM 2020 abstract
2020	Installation and documentation of remote access (VPN) connection for CRAI during and after the Covid pandemic	Research support documentation
2021	Fuster-Garcia, E., Albarracín, J.J., Hovden, I.T., Ávarez-Torres, M., Rovira, A., Oleaga, L., Revert, A.J., Filice S., García-Gómez, J.M., Emblem, K.E. The use of a DSC-MRI perfusion atlas for cerebral blood volume normalization and its impact in improving prognostic estimation	ISMRM 2021 abstract and poster

Table 2: Oral communications (mostly presentation slides) highlighting the various research meetings and discussions of the doctoral fellowship.

Year	Title	Type
2018	Geometrisk korreksjon av EPI for perfusjonsbilder	Presentation
2019	Echo-planar Imaging distortion correction in Glioblastoma patients	Presentation KRN PhD Seminar
2019	The Impact of EPI-based Distortion Correction of Dynamic Susceptibility Contrast MRI in Patients with Glioblastoma	Presentation MAGNETOMforum
2019	3. Semesterrapportering	Presentation
2019	Programvaretips for dyp læring	Presentations

2019	Workshop i bruk av Git og GitHub, avdeling for diagnostisk fysikk (ADF), Oslo universitetssykehus (OUS)	Presentation
2019	Visuell tolkning av (dype) konvolusjonelle nevraltnett	Presentation
2020	Hovden, I.T., Geier, O.M., Digernes, I., Fuster-Garcia, E., Løvland, G., Vik-Mo, E., Meling, T.R., Emblem, K.E., 2020. Increased cerebral blood volume in cortical and subcortical brain regions in Glioblastoma patients after EPI distortion correction	Presentation ISMRM 2020
2020	Two models for pushing tumor growth	Presentation
2020	Synthetic tumor growth models for validating displacement estimation algorithms on Glioblastoma progression	Presentation
2020	Installation and documentation of remote access (VPN) connection for CRAI during and after the Covid pandemic	Research support
2021	Validating the use of nonrigid registration methods for tracking tumor growth by benchmarking methods on synthetic growth cases with known ground truth displacements	Presentation
2021	Displacement in brain cancer	Presentation
2021	Displacements in brain cancer imaging	Presentation
2021	Synthetic and estimated tissue displacement in high-grade glioma	Presentation
2021	Retrospektiv analyse av glioblastom	Presentation
2021	Statistisk modellering av behandlingsrespons	Presentation
2021	Principal components, autoencoder and glioblastoma	Presentation
2020-2021	cancer-sim	Presentations
2022	Quantification of ventricle and tumor volume change in treatment of glioblastoma (tumors vs. ventricles)	Presentations
2022	CBV vs. ventricles	Presentation
2022	Developing reproducible research imaging datasets	Presentation
2019-2022	Hardware and software setup and installation support and user management for data analysis servers at Department of Physics and Computational Radiology and CRAI: gpu-fys, Miniserver1, Miniserver2, Miniserver3. Disposal by researchers, physicists, engineers and students at UiO and OUS	Research support

Acronyms and important symbols (by first appearance)

CNS	Central nervous system
MRI	Magnetic resonance imaging
ROI	Region of interest
T1w	T_1 weighted
T1wc	T_1 weighted post-contrast
T2w	T_2 weighted
FLAIR	Fluid-attenuated inversion recovery
PNS	Peripheral nervous system
CSF	Cerebrospinal fluid
BBB	Blood-brain barrier
CT	Computed tomography
PET	Positron emission tomography
DTI	Diffusion tensor imaging
BOLD	Blood oxygenation level dependent
EEG	Electroencephalography
MEG	Magnetoencephalography
GBM	Glioblastoma (multiforme)
AAIR	Age-adjusted incidence rate
WHO	World Health Organization
HGG	High-grade glioma
IDH	Isocitrate dehydrogenase
CRT	Chemoradiotherapy
TMZ	Temozolomide
CBV	Cerebral blood volume
RANO	Response assessment in neuro-oncology
NMR	Nuclear magnetic resonance
B	Magnetic field or flux density (vector field) [<i>Tesla</i>]
RF	Radiofrequency
T_1	Tissue dependent transversal (spin-lattice) relaxation time constant

T_2	Tissue dependent longitudinal (spin-spin) relaxation time constant
FID	Free induction decay
T_2^*	FID time constant
R_2^*	FID relaxation rate
TR	Repetition time
TE	Echo time
GE	Gradient echo
SE	Spin echo
Gd	Gadolinium
CA	Contrast agent
GBCA	Gd-based CA
TI	Inversion time
DSC	Dynamic susceptibility contrast
R_2	T_2 relaxation rate
AIF	Arterial input function
EPI	Echo-planar imaging
χ	Magnetic susceptibility (dimensionless quantity)
ΔB	Inhomogeneities in $\mathbf{B}$ (scalar field)
T	Dense voxel coordinate displacement transformation
$\mathbf{d}$	Voxel coordinate displacement field (vector field)
FSL	FMRIB Software Library
TOPUP	EPI distortion correction method from FSL
EPIC	EPI distortion correction method
DCT	Discrete cosine transform
DFT	Discrete Fourier transform
SyN	Symmetric normalization
CC	Cross-correlation
ANTs	Advanced normalization tools
LDDMM	Large deformation diffeomorphic metric mapping
MI	Mutual information
DICOM	Digital imaging and communications in medicine

NIFTI Neuroimaging informatics technology initiative
SPM Statistical parametric mapping
MNI Montreal neurological institute
ICBM International consortium for brain mapping
ANOVA Analysis of variance
AUC-ROC Area under the receiving operating characteristic curve
KM Kaplan-Meier
DL Deep learning
BIDS Brain imaging data structure
DVC Data version control
QC Quality control
RBF Radial basis function
AE Autoencoder
PCA Principal component analysis
SVD Singular value decomposition
NIPALS Non-linear iterative partial least squares

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1. Introduction

Brain cancer is a deadly form of central nervous system (CNS) cancer within the restricted space of the skull in the brain leading to poor treatment options and prognosis. Magnetic resonance imaging (MRI) is the preferred method for imaging and assessing response from all stages of treatment, involving pre-surgical planning, surgery, chemo and radiotherapy.

MRI provides excellent tissue contrast for imaging cancer and treatment specific biological processes. Some examples are quantification of volume change in delineated regions of interest (ROIs), detecting structural deformations from the mass effect of a growing tumor, and detecting intensity increase from active tumor regions as a result of endogenous magnetic contrast agent accumulation on T1-weighted post-contrast (T1wc) MRI. Two other examples are intensity image increase from swelling and inflammatory regions from treatment on T2-weighted (T2w) fluid attenuated inversion recovery (T2w-FLAIR) MRI, as well as from cerebral blood volume increase on perfusion MRI.

Since brain cancer diagnostics and prognostics depend on these MRI methods, it is essential that they provide stable and comparable images and values. The thesis tackles such issues by investigating diagnostic and prognostic aspects and utilities of various image geometry and intensity correction methods as well as deformable registration.

The main outcome of this work is an investigation into tracking clinically meaningful imaging properties of single series and longitudinal MRI of brain cancer. It provides methodology to achieve fine grained analysis of structural and functional changes as function of disease progression and treatment response. This may enable better and earlier stratification of

brain cancer patients into different treatment regimen and thus more personalized treatment options.

2. Aims

The three publications which are the main scientific contributions in the doctoral work, constitute the following aims:

Paper 1

Investigate the impact of magnetic susceptibility distortion correction on geometry and intensity of cerebral blood volume estimated from perfusion MRI.

Paper 2

Develop tissue displacement biomarkers from deformable registration with association to RANO treatment assessment and overall survival prediction.

Paper 3

Develop a tumor tissue deformation model for performing parametric evaluations of geometric accuracy of deformable registration methods in brain tumor MRI.

3. Background

3.1. The brain

The brain is a vital organ that together with the spinal cord forms the CNS. This is where we process and interpret thoughts, memory, emotion, touch, motor skills, vision, breathing, temperature, hunger and every process that regulates our body.

It runs on chemical energy, mostly glucose transmitted through the blood supply, to process and make sense of sensory input using combined electrical and chemical signals within and across functional tissue of various brain regions. Sensory information such as touch, vision, hearing and smell are transmitted through spinal nerves from either the spinal cord or cranial nerves which make up the peripheral nervous system (PNS).

Some characteristic properties of the brain are hollow-like cavities called ventricles, which are filled with a colorless watery fluid called cerebrospinal fluid (CSF). The brain is also immersed in this CSF which can flow from the ventricles through special drainage canals. The CSF cushions the brain from injury and is constantly being absorbed and replenished. As an effect it washes out waste and impurities as well as delivers additional nutrients (1).

3.1.1. Brain matter and cellular composition

The average adult healthy brain is a mass of about 1.3 kg consisting of approximately 60 % fat and 40 % water, protein, carbohydrates and salts (1). On a cellular level, its composition is mainly formed by nerve (neurons) and glial cells which carries out computation and nourishment tasks, respectively. A study found that on average, the human brain contains about 86 billion neurons and about the same amount of non-neuronal cells (2). The location of these cells, however, depends on brain structure and function. Only about 16 billion

neurons exist in the cortical gray and white matter, with most of the remaining neurons are located in the cerebellum (hindbrain) (2,3). Cortical gray and white matter may take up as much as 80 % of the total brain volume (2,4).

In general, neurons have their cell body (the soma) located in outer layers of the various brain regions and structures. This describes the gray matter of the brain. Within the gray matter, neurons can pick up messages from other nerve cells from dendrites, over synaptic gaps. Neurons transmit signals through long nerve fibers called axons, which connect brain regions to each other. These nerve fiber tracts make up the white matter, which is the lighter inner section underneath gray matter.

Some types of glial cells are astrocytes which are involved in numerous functions such as blood-brain barrier (BBB), homeostasis and neuronal growth, and oligodendrocytes which are involved in insulating neuronal axons for faster signal transmission. Oligodendrocytes do this by creating and adding a myelin (fat) layer to axons within the white matter. The color difference between gray and white matter in the brain mainly arises from the whiteness of myelin. Unlike most cell bodies of neurons existing in gray matter, their axons exist in both white and gray matter. However, only axons in white matter are myelinated. Some other cell types in the brain are endothelial cells (in blood vessels) and ependymal cells (in ventricular walls (5) (Figure 1).

Figure 1 here

3.1.2. Brain structure

The brain is divided into the cerebrum (main part), cerebellum (hindbrain) and brain stem.

The cerebrum and cerebellum have a symmetric structure consisting of left and right

hemispheres. The hemispheres of the cerebrum are connected through a c-shaped nerve fiber structure called the corpus callosum. Each cerebrum hemisphere has four distinct parts; the frontal, parietal, temporal and occipital lobe as seen in Figure 2.

Figure 2 here

<https://www.hopkinsmedicine.org/health/conditions-and-diseases/anatomy-of-the-brain>

The outer gray matter of the cerebrum is the cortex (latin for “cork, “bark”), for which Figure 3 shows the various cortical regions. The cortex has many ridges (gyri) and folds (sulci), which leads to a large total cortical surface within the confined area of the skull. Deep brain structures are further classified into subcortical regions, most of which are located within the cerebrum (Figure 4). Gray matter exists also in some subcortical region, for instance the thalamus.

Figure 3 here

Figure 4 here

<http://what-when-how.com/neuroscience/overview-of-the-central-nervous-system-gross-anatomy-of-the-brain-part-1/>

3.1.3. Brain function

Various regions are known to carry out specific tasks. The frontal lobes are associated with higher-level functions such as personality characteristics, decision making, complex body movement (motor strip), producing speech and short-term memory. Occipital lobe is exclusively associated with vision, while the parietal lobe is associated with interpreting language and words, sense of touch and smell, and spatial and visual perception among others. The temporal lobe is associated with language understanding, hearing, navigation

and long-term memory among others. Some important subcortical regions are hypothalamus for controlling body temperature and hunger, hippocampus (in the temporal lobe) for long-term memory and midbrain for hearing and movement control, among others. Last, the cerebellum is associated with lower-level functions such as muscle movement and posture (1,3,6).

Language and speech are some of the functions that occur commonly in only one of the hemispheres, such as the left hemisphere typically for right-handed people. Also, communication between the various regions is necessary in performing some tasks, such as speech and learning.

A neuron-centric description of brain function is that gray matter is responsible for processing and interpreting information (through neurons), while white matter transmits that information to other parts of the CNS (through axon fiber bundles). The neuron and its interconnections are the most essential parts in the computational description of the brain attempting to explain all mental processes known as cognition. The brains' functional characteristics are however not limited to sensory processing by neurons. For instance, blood vessels and non-neuronal cells as mentioned previously play essential roles in nourishment, protection and structural support. Much is yet to be discovered about the brain. The glymphatic system is another example of brain function which was recently classified as a system for waste clearance in the CNS (7).

3.1.4. Eloquent areas

In treatment such as surgery, it is important to avoid damage to areas that are essential for the kinds of functional sensory processing described previously. An eloquent area or eloquent cortex is a region that, if removed, will result in loss of sensory processing, or

linguistic ability, or paralysis (8,9). The most common eloquent areas are in the left temporal and frontal lobes. Some examples are Wernicke's area of speech comprehension in the temporal lobe, and Broca's area of speech production in the frontal lobe. Moreover, a surgeon must make sure to not damage important axon fiber bundles between regions.

3.1.5. Conventional imaging planes

Like other tomographic imaging techniques, brain MRI follows conventions in axial, sagittal and coronal sections as illustrated in Figure 5.

Figure 5 here

The most common image view is the axial view of a brain, which typically shows the characteristic symmetric structures involving the lateral ventricles.

3.1.6. Imaging brain structure and function

There are various techniques for imaging brain structure and function, such as MRI, computed tomography (CT) and positron emission tomography (PET). The thesis focuses on MRI, which will be described later. Most of these techniques image tissue on a macroscopic level due to limitations in spatial resolution (0.5 to 5 mm^3). They are generally non-invasive methods, meaning that no physical procedure (such as surgery) is necessary for imaging. Intravenous injection of a contrast agent is common to increase image contrast in regions where it accumulates, which then makes the imaging method an invasive method.

3.1.6.1. Imaging brain structure

T1w MRI directly presents gray matter as having lower intensity values (are grayer) than the white matter regions. This is a result of differences in T1 relaxation times whereby grey

matter exhibit longer T1-times than white matter. Typically, various combinations of T1w and T2w in MRIs result in imaging the brain structure of interest, which may involve imaging with an intravenous MR active (paramagnetic) compound to highlight pathology such as tumors (=contrast agent). Moreover, diffusion tensor imaging (DTI) based tractography is an advanced technique to map and track the white matter axon fiber bundles, which is useful in surgical planning. This kind of tracking is not investigated in the thesis.

The structural tracking in the thesis amounts to track and interpret intensity values and displacement in high-resolution MRI that are of clinical interest (such as structural deformations) from longitudinal MRI of cancer progression and treatment follow-up

3.1.6.2. Imaging brain function

Functional imaging typically acquires images with lower spatial resolution than structural imaging due to the requirement for high temporal resolution. Blood oxygenation level dependent (BOLD) imaging is the most common functional MRI technique where small variations in blood oxy/deoxygenation levels related to sensory or auditory processing is detected based on their differential magnetic susceptibility (deoxygenated hemoglobin is paramagnetic and oxygenated hemoglobin is diamagnetic). This is called the haemodynamic response resulting from delivering nutrients (like oxygen and glucose) to neuronal tissue through blood flow. BOLD fMRI may be applied to determine eloquent areas prior to surgical removal of brain tumors. Electroencephalography (EEG) and Magnetoencephalography (MEG) are two complementary non-invasive techniques for directly recording electric and magnetic field potentials, respectively, resulting in higher temporal resolution signals than BOLD fMRI. EEG and MEG are not imaging methods but may accompany medical imaging to further elucidate brain function. The functional side of

brain cancer MRI is not focused on direct imaging of cognitive processes, but rather on imaging vascular properties of the brain and disease that may improve diagnostics and treatment. One such method, blood perfusion MRI, is the functional imaging method investigated in the thesis. Here, the consistency of these functional blood values from perfusion MRI during geometric susceptibility distortion correction, is investigated through careful tracking their pixel-wise intensity value and displacement.

3.2. Brain cancer

Brain cancer is cancer in the CNS characterized by various abnormalities in cell growth and death occurring within the brain, either as primary tumors where the cancer originates from cells within the brain, or as secondary tumors originating from cancer in other parts of the body and then spreading to the brain and forming secondary tumors as metastases (10). Glioblastoma (GBM), the main type of cancer investigated in the thesis, is the most common, and most deadly, type of primary brain tumor (11).

3.2.1. Incidence

Although incidence is low compared to other types of cancers (12), brain and other CNS tumors are among the leading causes of cancer deaths for young adults with only one-third of individuals surviving at least 5 years after diagnosis (13,14). The overall age-adjusted incidence rate (AAIR (15)) of GBM in the United States is 3.22/100000 persons and increases with age. Moreover, the 5-year relative survival varies by age at diagnosis and by sex (11) (Figure 6).

Figure 6 here from (11)

In general, AAIR of malignant brain and other CNS tumors are higher in western and European countries than in other parts of the world (roughly AAIR / 100000 ~6 vs. ~3), and dominated by astrocytic tumors in males (13,16–18). Moreover, cancers in other parts of the body such as lung cancer with ~7 times higher incidence than primary CNS tumors in 2020 (12), may also contribute to increased mortality of CNS tumors when causing secondary brain tumor metastases.

3.2.2. Characterization and grading

The World Health Organization (WHO) uses a combination of MRI, histopathological and molecular features for CNS tumor characterization, which typically involves determining the presumed cell of origin and a grade of aggressiveness (I-IV) together with various genotype and phenotype markers (19,20). There are more than 100 different subtypes of CNS tumors, of either malignant or benign type (19). Gliomas consist of multiple subtypes of astrocytic tumors originating from glial cells of the brain and make up approximately 80 % of all malignant brain tumors. They are the most common primary CNS brain tumors (21). Of gliomas, GBM is the most aggressive type (WHO grade IV), and it comprises of approximately 57 % of all gliomas and 48 % of all primary malignant CNS tumors (22). Grade III and IV gliomas are commonly referred to as high-grade gliomas (HGG). The grade of aggressiveness of a glioma is traditionally determined by comparing cells of origin with different levels of tumor cell differentiation on light microscope of histology tissue samples. Additional characterization using molecular features such as mutation in the gene coding for the enzyme isocitrate dehydrogenase (IDH) further distinguishes subtypes of glioma. Generally, the prognosis of an IDH-mutant glioma is better than the IDH wild-type

counterpart. An up to date overview of the grading system for glioma can be found in this recent thesis (23).

3.2.3. Treatment

Regardless of the type of brain cancer, high quality imaging methods are important to ensure the best suited treatment regime and follow-up, and thereby highest possible quality of life for the patient. For GBM, a standard treatment (24) consisting of tumor resection followed by radiation therapy and concomitant and adjuvant chemotherapy (CRT with temozolomide (TMZ)), leads to a dismal median overall survival of 12-15 months with less than 5 % of all patients surviving 5 years after diagnosis (25–27). Maximal surgical resection of the tumor according to high intensity regions on T1wc MRI is the standard practice and associated with survival benefits (28). However, resecting also larger regions with high intensity value on T2w-FLAIR surrounding the T1wc enhanced regions may also lead to increased survival (29). Biopsies may be collected both before and during treatment for optional histopathological assessment (30).

3.2.4. Presentation on MRI

On contrast enhanced T1w MRI, a GBM usually presents as an irregularly shaped mass with a dense hyperintense ring of enhancement, and with a hypointense center of necrosis (Figure 7 and Figure 8).

Figure 7 here

Figure 8 here

The tumor may also be surrounded by vasogenic edema, hemorrhage, and ventricular and midline shifts (25,27). T2w and T2w-FLAIR MRI are hyperintense at pathology such as

edema. Tumoral and peritumoral cerebral blood volume (CBV) values provide additional clinical value in follow-up of GBM (31,32). This set of MRI sequences are frequently used in GBM follow-up examinations (Figure 9).

Figure 9 here

3.2.5. Treatment response assessment

3.2.5.1. RANO

Response Assessment in Neuro-Oncology (RANO) is a consensus for how to categorize treatment response of HGG into the classes complete response, partial response, stable disease and progression (33). In general terms, response is working treatment leading to less cancer, while progression is the opposite leading to more cancer.

At its core, the assessment is performed at some time point during treatment by measuring the length of the two longest perpendicular diameters of the contrast enhanced tumor at a two-dimensional T1w scan, then computing the product of the diameters. This product is then compared to the corresponding product from a pretreatment baseline scan to determine response, and to the smallest product (at either baseline or a later time point) to determine progression. The required pretreatment baseline scan must be performed shortly after surgery, but before initiation of concomitant and adjuvant CRT.

Percentage thresholds of change of the products as well as complementary and clinical information are used in the assessment. Measuring perpendicular diameters of contrast enhanced tumor is not always feasible for reasons such as presence of cystic or necrotic tumor, surgical cavities or lack of disruption of the BBB. RANO imposes guidelines for handling such cases by distinguishing between measurable and non-measurable lesions

(33,34). A highly infiltrative tumor may for instance be non-measurable from lack of contrast enhancement on T1w scans but still presenting as large regions on T2w or T2w-FLAIR scans. RANO classification is difficult for this scenario. Some other important clinical factors used in RANO are usage of corticosteroids and general clinical status (35) of the patient.

Presence of pseudoprogression and complex tumor behavior from novel and advanced treatment such as immunotherapy challenge the accuracy of RANO. It is likely that more robust methods such as automatic volumetric measurements and analysis from segmentation pipelines (36,37) will replace RANO in the future. No patients in the longitudinal exams in the second publication experienced a complete response from the standard treatment. Here the following combined RANO+pseudoprogression classes were used instead; stable disease, pseudoprogression, partial response and progression.

3.2.5.2. Progression vs. pseudoprogression

Pseudoprogression is a type of classification of treatment response where it is not possible to distinguish between true (early) progression of the cancer and treatment effects on follow-up MRI of GBM (38,39). A common such scenario is when it is not possible to determine whether an intensity increase in the T2w-FLAIR image is caused by an increase in amount of cancer cells (thereby progression of non-enhancing tumor), or by inflammatory effects of the chemo- and radiotherapy (pseudoprogression) (40,41). Or, detecting intensity increase from contrast agent accumulation in T1w MRI that is not caused by cancer progression (enhancing tumor) but likely by increased permeability of the tumor vasculature from irradiation (33).

Better understanding and analysis of fine-grained imaging changes associated with the disease and treatment (such as displacement (42), tumor shape (43) and various radiological

features (38,44)), may lead to insights for better distinguishing progression from pseudo-progression.

3.3. MRI physics

Medical MRI (45,46) is a mainly non-invasive imaging method that exposes a near field magnetic interaction between tissue and external magnetic fields, to capture signals that are proportional to the proton density at various locations in the tissue. This interaction is called nuclear magnetic resonance (NMR), which is based on the fact that certain atomic nuclei with non-zero angular momentum (spin) absorb and re-emit electromagnetic radiation when exposed to a magnetic field (47,48). One such atomic nucleus is the single proton contained inside the hydrogen atom, which in the body is well represented in water (H_2O).

3.3.1. Spinning protons

Varying concentration of water (and to a lesser extent lipids) in tissue is responsible for making up the MRI signal. A spinning proton has a magnetic dipole moment which is a vector quantity that is defined by its spin. When experiencing magnetic induction (flux density) through a vector field $\mathbf{B}$, a proton is capable of spinning in either a low or high energy quantum state with the magnetic dipole moment vector aligned either parallel or antiparallel to $\mathbf{B}$. This effect is best seen in a static uniform magnetic field ($\mathbf{B} = \mathbf{B}_0$). The angular frequency of the spin ω (the Larmor frequency), is proportional to the magnetic field $\mathbf{B}$ according to $\omega = \gamma \mathbf{B}$ (Larmour equation), where γ is the gyromagnetic ratio. This is called Larmour precession.

3.3.2. Transversal magnetization

The basic principle of MRI is to control, spatially localize and record net proton spin densities by utilizing Larmour precession using spatially encoding spin dephasing magnetic field gradients and additional sender and receiver coils for emitting and receiving radiofrequency (RF) signals. When only exposed to a strong magnetic vector field $\mathbf{B}$ (e.g. 3 Tesla), protons are aligned in their low energy (equilibrium) state and not emitting electromagnetic radiation. However, when a well-defined sequence of RF pulses with intrinsic frequency equal to the Larmor frequency for a given spatial location, is emitted through a transversal (orthogonal) weaker dynamic magnetic field, net proton spins are knocked out of their equilibrium state. A net transversal spin magnetization vector field $\mathbf{M}_T$ can then be recorded by induced currents in orthogonal receiver coils during the timespan that the spins return to equilibrium. This process is called relaxation.

3.3.3. Relaxation

Let $\mathbf{i}, \mathbf{j}, \mathbf{k}$ be the orthonormal basis vectors of three-dimensional x, y, z space, i.e. $\mathbf{i} = [1 \ 0 \ 0]^T$, $\mathbf{j} = [0 \ 1 \ 0]^T$ and $\mathbf{k} = [0 \ 0 \ 1]^T$. The Bloch equations (47,49) describe the relation between the magnetic field (flux density) $\mathbf{B}$, total spin magnetization $\mathbf{M}$ and transversal (T_2) and longitudinal (T_1) relaxation time constants according to

$$\frac{dM_x}{dt} = \gamma(\mathbf{M} \times \mathbf{B})_i - \frac{M_x}{T_2} = \gamma(M_y B_z - M_z B_y) - \frac{M_x}{T_2} \quad (3.1)$$

$$\frac{dM_y}{dt} = \gamma(\mathbf{M} \times \mathbf{B})_j - \frac{M_y}{T_2} = \gamma(M_z B_x - M_x B_z) - \frac{M_y}{T_2} \quad (3.2)$$

$$\frac{dM_z}{dt} = \gamma(\mathbf{M} \times \mathbf{B})_k + \frac{M_0 - M_z}{T_1} = \gamma(M_x B_y - M_y B_x) + \frac{M_0 - M_z}{T_1} \quad (3.3)$$

T_1 and T_2 are tissue-specific constants and MRI sequences (a given combination of RF-excitations, magnetic gradients and received coil signal readouts) can be designed to maximize image contrast between different tissues of interest. Broadly speaking, T_1 results from thermal agitation while T_2 results from nuclear interactions. The relaxations occur exponentially and during Larmor precession and for which the solutions to the Bloch equations are

$$M_x(t) = e^{-\frac{t}{T_2}}[M_x(0) \cos(\omega_0 t) + M_y(0) \sin(\omega_0 t)] \quad (3.4)$$

$$M_y(t) = e^{-\frac{t}{T_2}}[M_y(0) \cos(\omega_0 t) - M_x(0) \sin(\omega_0 t)] \quad (3.5)$$

$$M_z(t) = M_z(0)e^{-\frac{t}{T_1}} + M_0(1 - e^{-\frac{t}{T_1}}) \quad (3.6)$$

Equilibrium is found with $t \rightarrow \infty$ where $M_x(\infty) = M_y(\infty) = 0$ and $M_z(\infty) = M_0$. T_1 relaxation is called spin-lattice relaxation since T_1 relaxation ends in thermodynamic equilibrium with its surroundings (the “lattice”). Comparingly, T_2 relaxation is called spin-spin relaxation since it is caused by the spins interacting with each other, leading to dephasing.

In practice, spins are also phase distorted due to inhomogeneities in the magnetic field (ΔB) caused by internal and external factors. In general, external factors are related to the scanner itself, while internal factors are related to the imaged object. Some external factors

may be various scanner imperfections such as static field inhomogeneities (50), poor RF coil uniformity or eddy currents from switching gradients, which can be corrected for by shimming techniques and specialized imaging sequences, etc., as reviewed elsewhere (51). Some examples of internal factors are presence of high water density, air and iron leading to rapid spatial transitions in magnetic susceptibility. Correction for distortions caused by factors of the imaged object may be more challenging than correcting distortions caused by external factors, since the extent of distortions increases linearly with field strength according to the Larmor equation. The field inhomogeneities leads to the more rapid T_2^* relaxation, which is called free induction decay (FID). It can be decomposed into $R_2^* = 1/T_2^* = 1/T_2 + 1/T_2'$, where T_2' is affected by ΔB .

For a visual demonstration video of relaxation and the associated T_1 , T_2 and T_2^* time constants, please visit the following web link:

https://upload.wikimedia.org/wikipedia/commons/1/11/Proton_spin_MRI.webm

3.3.4. T_1 and T_2 weighting

In case of a two-dimensional image acquisition sequence with a slice-selective magnetic z-gradient applied to only collect transversal magnetization from a single slice of tissue, the total recorded data may be regarded as snapshots of this relaxation process (for a selected time t leading to a particular “weighting” of T_1 and T_2 in the image). Thus, the timing of acquisition during these relaxation processes, combined with tissue specific relaxation constants T_1 and T_2 , determines the amount of T_1 and T_2 weighing in the MRI.

The two most basic parameters for timing acquisition of snapshots (or “echoes”) during relaxation processes are repetition time (TR) and echo time (TE). These are integral parts of

the RF pulse sequence which will be explained later. An effective image acquisition results in complex transversal magnetization values that were recorded from multiple repeated relaxation processes in a reference frame rotating around the z-axis (i.e. $\mathbf{M}_T = \mathbf{M}_{xy}$). The selection of TR and TE affects the weighting (52) of the tissue specific T_1 and T_2 relaxation constants according to

$$|\mathbf{M}_T| \propto M_0(1 - e^{-\frac{TR}{T_1}})e^{-\frac{TE}{T_2}} \quad (3.7)$$

T1w MRI is achieved when TR is short relative to the various T_1 tissue constants so that the degree of longitudinal magnetization recovery is highly tissue dependent. TE affects the degree of T2w MRI similarly. The most dominating weighting is used to describe the image. T2w is known to better express contrast differences in pathology than T1w, but also presents homogenous and high intensity values in fluid regions. T1w and T2w MRI are typically high-resolution structural images, depending on the pulse sequence (Figure 9).

3.3.5. k-space frequency domain

For two-dimensional MRI, the total recorded transversal magnetization is the composite magnetization from all spatial positions in the 2D slice. The degree of frequency and phase modulation is position dependent (through use of magnetic gradients), and the resulting complex spatial frequency domain is named k-space (53) and can be written as

$$\mathbf{M}_T(k_x, k_y) = M_x(k_x, k_y) + jM_y(k_x, k_y) \quad (3.8)$$

where j is the imaginary unit.

M_T contains signals that are induced in receiver coils and are naturally in the complex spatial frequency domain if additional time-varying spin dephasing magnetic field gradients are used to restrict the signals to specific locations in the tissue and k-space. In particular, the signals induced in the receiver coils are called “echoes” and they are initiated by either RF-pulses directly or by specific time-varying field gradients in the pulse sequence. An MRI scan typically acquires signals from either gradient echoes (GE) or spin echoes (SE).

3.3.6. Spin echo and gradient echo

These are the essential building blocks of a pulse sequence. RF pulses centered at the Larmor frequency knocks spins out of equilibrium to precess with a certain angle around the field direction. Slice, phase and frequency (readout) encoding magnetic field gradients are then utilized to encode echo signals to various z-slices, as well as to various x and y-locations of k-space, respectively.

A spin echo is initiated by a 90-degree RF pulse under the influence of a slice-selective gradient. This leads to transversal magnetization (an echo) that gets phase encoded to a y-location in k-space. An additional 180-degree RF pulse is then applied on the same slice, which leads to re-focusing away most unwanted spin phase distortion from ΔB . After a designated TE, a new echo forms that is read into a single horizontal line of k-space with a frequency encoding gradient. A spin echo thus contains only the T_2 component of spin-spin relaxation (Figure 10).

Figure 10 here

The gradient echo is induced more directly using a RF pulse with variable flip angle and similar slice and phase-encode gradients to the spin echo. Here, a small opposite sign

frequency gradient is applied just before formation of the echo, to ensure that the echo is read into a complete horizontal line in k-space. For spin echo, the same effect is achieved with the 180-degree RF-pulse. Gradient echo has no re-focusing RF-pulse, so it reads the raw T_2^* (FID) signal (Figure 11).

Figure 11 here

3.3.7. Pulse sequence

An inherent challenge in MRI is to record as much as possible of transversal magnetization in reasonable time, while also spatially encoding the signals so that an image can be reconstructed with enough spatial resolution. This is the task of the MRI pulse sequence and is characterized by the way k-space data is acquired. It consists of repetitive applications of RF-pulses and magnetic field gradients to achieve and record either spin or gradient echoes.

As illustrated in Figure 10 and Figure 11, k-space encoding is achieved by applying additional spatial gradients on the magnetic field. Not only the strength but also the time-duration of the applied magnetic field gradient G dictates where to spatially localize spin densities and their corresponding entries in k-space. Hence the k -variables in Equation (3.8) are expressed in forms of the time integrals

$$k = \gamma \int_0^t G(\tau) d\tau$$

(3.9)

In general, a pulse sequence has certain TE and TR values resulting in specific formation of T1w and T2w echoes.

3.3.8. Spatial image domain

For three-dimensional MRI, the final imaging volume I (in complex form) is the inverse Fourier transform (54) of k-space as follows

$$I(x, y, z) = \frac{1}{2\pi} \iiint_{k_x k_y k_z} \mathbf{M}_T(k_x, k_y, k_z) e^{j(k_x x + k_y y + k_z z)} dk_x dk_y dk_z \quad (3.10)$$

where $\mathbf{M}_T$ is the k-space encoded transversal magnetization for all z-slices of the imaged object. Note that for three-dimensional MRI, phase encoding is applied in two dimensions, where the second phase encoding direction replaces the slice selection gradient used for two-dimensional MRI. An intensity image is found by taking the complex modulus of I .

3.3.9. Contrast agent

The pulse sequence acquisition may be accompanied by intravenous injection of a Gadolinium (Gd) based contrast agent (GBCA) targeted to alter the intensity values in or around tissue where it is present. T1w MRI with BGCA increases the image intensity values in regions where the contrast agent (CA) is accumulated. T1w MRI with GBCA typically reveals active tumor regions since the CA tends to accumulate in regions with disrupted BBB associated with active tumor.

3.3.10. Advanced MRI

Specialized MRI pulse sequences were developed for maximizing image contrast differences in tissue and regions that are of medical interest.

3.3.10.1. Fluid-attenuated inversion recovery

FLAIR is a specialized MRI sequence for suppressing the signal in T1w or T2w images originating from fluids such as CSF. In simplest form, the technique flips the longitudinal magnetization vector of spins and reads transversal magnetization with appropriate timing (inversion time (TI)) such that known magnetization for CSF is zero at reading. CSF is thus dark in T2w-FLAIR images whereas pathological tissue associated with edema remains bright, thereby improving the conspicuity of the pathology. In cancer MRI, such pathological tissue can be peritumoral regions with inflammation (edema) (Figure 9).

T2w-FLAIR is a popular method in cancer MRI since it is sensitive to detecting a range of localized brain pathologies and is thus suited for efficient screening. Moreover, combining multiple sequences in an analysis (multiparametric MRI) may lead to increased elucidation of disease, such as differentiating between IDH mutant and wild-type GBM (55).

3.3.10.2. Dynamic susceptibility contrast

An advanced MRI technique used to quantify cerebral hemodynamic parameters, like CBV, is called dynamic susceptibility contrast (DSC) MRI. DSC-MRI is, simply speaking, rapidly acquired T2w volumes during intravenous injection of a GBCA. The imaging method trades some spatial resolution in favor of increased temporal resolution in order to capture vessel dynamics from a rapid CA passage into the brain and is thus called (blood) perfusion MRI.

The presence of a CA induces magnetic susceptibility differences in or around the blood vessels, which are semi-quantifiable through the induced increase in T_2 relaxation rates in response to the presence of the CA in tissue according to $R_2 = 1/T_2 = 1/T_2(0) + r_2[Gd]$, where r_2 is the in-vivo transversal relaxation rate for a specific concentration of Gadolinium

(mmol/L). Visually, this is characterized as a “dip” in voxel intensities on the DSC-MRI as the CA passes through the brain vessels and is illustrated in Figure 12 (56).

Figure 12 here

Disruption of the BBB in brain cancer in or around tumor regions may lead to much of the CA leaking into extracellular space. The pharmacokinetic modeling in DSC-MRI assumes no disruption of the BBB and for such cases leakage correction (57) is necessary. CA leakage may resultingly lead to lowered values in tumoral regions when compared to healthy regions as depicted in Figure 9.

3.3.10.2.1. Pharmacokinetic modeling

Kinetic modelling assumes knowledge of CA in tissue over time. DSC-MRI measures signal change, which then needs to be converted to a metric which is proportional to CA concentration. It is commonly assumed the change in relaxation rate is directly proportional to CA concentration

$$\Delta R_2 \propto r_2[Gd]$$

(3.11)

By further assuming a mono-exponential relationship between signal and ΔR_2 , we can derive the following concentration-time curve where S_0 is the measured (average) signal prior to CA arrival and $S(t)$ is the temporal signal (magnitude) measured during CA passage

$$\Delta R_2(t) \propto -\frac{1}{TE} \ln \left(\frac{S(t)}{S_0} \right)$$

(3.12)

CBV can then be semi-quantified by computing the area under the concentration-time curve as follows (56,58)

$$CBV \propto \int \Delta R_2 dt$$

(3.13)

3.3.10.2.2. Spin-echo vs. gradient-echo dynamic susceptibility

contrast and vascularity

Equation (3.12) and (3.13) are for SE DSC-MRI. While SE DSC-MRI describe T_2 relaxation, GE DSC-MRI describe T_2^* relaxation. It is generally accepted that SE DSC image the microvasculature of blood perfusion by utilizing a GBCA to alter relaxation of blood inside the vessels. Since GE DSC is made of the FID signal, however, intra and inter-voxel dephasing as well as signal loss results in imaging relaxation processes that are on a spatial scale that is larger than the vessels. This may result “dips” in image intensity in regions outside but close to vessels induced from GBCA inside vessels. GE DSC is thus known to image macrovasculature. The signals from GE DSC are typically stronger than from SE DSC. For this reason, CBV typically contains higher intensity values for GE DSC than for SE DSC.

There are more precise ways of quantifying CBV from DSC-MRI using deconvolution with an arterial input function (AIF) (56,58–60). AIF here refers to the CA concentration in blood-plasma in an artery measured over time. These methods were mostly intermitted in the thesis due to lack of manual AIF measurements and known limitations and additional sources of errors from computerized AIF estimation for DSC-MRI and similar methods (61,62). Instead, careful intra-patient normalization of CBV with normal-appearing white matter masks were performed.

3.3.10.3. Echo planar imaging

Single-shot echo planar imaging (EPI) (63) is the technique commonly used in DSC-MRI, DTI and BOLD fMRI. It is a two-dimensional fast acquisition method where multiple individually phase encoded echoes are produced from a single spin or gradient echo readout. This enables all k-space lines to be recorded from a single SE or GE signal. The most common type is SE EPI. Here, the re-focused signal is split into multiple echoes with different phase and frequency encoding (Figure 13).

Figure 13 here

The EPI pulse sequence is constructed in such a way that each echo is read by following a rectilinear zig-zag path in k-space (Figure 15 (E)). More descriptions on EPI MRI theory can be found in these relevant Master's theses (64,65).

3.4. *Magnetic susceptibility*

Magnetic susceptibility χ is a quantitative measure of a material's ability to become magnetized when exposed to a magnetic field, ranging -1 for superconductors to $\sim 10^5$ for strongly ferromagnetic materials (66).

3.4.1. Dia-, para- and ferromagnetism

Human tissues can either be diamagnetic ($\chi < 0$) or paramagnetic ($\chi > 0$), describing this tendency in form of either repelling or attracting the external magnetic field. Repelling or attracting ends with termination of the external magnetic field. If a material can retain internal magnetization after being exposed to an external magnetic field (such as iron) or even without magnetic exposure, it is ferromagnetic ($\chi \gg 0$).

In MRI, magnetic susceptibility interacts with the magnetic field $\mathbf{B}$, leading to a longitudinal magnetization of proton spins $\mathbf{M}_z$ according to

$$\mathbf{M}_z = \frac{\chi}{\mu_0 \mu_r} \mathbf{B} \quad (3.14)$$

where $\mu_0 = 4\pi 10^{-7} [H/m]$ (Henry/meter) is the permeability of perfect vacuum and μ_r is relative permeability (67). Relative permeability and magnetic susceptibility are related according to $\chi = \mu_r - 1$.

3.4.2. The susceptibility sensitive EPI sequence

As described in section 3.3, presence of an exogenous paramagnetic CA (e.g. Gd with $\chi \cong 0.32$) during DSC-MRI will affect T_2 relaxation by altering the susceptibility of the tissue where it is present.

Although susceptibility for living tissue is comparably weak ($|\chi| \ll 1$), local variations in χ can lead to minor field inhomogeneities (ΔB) resulting in undesired geometric and intensity distortions in MRI. EPI (63), which is the MRI sequence used for each axial slice ($\sim 100 [ms]$) in each volume in DSC-MRI, possesses such distortions. For example, regions in and around the sinuses in the frontal lobe or ear canals contain sharp transitions from water-heavy regions (water $\chi = -9.05 * 10^{-6}$) to air ($\chi = 0.36 * 10^{-6}$) (66), which typically leads to geometric and intensity distortions in EPI. Geometrically, this can result in anteroposterior voxel displacement of a centimeter or more (68). Figure 14 presents simulated distortions for GE EPI along with the inhomogeneity field (69).

Figure 14 here

The thesis assumes two-dimensional (axial) EPI by applying a slice selective gradient in the z-direction, so the z-dimension in Equation (3.10) can be omitted. An EPI consists of k-space magnetization acquired from a single RF excitation (single-shot) in a zig-zag (blipped trapezoidal) manner, and with significant longer time spent on traversing from one side to the other along the phase-encode (y)-direction than along the frequency-encode (x)-direction. With one echo to fill in a single horizontal (x) line (readout) of k-space and N echoes to fill all of k-space, this time difference is approximately N . See Figure 10 for a depiction of EPI distortions and k-space traversal.

3.4.3. Effect of susceptibility variations on EPI

The field inhomogeneities from magnetic susceptibility variations are also dependent on time (70)

$$\delta B(x, y, t) = \gamma \int_0^t \Delta B(x, y, \tau) d\tau \quad (3.15)$$

and will affect the k-space encoding gradients (Equation (3.9)). In two-dimensional EPI, this results in geometrical and intensity distortions according to

$$\tilde{I}(x, y, t) = \frac{1}{2\pi} \iint_{k_x k_y} \mathbf{M}_T(k_x, k_y) e^{j(k_x x + k_y y + \delta B(x, y, t))} e^{-\frac{t}{T_2^*}} dk_x dk_y \quad (3.16)$$

The resulting real distortions are shown for GE and SE EPI in Figure 15.

Figure 15 here

Equation (3.16) also introduces another distortion in EPI which is caused by FID. This leads to blurring and can be corrected for using specialized methods (71) not assessed in the thesis. Due to the zig-zag sampling of k-space in EPI, both spatial and blurring distortion is much more prominent in the phase-encode (y)-direction than in the frequency-encode/readout (x)-direction. The sampling scheme also leads to a weaker effective gradient, and thus lower acquisition bandwidth, in the phase-encoding direction than in the frequency-encoding direction, which explains why minor field imperfections distort the EPIs primarily along the phase-encode direction (69).

3.5. Voxel tracking

Voxel tracking is the common denominator in the three publications in the thesis, where the objective is tracking displacement and possibly intensity shift of voxels between two MRI scans. The true track of a voxel restricted piece of tissue may be complex. This work focuses on tracking only the final displacement vector and intensity shift (Figure 16).

Figure 16 here

Assume that the displacement $\mathbf{d}(\mathbf{x})$, $\mathbf{x}, \mathbf{d} \in \mathbb{R}^3$ (i.e. $\mathbf{x} = [x \ y \ z]^T$ and $\mathbf{d}(\mathbf{x}) = [\Delta x(\mathbf{x}) \ \Delta y(\mathbf{x}) \ \Delta z(\mathbf{x})]^T$) and intensity change ΔI of a voxel restricted piece of tissue is known between two MRI scans I_t, I_{t+1} with sufficient high isotropic voxel resolution (e.g. 1 mm^3). If allowing any displacement and intensity change of voxels, the macroscopic spatiotemporal transformation from MRI I_t to MRI I_{t+1} can be written as

$$I_{t+1}(\mathbf{x}) = (I_t + \Delta I) \circ T$$

(3.17)

where $\circ$ is the function composition operator, i.e. $g \circ f = g(f(x))$ and $T: \mathbb{R}^3 \rightarrow \mathbb{R}^3$ is a non-linear dense transformation of voxel coordinates;

$$T(x) = x - d(x)$$

(3.18)

In Equation (3.18), $d(x)$ is a displacement vector field describing the tissue displacement from MRI I_t to MRI I_{t+1} at starting voxel coordinate position x . Equation (3.17) assumes that the voxel intensity change ΔI is known in the frame of the first MRI I_t , i.e. before applying the nonlinear displacement transformation T .

3.6. EPI correction

As described in section 3.4, EPI geometric susceptibility distortion occurs primarily due to the low bandwidth in the phase-encode direction. As a result, ΔB causes additional shifts in phase of the nuclear spins, leading to pixel shifts along the y-axis in the axial EPI by a factor that is proportional to ΔB .

Specifically, both sign and magnitude of ΔB as well as direction of phase-encode traversal of k-space during EPI acquisition contributes to the final distortion in the EPI. A common EPI acquisition consists of positive (bottom-up) phase-encode traversal and for this type phase distortions results in a compression or squeezing effect along the y-axis in the EPI in addition to intensity distortions as seen in Figure 14 and Figure 15. Opposite phase-encode transversal results comparably in a stretching effect, which was the case for our DSC-MRI EPIs (Figure 15).

Generally correct assumptions are that

1. Pixel displacement d along the axial y-direction of the EPI is proportional to ΔB

2. The associated pixel intensity distortion ΔI is proportional to ΔB
3. d and ΔI is equal in magnitude but have opposite sign when describing an EPI pair with positive and negative phase-encode direction (Figure 10).

The correction methods in the thesis (FSL TOPUP (69) and EPIC (68)) makes these assumptions in order to formulate EPI distortion correction into a voxel tracking problem.

3.6.1. The voxel tracking problem for EPI correction

Let $\mathbf{x}_+$ and $\mathbf{x}_-$ be the voxel position coordinates for a positive and negative phase-encode EPI, and $\mathbf{x}$ the corresponding coordinates for a distortion corrected EPI. The opposite sign assumption of the displacement in 3. inherent in the EPIs can be described by the transformation pair $T_+, T_-: \mathbb{R}^3 \rightarrow \mathbb{R}^3$

$$T_+(\mathbf{x}): \mathbf{x} \rightarrow \mathbf{x}_+ = [x \quad y + d(\mathbf{x}) \quad z]^T \quad (3.19)$$

$$T_-(\mathbf{x}): \mathbf{x} \rightarrow \mathbf{x}_- = [x \quad y - d(\mathbf{x}) \quad z]^T \quad (3.20)$$

Furthermore, the relation between the EPIs in terms of geometrical and intensity distortions can be formulated similar to Equation (3.17)

$$\left| \frac{\partial T_+}{\partial \mathbf{x}} \right|_{\mathbf{x}_+} (\tilde{I}_+ \circ T_+) = \left| \frac{\partial T_-}{\partial \mathbf{x}} \right|_{\mathbf{x}_-} (\tilde{I}_- \circ T_-) \quad (3.21)$$

where $\tilde{I}_+$ and $\tilde{I}_-$ is the positive and negative phase-encode (distorted) EPI.

FSL TOPUP and EPIC uses the formulation in Equation (3.21) in slightly different ways to estimate a field that can be used to distortion correct the EPI. The difference between the methods is the type of field as well as the type of model used together with the field to

perform correction. TOPUP estimated the off-resonance (scalar) field ΔB , while EPIC estimates the y-displacement (scalar) field d (Figure 17).

Figure 17 here

These are termed reverse gradient methods (reversed phase-encode correction methods) since the field is estimated by reversing the gradients (the transformations T) as will be explained in the next subsections. Moreover, this EPI correction is performed retrospectively after having captured two EPI scans with opposite phase-encode direction. Other EPI correction methods, such as direct field mapping using a double echo GE sequence (70), deformable (non-rigid) registration (72,73) or point spread function mapping (74), are not investigated in the thesis. For a comparison of the different methods, see these theses (64,75). The reverse gradient correction methods can be performed on either SE or GE EPIs, however due to additional signal loss (drop-out) associated with GE, it is recommended to estimate the field from SE EPI. As stated in section 2, the aim of the first paper was to investigate the impact of EPI distortion correction on CBV estimation (computed from DSC-MRI consisting of EPIs). Additional signal loss in GE (not accounted for in the thesis) is seen in the frontal areas in the axial CBV maps in Figure 17.

3.6.2. FSL TOPUP

TOPUP estimates ΔB (from Equation (3.15)) as a linear combination of spatial basis functions consisting of a truncated two-dimensional discrete cosine transform (DCT). DCT can be characterized as a real-valued version of the discrete Fourier transform (DFT), but which is asymmetric and has twice the frequency resolution when compared to DFT ((76), Chapter 7.4). These characteristics of DCT makes it well suited for modeling ΔB . TOPUP specifically estimates $18 \cdot 18 \cdot 7 = 2268$ basis weights using a reverse gradient method

based on Equation (3.21). Details of the estimation method is thoroughly explained in the reference paper (69).

Equation (3.16) can be re-written as

$$\tilde{S} \propto \tilde{\mathbf{M}}_T = \iint_{xy} I(x, y) e^{-j(k_x x + k_y y + \delta B(x, y, t))} dx dy \quad (3.22)$$

and further discretized in form of the matrix-based transform ((76), Chapter 7.2) $\tilde{S} = AI$, where A implements the two-dimensional DFT. The main idea of correction in TOPUP is that there exists a transform F that is like A but which contains zero magnetic susceptibility distortions ($\Delta B = 0$), such that the distorted EPI can be expressed as

$$\tilde{I} = FAI = KI \quad (3.23)$$

A Moore-Penrose pseudo-inverse K^+ of K can be computed to estimate the distortion corrected image $\hat{I} = K^+ \tilde{I}$. However, this results in ringing artifacts in areas with large compression (due to resulting signal loss). Instead, since capturing both positive $\tilde{I}_+$ and negative $\tilde{I}_-$ phase-encode EPIs it is possible to express the distortion correction problem as

$$\begin{bmatrix} \tilde{I}_+ \\ \tilde{I}_- \end{bmatrix} = \begin{bmatrix} K_+ \\ K_- \end{bmatrix} I \quad (3.24)$$

With K_+ and K_- being the corresponding matrix transforms (termed interpolation matrices).

A distortion corrected image $\hat{I}$ without artefacts produced by the Moore-Penrose pseudo-inverse can then be computed by the generalized inverse of the augmented matrix $\begin{bmatrix} K_+ \\ K_- \end{bmatrix}$

$$\hat{I} = \left(\begin{bmatrix} K_+^T & K_-^T \end{bmatrix} \begin{bmatrix} K_+ \\ K_- \end{bmatrix} \right)^{-1} \begin{bmatrix} K_+^T & K_-^T \end{bmatrix} \begin{bmatrix} \tilde{I}_+ \\ \tilde{I}_- \end{bmatrix}$$

(3.25)

To summarize, TOPUP models ΔB as a linear combination of DCT spatial basis functions as well as the image formation process of positive and negative phase-encode SE EPIs, to obtain a distortion corrected EPI from a generalized inverse. TOPUP is the magnetic susceptibility distortion correction method provided by the FMRIB Software Library (FSL) (77).

3.6.3. EPIC

EPIC modifies Equation (3.21) by reversing the sign of the y -displacement d within the transformations T_+ and T_- and the Jacobian intensity modulations. It is then re-formulated into a cost function of the form

$$\begin{aligned} f(d) &= \left| \left| \frac{\partial T_-}{\partial \mathbf{x}} \right|_{\mathbf{x}(\tilde{I}_+ \circ T_-)} - \left| \frac{\partial T_+}{\partial \mathbf{x}} \right|_{\mathbf{x}(\tilde{I}_- \circ T_+)} \right|^2 + \lambda_1 d^2 + \lambda_2 \nabla d \\ &= \left| \left(1 - \frac{\partial d}{\partial y} \right) (\tilde{I}_+ \circ T_-) - \left(1 + \frac{\partial d}{\partial y} \right) (\tilde{I}_- \circ T_+) \right|^2 + \lambda_1 d^2 + \lambda_2 \nabla d \end{aligned}$$

(3.26)

where λ_1 and λ_2 are added regularization parameters that control the quality of the displacement estimation. $\lambda_1 = 0$ and $\lambda_2 = 10^4$ were used as in the reference paper (68). The displacement d for each voxel is then estimated using the following Hessian-based optimization:

0. Initialize the displacement field d to zero
1. Smooth the original positive and negative phase-encode EPIs using a Gaussian kernel with standard deviation to $3.5 - 4 \text{ mm}$

2. Compute the Hessian H_f and gradient ∇f of f for the current displacement field d
3. Solve the quadratic form approximation $H_f \cdot v = -\nabla f$ for v
4. Update the displacement field by $d = d + v$
5. Decrease the standard deviation (width) of the Gaussian smoothing kernel by 0.25 – 0.5 mm

Step 1.-5. is then repeated until there is no smoothing. Having the final estimated displacement d for each voxel, a distortion corrected EPI $\hat{I}$ is then computed from either of the positive or negative phase-encode EPI according to

$$\hat{I} = \left(1 - \frac{\partial d}{\partial y}\right) (\tilde{I}_+ \circ T_-) = \left(1 + \frac{\partial d}{\partial y}\right) (\tilde{I}_- \circ T_+)$$

(3.27)

In summary, EPIC estimates the voxel displacement associated with EPI geometric distortion by negating the sign of displacement in Equation (3.21) in order to describe the mapping from distorted to non-distorted space for both positive and negative phase-encode EPIs. This allows re-formulating EPI distortion correction to a Hessian-based optimization problem as described above. The displacement is iteratively estimated together with Gaussian smoothing of decreasing width, to ensure increasingly fine-grained displacement estimation, and thus convergence over the iterations. The final estimated displacement field is then used to perform EPI distortion correction from either of the positive or negative phase-encode EPIs. Like TOPUP, both displacement and intensity shift of voxels is corrected. For an example of incorporating EPIC into a clinical workflow, see this recent Master's thesis (64). TOPUP and EPIC, among others, were also investigated in another recent Master's thesis (78).

3.6.4. Relation between displacement and intensity distortions and field inhomogeneities

One important insight in EPI geometric susceptibility distortion correction is that both ΔB , d and ΔI are related according to

$$\frac{\partial d}{\partial y} = T\gamma \frac{\partial \Delta B}{\partial y} = \Delta I$$

(3.28)

where $T = N\Delta t$ is the total time spent on a single-slice, single-shot EPI k-space recording, Δt is the time used to record an echo into a single frequency-encoded k-space line, and N the number of k-space acquisition lines. γ is the gyromagnetic ratio connecting the magnetic field strength to resonance frequency as explained in section 3.3. Opposed to Equation (3.17), ΔI here belongs to the displaced (corrected) image space ($\hat{I}$). The partial derivative of the estimated y-displacement is the shift in voxel intensity and is proportional to the field inhomogeneities, EPI acquisition time and gyromagnetic ratio.

3.7. Deformable registration

Registration (or co-registration) describes the process of spatially aligning images and matching anatomical structures within or across multiple patients. This is an essential preprocessing step in multi-image analysis. An example of deformable registration is a non-linear, non-rigid alignment of two MRIs that estimates a dense displacement field to describe the spatial transformation from one MRI to another. Deformable registration results in displacement-only voxel tracking.

Non-linear and non-rigid means, opposed to linear rigid or affine (79), that there are non-linear local spatial correspondences in the transformation, such as spatial warps. With the

aim to estimate physical displacement of tissue voxels, deformable (non-linear and non-rigid) registration is only valid first after having applied linear registration to rule out rigid and affine global correspondences between two images (80) (Figure 18).

Figure 18 here

3.7.1. The voxel tracking problem for deformable registration

For any type of registration, a moving image M is registered to a fixed image F by optimizing an objective function f with respect to a transformation model T according to

$$f(T) = A(F, M \circ T) + R(T)$$

(3.29)

where A is a function quantifying the spatial alignment between the images (e.g., cross-correlation) and R is a regularization term (81). Registered images are achieved by finding a T by either maximization or minimization of f depending on the definition of A and R and applying it to M . For deformable registration, T in Equation (3.29) describes a vector field of the estimated displacement of each voxel coordinate from the first MRI to the second MRI as described by Equation (3.18). It is a nonparametric deformation model described by a non-linear dense transformation. For rigid and affine (linear) registration T is a 4×4 homogenous transformation matrix to globally map each voxel coordinate in M to F (79). Otherwise, the rigid and affine registration problem is defined like Equation (3.29). Only monomodal (e.g. T1w to T1w) deformable registration is investigated in the thesis.

Deformable medical image registration may be grouped according being based on physical models, interpolation and approximation theory, ap-priori knowledge or specific tasks (81,82). Some deformable registration methods estimate both the forward and backward

displacement field allowing to transform each MRI into the other MRI in terms of displacement only (inverse consistency). A mapping preserves topology (is homeomorphic) if it is continuous, onto and locally one-to-one both forwards and backwards. Topology preserving mappings that are differentiable contain Jacobian determinants that are greater than zero. These mappings are termed diffeomorphic if they are also invertible. A symmetric mapping is achieved if the forward and backward displacement vectors describe the shortest displacement paths possible (are geodesics) and are equal in magnitudes (83). A consequence of symmetric mapping is that the forward and backward displacement vectors meet in a midpoint that is half the distance from their origins (termed symmetric normalization, SyN) (84).

The main deformable registration method in the thesis is termed symmetric diffeomorphic image normalization (ANTs SyN) with cross-correlation (CC) for quantification of spatial alignment (A) (85) and is bundled with the advanced normalization tools (ANTs) software package (86). ANTs SyN CC performs well compared to other deformable medical registration algorithms (87), which is also shown in the third publication. ANTs SyN extends a physics-based deformation model in the Lagrangian specification of a velocity field (88) by using a symmetric formulation of forward and backward velocity fields for describing voxel displacement (85). It belongs to a group of registration algorithms called large deformation diffeomorphic metric mapping (LDDMM) (89,90) in which diffeomorphic mapping is ensured by constraining the velocity field to be smooth in the regularization term R (81,89). The preceding intra-patient rigid registrations were performed with ANTs (86) with the well-known mutual information (MI) image similarity metric (84) as A .

3.8. Deformation biomarkers

Voxel-wise displacements estimated from deformable registration of longitudinal MRI lay the basis for longitudinal MRI analysis in the thesis. General quantifications of tumoral displacement and peritumoral compression may be obtained by computing displacement magnitudes and quantized divergences as follows: By writing out the voxel-wise displacement vector field $\mathbf{d}$ to component form (using the $\mathbf{i}, \mathbf{j}, \mathbf{k}$ orthonormal basis vectors) $\mathbf{d}(\mathbf{x}) = M(\mathbf{x})\mathbf{i} + N(\mathbf{x})\mathbf{j} + P(\mathbf{x})\mathbf{k}$, divergence is a scalar field computed by summarizing partial derivatives of $\mathbf{d}$ such that (91)

$$\text{div } \mathbf{d}(\mathbf{x}) = \nabla \cdot \mathbf{d} = \frac{\partial M}{\partial x} \big|_x + \frac{\partial N}{\partial y} \big|_x + \frac{\partial P}{\partial z} \big|_x \quad (3.30)$$

Displacement magnitudes describe a displacement scalar field computed as

$$|\mathbf{d}| = \sqrt{M^2 + N^2 + P^2} \quad (3.31)$$

In our second paper, divergence and magnitude maps were used to develop four biomarkers as illustrated in Figure 19.

Figure 19 here

These values can furthermore be analyzed within peritumoral ROIs as described in the second paper. Particularly interesting regions are the peritumoral regions presenting with negative divergence (i.e. $\nabla \cdot \mathbf{d} < 0$) from a longitudinal MRI pair, providing a basis for quantifying peritumoral tissue compression.

3.9. Deformation model

A simple and robust deformation model of general macroscopic shrink and/or growth behavior in GBM was developed (Figure 20). It models either shrinkage of regions from disbanded cancer tissue or successful surgery, radiation- and chemotherapy, or expansion/enlargement of regions as a result of cancer growth (92–94). In the third paper, it was used to generate synthetic expansion deformations for benchmarking deformable registration methods. It was inspired from real-world longitudinal MRI such as Figure 8 presenting tumoral expansion from a pushing GBM phenotype, and Figure 7 presenting both shrinkage and expansion from an infiltrative phenotype.

Figure 20 here

For a single execution, the algorithm creates a realistic displacement field $\mathbf{d}(M_l, M_b, \alpha, \beta, \gamma)$ using the information from the outlined lesion M_l and brain M_b masks, merged with three simulation parameters:

1. Maximum tissue displacement α [mm]
2. Infiltration β
3. Growth irregularity γ

By varying these three simulation parameters, it creates displacement fields and associated deformed scans as illustrated in Figure 21.

Figure 21 here

See Table 3 for a complete overview of the input data, simulation parameters and output as well as internal fixed parameters of the deformation model.

Table 3: Parameters of the synthetic deformation model. Shrinkage is modeled with a negative maximum displacement $\alpha < 0$, and growth with a positive $\alpha > 0$.

Input	Symbol	Range	Type	Description
Lesion mask	M_l	$[0,1]_2$	Binary scalar field	
Brain mask	M_b	$[0,1]_2$	Binary scalar field	
Displacement	α	$\mathbb{R}$	Scalar [mm]	Maximum tissue displacement
Infiltration	β	$[0,1]$	Scalar	Intensity decay fraction; 0: most infiltration, 1: least infiltration
Irregularity	γ	$< 0,1]$	Scalar	Perlin noise resolution; ~ 0 : highest irregularity, 1: lowest irregularity
Noise	δ	$\mathbb{R}$	Scalar	Perlin noise maximum magnitude; fixed default = 0.6
Standard deviation	σ	$\mathbb{R}$	Scalar	Of g ; fixed default = 5
Number of vectors	N_s	$[1, N]$	Integer	Number of directions for computing deformations; fixed default = 32
Angle deviation	θ	$< 0,90 >$	Scalar	2θ is the top angle of the directional cones; fixed default = 7°
Output				
Model	$d(M_l, M_b, \alpha, \beta, \gamma)$	$ d \in [0, \alpha + \delta]$	Vector field	

3.9.1. Description

TODO: This subsection is also in supplementary material for the third publication. Could remove. Let w, h, d be the width, height and depth of the bounding box for the outlined tumor segmentation mask M_l registered to 1 mm^3 voxel-isotropic approximate MNI space as described in section 3.11.

The algorithm initially takes w, h, d as inputs to compute a three-dimensional Gaussian scalar field g consisting of σ standard normal deviations in each dimension, parameterized in equally spaced intervals and with resolution N according to Equations (3.32) and (3.33).

$$g(x, y, z) = -e^{-\frac{x^2+y^2+z^2}{2}} \quad (3.32)$$

$$\begin{bmatrix} x \\ y \\ z \end{bmatrix} \in \begin{bmatrix} [-\sigma, \sigma]_{N(w)} \\ [-\sigma, \sigma]_{N(h)} \\ [-\sigma, \sigma]_{N(d)} \end{bmatrix}, \quad N(l) = \begin{cases} l + 1, & l \text{ odd} \\ l, & l \text{ even} \end{cases} \quad (3.33)$$

$N(l)$ in Equation (3.33) results in an even number of sampling steps along each bounding box dimension of the lesion mask. This negligible simplification is required to be able to access the geometric center of the bounding box by matrix indexing, which makes various indexing operations in the algorithm easier. A selection of $\sigma = 5$ standard deviations ensures that the elliptic scalar field g is within the tumor bounding box entirely ($\sim 100\%$). See Figure 22 for an illustration of the one-dimensional variant of g .

Figure 22 here

An initial model displacement vector field $\mathbf{d}(M_l)$ is then computed from the gradient (partial derivatives with respect to x, y and z) of g by $\mathbf{d} = \nabla g$. Figure 23 illustrates how $\mathbf{d}$ is computed from the tumor mask M_l for various spatial dimensions.

Figure 23 here

Figure 24 (C) displays an ellipsoid and multiple directional cone shapes that are computed from $\mathbf{d}$. The purpose of the directional cones is guiding iterative deformation of $\mathbf{d}$ in terms of displacing the vector positions in $\mathbf{d}$ by $\mathbf{d}$ itself by an amount defined by the infiltration

parameter β , and then linearly interpolating the displaced components of $\mathbf{d}$ to get a smooth displacement field.

Figure 24 here

The binary ellipsoid mask M_e in Figure 24 (C) is defined as

$$M_e := g < -e^{\frac{1}{2}} \quad (3.34)$$

The surface of M_e defines the locations with highest spatial intensity change in g , and resultingly the starting positions of the largest gradient magnitudes in $\mathbf{d}$. This is the inflection surface of G defined by $\nabla^2 g = 0$. The algorithm then scales $\mathbf{d}$ to have a maximum gradient magnitude of 1 by $\mathbf{d} = \frac{\mathbf{d}}{|\mathbf{d}|}$ and finds the approximate unit normal vectors V for the surface of M_e in MNI voxel-isotropic resolution, by extracting vectors $V \in \mathbb{R}^{N \times 3}$ from $\mathbf{d}$ that have starting positions in the center of the voxels in a convex ellipsoid mask M according to Equations (3.35) and (3.36)

$$V = \mathbf{d}[M] \quad (3.35)$$

$$M := M_e \text{ where } \|V\|_F > 0.99 \quad (3.36)$$

where $[]$ describes tree-dimensional binary mask matrix indexing and $\|V\|_F \in \mathbb{R}^{N \times 1}$ is the Frobenius norm of V along its second axis dimension, which computes gradient magnitudes. To speed up the algorithm, a fixed subset of N_s maximum spread normal vectors $V_s \in \mathbb{R}^{N_s \times 3}$ is selected from V according to Pseudocode 1. A default $N_s = 32$ was selected empirically as

a good trade-off between directional accuracy and computational efficiency for 1 [mm³] isotropic voxel resolution and observed growth cases in the longitudinal MRI data.

A gradient magnitude threshold of 0.99 is suitable for realistic GBM bounding box dimensions in 1 [mm³] voxel-isotropic space, but would possibly need to be lowered with lower isotropic resolutions to ensure extraction of $\geq N_s$ normal vectors. A cone is then computed for each vector in V_s based on a fixed deviation θ in angles between each vector in V_s and $\mathbf{d}$ according to Pseudocode 2. 2θ is the resulting top angle in the generated cones as illustrated in Figure 24. A default of $\theta = 7^\circ$ was selected empirically.

The final mask M displayed in Figure 24 (C) the conjunction of the ellipsoid mask M_c and all computed s cone masks $M_{c,i}$ from Pseudocode 2 according to Equation (3.37)

$$M = M_e \wedge \bigwedge_i^s M_{c,i} \quad (3.37)$$

Pseudocode 3 describes the next and main part of the algorithm deforming $\mathbf{d}$ by an amount β proportional to the maximum distance to the end of the brain (Figure 25), to create the infiltrative displacement field $\mathbf{d}_\beta$. An infiltrative gaussian g_β was created similarly.

Figure 25 here

The final model displacement field is computed according to Equation (3.38)

$$\mathbf{d}(M_l, M_b, \alpha, \beta, \gamma) = \left| \alpha \cdot \mathbf{d}_\beta(M_l, M_b) + \mathbf{p}(\gamma) \right|_{M_b} \quad (3.38)$$

where $\mathbf{p}$ is a Perlin noise (95) vector field and $||_{M_b}$ restricts displacement to only occur inside the brain mask. For the latter task, displacements surpassing the brain mask were shortened to end at the brain mask barrier.

3.10. *Overview of data*

The data analyzed in this thesis is of mainly two types; MR image and complementary data. The image data of a captured MRI volume is like any type of volume data after the sophisticated physics and mathematical post-processing on the MRI machine and software described in previous sections. A structural MRI volume may for instance be described as a three-dimensional grid consisting of equally (isotropic) or unequally (anisotropic) spaced integer or floating-point values, representing the imaged gray scale intensity value at various anatomical locations. Longitudinal, multi-sequence and functional MRI result in an additional fourth dimension (representing either time or image channel) of the volume after having performed necessary pre-processing steps.

Complementary data, such as segmentation of lesions and brain regions, survival and RANO status were collected and linked to the image data to ensure clinical relevance of the analyses.

3.11. *Preprocessing and organization*

High-quality MRI preprocessing has been essential throughout the entire thesis' work, and much dependent on analysis approach in each publication. A common denominator has been to ensure, for each patient, that all structural (T1w, T2w, etc.) and perfusion (DSC) MRI sequences are properly spatially aligned both between different series and longitudinally for the same series. These challenges are solved by intra-modal and inter-modal rigid

registration, respectively. Various intensity normalization methods have been important additional steps to ensure intra-subject intensity consistency of both structural and perfusion MRI when involving more than one exam per subject in the analysis.

With the main objective of investigating how geometric distortion from a specific type of functional MRI sequence impacts CBV, paper one performed analysis in native low-resolution functional (perfusion) space. The preprocessing carried out for structural MRIs were 1. removal of facial structures (spm_deface), 2. DICOM to NIFTI conversion and 3. rigid and non-rigid registration to transform structural MRIs and a template of brain regions to patient-specific low-resolution DSC space. The de-facing and registrations were performed with SPM12 (Statistical Parametric Mapping; spm_deface) (96) and ANTs (86), while DICOM to NIFTI file format conversion was performed with dcm2niix (97). K-nearest neighbor interpolation was used at all relevant steps. The DSC-MRIs were corrected for head motion using nordicICE (v. 4.0.0, NordicNeuroLab, Bergen, Norway), before applying either TOPUP (69) or EPIC (68) geometric susceptibility distortion correction as the main analysis methods to investigate. CBV maps from DSC-MRI were corrected for contrast agent extravasation (57) and normalized relative to healthy white matter values.

The objectives of paper two and three were to quantify and model tumor-induced structural changes. Thus, the focus here on structural effects, incentivized to work with the MRIs in high-resolution structural (anatomical) space. The MRI preprocessing steps follow much of the scientific recommendations for developing clinical imaging biomarkers (98), with some additional steps for alignment of MRIs to a common approximate reference space and longitudinal intensity normalization. The full preprocessing pipeline for structural MRI can be summarized as 1. DICOM to NIFTI conversion, 2. denoising, 3. correction for nonuniform

intensities, 4. voxel isotropic resampling, 5. brain extraction, then 6. longitudinal intensity normalization and 7. spatial normalization. DICOM to NIFTI file format conversion were, again, carried out with dcm2niix (97), then the NIFTI files were de-noised with a spatially adaptive filter (99) and corrected for nonuniform intensities with the N4ITK algorithm (100). Voxel isotropic resampling for the cases of anisotropic MRI voxels, were performed with FLIRT (101) using linear interpolation, brain extraction with BET (102), and longitudinal intensity normalization by piece-wise linear histogram matching within brain masks (103,104). Lastly, all MRIs were intra-patient rigid registered based on a structural MRI, then inter-patient spatially normalized by rigid and affine registration to the Montreal Neurological Institute (MNI)-International Consortium for Brain Mapping (ICBM)-152 2009c nonlinear symmetric T1w or T2w template (105,106). All registrations were performed using ANTs.

Version controlled datasets (107) following brain imaging data structure (BIDS) (108) recommendations were standards of practice in most of the thesis' work. Moreover, suited visualization tools were important and dependent on the preprocessing and analysis steps. The perfusion module of nordicICE was used in the thesis to generate CBV maps from uncorrected and TOPUP and EPIC corrected DSC-MRI. The data version control (DVC), BIDS file structure and a summary of the encountered visualization tools and scripting practices are described as supplementary methods. A short section about the usage and justification for various interpolation methods in the preprocessing is provided in supplementary material.

3.12. *Statistical methods*

The following section contains a short description of the various statistical methods encountered in the thesis. Wilcoxon, Kruskal-Wallis, and one-way analysis of variance are statistical hypothesis tests for measuring differences among populations of measurements, while Bonferroni and Benjamin and Hochberg are correction methods for multiple hypotheses tests. Dice similarity coefficient is a metric measuring spatial alignment of two binary segmentation masks. Neighborhood cross-correlation and mutual information are two similarity metrics commonly used in image registration. Last, survival analysis describes a collection of statistical methods to model and predict the time-to-death typically from longitudinal patient data.

3.12.1. Wilcoxon signed rank test

This is a nonparametric statistical hypothesis test if two dependent paired samples come from the same distribution (109). It accepts non-normally distributed data and tests whether the distribution of differences in median between the paired samples is symmetric about zero. A parametric analog to the Wilcoxon test that assumes normally distributed data is the paired Student's t-test.

3.12.2. Kruskal-Wallis test

Another nonparametric statistical hypothesis test for significance in median differences between two or more independent populations of observation data. It accepts non-normally, but similarly shaped distributed data. It is an extension of the Mann-Whitney U test for more than two groups. The parametric equivalent of the Kruskal-Wallis test is the one-way analysis of variance (ANOVA).

3.12.3. One-way analysis of variance

A parametric statistical hypothesis test for whether the population means of two or more groups differ. With the null hypothesis that samples in all groups are from populations with the same mean values, it estimates variances and produces an F-statistic to test for significance. One-way ANOVA assumes independent and identically normally distributed values. Tukey's method for multiple comparisons is used in ANOVA to create confidence intervals for all pairwise differences between the group means. By setting a family error rate of typically 0.05, significant difference in population means is indicated if a confidence interval does not include zero.

3.12.4. Bonferroni

This is a simple method to correct for multiple hypotheses tests that could otherwise result in type I errors (e.g., falsely rejecting a true null hypothesis). When performing N tests and with a significance cutoff of $\alpha = 0.05$, the corrected cutoff for each test i is $p_i \leq \alpha/N$. It controls the family-wise error rate (probability of making at least one type I error) at $\leq \alpha$. The correction is conservative and gives a greater risk of failure to reject a false null hypothesis (type II errors) than more advanced methods.

3.12.5. Benjamin and Hochberg

A correction for multiple hypotheses tests that controls the false discovery rate, i.e., rate of type I errors. First an accepted false discovery rate is determined, e.g., $q = 0.2$. Then, the p -values from all N tests are ranked from smallest to largest with rank $r = 1$ given to the smallest, rank $r = 2$ to the second smallest, etc. A Benjamin-Hochberg critical value for each test is then computed according to $\frac{r}{N}q$. The corrected cutoff for

each test is then determined from the test with the largest p -value that is less than its Benjamin-Hochberg critical value. All tests with this or lower p -value are considered significant.

3.12.6. Dice similarity coefficient

Dice similarity coefficient (110) is commonly used to measure spatial alignment of two binary segmentation masks. It ranges between 0 and 1 and can be viewed as a similarity measure over sets. Assume that mask X and Y is defined as a collection of voxels. The Dice coefficient between the two masks can be computed as $Dice = \frac{2|X \cap Y|}{|X| + |Y|}$ where the numerator is two times the count of intersecting voxels between the masks and the denominator is the total count of voxels for the masks.

3.12.7. Neighborhood cross-correlation

An image intensity-based statistical measure of local spatial alignment between two volumes where cross-correlation is computed for multiple sub volume (neighbor) pairs using a sliding cube method. It is thus suited for deformable registration tasks and works best for same sequence (monomodal) image pairs (e.g. T1w to T1w MRI). For registering the volume M to F , it may be written as (84)

$$CC(\mathbf{x}) = \frac{\sum_i ((F(\mathbf{x}_i) - \mu_{F(\mathbf{x})})(M(\mathbf{x}_i) - \mu_{M(\mathbf{x})}))^2}{\sum_i (F(\mathbf{x}_i) - \mu_{F(\mathbf{x})})^2 \sum_i (M(\mathbf{x}_i) - \mu_{M(\mathbf{x})})^2}$$

(3.39)

where the voxel coordinate vector $\mathbf{x}$ is at the center of a N^3 cube, μ is the mean value within the cube and $\mathbf{x}_i$ iterates through the voxel coordinates of that cube. The cube dimension (or neighborhood size) when using the ANTs SyN algorithm in the thesis was the

default of $N = 9 \text{ mm}^3$. Using neighborhood CC as a deformable registration loss metric involves computing its gradient, which is described in the ANTs SyN CC paper (85).

3.12.8. Mutual information

An image intensity-based statistical measure of global spatial alignment between two volumes based on information theory. Here, the intensity values of the two volumes are regarded as samples from two random processes. This leads to an interpretation of the area under curve normalized intensity histogram of a volume F as an empirical probability density function p_F of the most likely intensity values. MI is a measure of how well a spatially localized intensity value M_j in the second volume M can be predicted given the corresponding intensity value F_i in the first volume F . Specifically, it is the difference between the information contained in each volume and the joint information contained in the volumes according to (111)

$$MI(F; M) = \mathcal{H}(F) + \mathcal{H}(M) - \mathcal{H}(F, M) \quad (3.40)$$

where $\mathcal{H}(F)$ and $\mathcal{H}(M)$ is entropy of the fixed and moving volumes,

$$\mathcal{H}(F) = - \sum_i p_F(F_i) \log(p_F(F_i)) \quad (3.41)$$

and $\mathcal{H}(F, M)$ their joint entropy,

$$\mathcal{H}(F, M) = - \sum_i \sum_j p(F_i, M_j) \log(p(F_i, M_j)) \quad (3.42)$$

where p is the joint (2D) probability density function of the volumes. Mutual information can also be described as a special case of relative entropy, or Kullback-Leibler divergence. It

is well suited for multimodal (e.g. T2w to T1w MRI) registration tasks. For deformable registration, it provides faster but less accurate results than when using neighborhood cross-correlation. To optimize for registration transformation parameters, ANTs uses a variational method to find its gradient (84,112).

3.12.9. Survival analysis

Survival analysis (113) is a collection of statistical methods for modeling and predicting the time to which an event occurs. The predicted event in the thesis is patient death due to progression of disease. These models investigate the survival prediction capability of pre-selected input data (explanatory or predictor variables). The survival time of a patient after being included in a survival study is modeled by the random variable T . Some examples are months until death or progression of disease (progression-free survival) or patient age at death. If the survival time of a patient is not known exactly for reasons such as end of study or patient lost to follow-up or withdrawn from study for other reasons, it is censored (Figure 26 (113)). The analyses incorporate specific ways to handle censored data by introducing the censorship variable δ (0=censored, 1=death).

Figure 26 here

3.12.9.1. Survivor and hazard functions

The probability density function of death at a specific time t is described by the transition time distribution $f(t)$. The actual probability of surviving until a time t (the survival curve or survivor function $S(t)$) is found by integrating over $f(t)$ for all times larger than t

$$S(t) = P(T > t) = \int_t^{\infty} f(t)dt$$

(3.43)

In theory, $S(0) = 1$ and $S(\infty) = 0$. However, in practice, S is a step function since it is based on obtaining survival probabilities for different values of t . Central in survival analysis is computing the failure rate or hazard function $h(t)$, which is the chance of death for the next time interval, given that the patient has not died already;

$$h(t) = \lim_{\Delta t \rightarrow 0} \frac{P(T \leq t + \Delta t | T > t)}{\Delta t} = \frac{f(t)}{S(t)} = -\frac{d}{dt} \ln(S(t))$$

(3.44)

$h(t)$ is a conditional failure rate, or the instantaneous potential of death per unit time, given that the patient has survived until time t . It is not a probability and the obtained value will give a different number depending on the units of time used and may even be greater than 1. There is a relationship between $S(t)$ and $h(t)$; if one knows the form of $S(t)$, one can derive the corresponding $h(t)$ and vice versa as follows (113)

$$S(t) = e^{-\int_0^t h(u)du}$$

(3.45)

$$h(t) = -\frac{\frac{dS(t)}{dt}}{S(t)}$$

(3.46)

There are different ways to model the survival and hazard functions, dividing methods into nonparametric, semiparametric and parametric methods. Each impose different assumptions about the survival data.

3.12.9.2. Concordance index

$C - index$, or Harrell's concordance index (114), is a performance metric for survival models. It is a generalization of the area under the receiving operating characteristic curve (AUC-ROC) that considers censored survival data and is computed by summarizing the survival times and risk scores for all pairs of patients i and j ($i \neq j$) as follows:

$$C - index = \frac{\sum_{i,j} 1_{T_j < T_i} \cdot 1_{\eta_j > \eta_i} \cdot \delta_j}{\sum_{i,j} 1_{T_j < T_i} \cdot \delta_j} \quad (3.47)$$

where η_i is the risk score for patient i and

$$1_{T_j < T_i} = \begin{cases} 1, & T_j < T_i \\ 0, & \text{else} \end{cases} \quad (3.48)$$

$$1_{\eta_j > \eta_i} = \begin{cases} 1, & \eta_j > \eta_i \\ 0, & \text{else} \end{cases} \quad (3.49)$$

Like AUC-ROC, $C - index = 1$ corresponds to the best model prediction, while $C - index = 0.5$ corresponds to a random prediction. It represents the model's ability to correctly provide a reliable ranking of the survival times based on the individual risk scores. Continuous explanatory variables may be used as risk scores. In the second paper, the various displacement biomarkers were used as risk scores.

3.12.9.3. Kaplan-Meier

This is a nonparametric method where the survival curve $S(t)$ is estimated directly from the data by ordering the survival times (from smallest to largest) and associated estimated survival probabilities according to the product limit formula

$$\hat{S}(t) = \prod_{i|t_i \leq t} \hat{P}(T > t_i | T \geq t_i) = \prod_{i|t_i \leq t} (1 - \frac{d_i}{n_i}) \quad (3.50)$$

where d_i is the number of deaths that happened at time t_i and n_i the number of patients known to have survived up to time t_i (i.e. not diseased or censored). Kaplan-Meier (KM) allows only categorical explanatory variables. For testing significance in differences in KM survival time prediction capability between two subgroups (e.g. using a placebo vs. treatment explanatory variable), the log-rank test can be used.

Log-rank test for two subgroups

This is a nonparametric large-sample chi-square test for comparing the survival curves of two subgroups. With the null hypothesis that the two subgroups have a common survivor function, it tests for significance with the approximate formula

$$\chi^2 = \sum_i \frac{(O_i - E_i)^2}{E_i} \quad (3.51)$$

where O_i and E_i are formulas for observed and expected deaths for subgroup i as explained elsewhere (113).

3.12.9.4. Cox proportional hazards regression

This is a semiparametric method assuming a proportional hazards model. It separates time dependency (t) from explanatory variable dependency (x) in the hazards function such that

$$h(t|x) = h_0 e^{\beta x} \quad (3.52)$$

where h_0 is a parametric baseline hazard function (e.g. a Weibull hazard model). Unlike KM, it allows continuous explanatory variables and the hazards function is estimated in terms of regression. Additive effects of categorical variables can be included in the model like KM analyses. Moreover, it is possible to estimate the β 's (in terms of maximum likelihood) in the exponential part of the model without deciding h_0 . These are some reasons why Cox proportional hazards regression is a popular survival analysis.

4. Summary of papers

The three publications perform voxel tracking with the aims described previously. This involves, among others, EPI correction for obtaining more accurate estimates of blood volumes in the first paper, developing prognostic tissue deformation biomarkers in the second paper, and measuring deformable registration accuracy for tumor growth assessment in the last paper.

4.1. Paper 1

We performed geometric susceptibility distortion correction to improve the spatial alignment of perfusion MRI and structural MRI, as well as consistency of blood volume estimates from perfusion MRI. We investigated two methods for correcting EPIs for geometric susceptibility distortions, FSL TOPUP and EPIC, as described in previous sections. The impact of the correction methods on estimated CBV values in GBM pre-treatment MRI of 45 patients was measured.

The raw EPIs in the DSC-MRI contained the stretching type of distortions described previously (Figure 15). Geometric distortion in the raw EPIs and the CBV map computed from raw DSC-MRI were various spatial misalignments particularly in frontal regions when

compared to non-EPI structural MRI. This yielded for both investigated SE and GE DSC-MRI (Figure 17).

Our main result was that this type of EPI distortion resulted in underestimated CBV values. By performing either of the TOPUP or EPIC distortion correction methods on the DSC EPIs and computing CBV from the distortion corrected EPIs, an increase in CBV values was observed when comparing to CBV values computed from distorted EPIs.

As described in previous sections, both TOPUP and EPIC modifies intensity values of voxels in the EPI in addition to displacing voxels when performing corrections. Correcting for the stretching type of distortion as a result of a top-down phase encode k-space traversal will lead to an increase in EPI intensity values (related to the method of displacement correction) in the distortion corrected EPIs. Our work showed that this type of EPI distortion correction also leads to significant intensity increase in CBV as measured by paired Wilcoxon signed rank tests. This effect was most prominent in cortical regions close to air-tissue transitions, which experience high variations in local tissue magnetic susceptibility and subsequent ΔB . Of tumoral regions, only TOPUP correction of SE EPIs led to significant CBV change. This change was a CBV increase in contrast enhanced regions. Second, we analyzed the volume change of multiple brain regions and tumor lesions associated with EPI correction. For this we used paired Wilcoxon signed rank tests on Dice similarity coefficients. Many regions experiencing significant CBV and Dice coefficient change were in cortical areas in the frontal, occipital and temporal lobes as illustrated in Figure 27.

Figure 27 here

In summary, this work highlighted the importance of performing EPI correction when assessing CBV values together with structural MRI in GBM. An EPI that possesses lowered

intensity values and stretched geometric distortions along the anteroposterior axis does not perfectly correspond to a high-resolution structural MRI. Since perfusion MRI utilizes EPIs, correction methods such as FSL TOPUP are warranted to ensure CBV values that correspond to tissue seen on structural MRI. Our results indicated that for this type of EPI distortion, CBV values from uncorrected EPIs tend to be underestimated and falsely displaced when compared to their true values and spatial locations in the cancerous brain.

4.2. Paper 2

Here we utilized deformable registration together with regions of interest, survival and RANO status, to derive and investigate deformation-based biomarkers. We analyzed their survival prediction capabilities, stratification capabilities into low and high survival subgroups, and association with RANO status.

We introduced four deformation biomarkers based on magnitude and divergence maps of displacement fields within peritumoral regions; two displacement biomarkers and two compression biomarkers (Figure 19). We defined subregions of peritumoral regions that had a negative divergence map as peritumoral tissue compression habitats. The displacement fields were computed from deformable registration of consecutive intervals of longitudinal MRI pairs of post-operative GBM. A total of 127 longitudinal studies from 23 patients with GBM were incorporated into the study.

Most of these patients experienced significant tissue deformations at later stages of the treatment as a result of recurring tumor mass effect. We stratified patients into Low and high survival subgroups according to an optimal threshold value for our biomarkers in terms of maximizing the C-index. In this way, we linked low and high survival subgroups with biomarker values describing high and low mass effect. Mean values of the biomarkers were

extracted from peritumoral regions as well as peritumoral compression regions. The analysis was carried out as follows:

- 1) Analysis of inpatient association of the median biomarkers with RANO progression status by pairwise Wilcoxon signed rank tests.
- 2) Analysis of the association of biomarkers with interpatient overall survival as well as with inpatient time-to-exitus for each interval image pair using Cox proportional hazards regression analyses.
- 3) Kaplan-Meier analysis and log-rank tests to investigate stratification capabilities of the biomarkers when divided for low and high survival subgroups.

For 1) we found that all biomarkers had significant higher values for the paired exams labeled as progressing compared to the pairs that were labeled with non-progression RANO status. This effect was most prominent for the compression biomarkers. The Cox analyses in 2) returned all biomarkers to be significantly associated with time-to-exitus. Only the compression biomarkers had a significant interpatient association with survival. Moreover, the highest hazard ratios were observed in the peritumoral compression habitats and were larger for compression biomarkers than for the displacement biomarkers. Last, 3) returned the compression biomarkers to have significant stratification capability into low and high survival subgroups. The stratification capability increased when restricting measurements to within peritumoral compression habitats. Figure 28 displays the biomarkers for one of the patients.

Figure 28 here

In summary, this work indicated that deformation biomarkers computed from deformable longitudinal registration in GBM, and particularly peritumoral compression biomarkers, may have prognostic significance in predicting survival outcomes in patients with GBM receiving standard treatment. High peritumoral compression as measured our divergence-based biomarker may indicate reduced survival prognosis. In general, clinically relevant effects of tumor growth on tissue may be predicted by these deformation biomarkers, such as early detection of recurrence. Moreover, peritumoral regions experiencing tissue compression as measured by negative divergence may be particularly relevant regions to examine during patient follow-up, as they may provide a causal link between solid stress and neurological dysfunction.

4.3. Paper 3

In this work we investigated the geometric accuracy of deformable registration-based tissue displacement estimates in tumoral regions. We created a framework for measuring deformable registration performance in GBM by generating realistic synthetic ground truth tissue deformations as possible projections of cancer progression and recurrence on structural MRIs.

This involved developing a tissue deformation model of cancer growth with a controlled set of clinically meaningful simulation parameters; 1) maximum radial tissue displacement α , 2) infiltration β and 3) growth irregularity γ as described previously. The deformation model thus allowed us to perform a parametric evaluation of deformable registration methods for use in tumor growth assessment.

We generated 12 synthetic deformations of early post-operative baseline T1wc MRI from 27 patients with GBM by varying our simulation parameters. We selected simulation

parameters to describe low and high tumor mass effect, low and high infiltration and no, intermediate and high irregularity. Figure 21 presents the 12 displacement fields $\mathbf{d}(M_l, M_b, \alpha, \beta, \gamma)$ and resulting deformed T1wc images for a given patient lesion M_l and brain M_b mask. These synthetically deformed T1wc MRIs were then regarded as possible projections of growth as seen on future follow-up scans.

Five well-known deformable registration methods were then set to estimate the voxel-wise displacement between each pair of baseline and synthetic follow-up scan. We analyzed the voxel-wise displacement estimation error from comparing our ground truth displacements with the estimated displacements from the deformable registration methods within edematous, contrast-enhanced and necrotic lesion regions. Pairwise Wilcoxon signed rank tests, Kruskal-Wallis tests and ANOVA with Tukey pair comparisons were conducted to investigate the significance in estimation errors when varying the simulation parameters as well as performance differences between the registration methods within the lesion tissue classes. We also performed a grid search (of α and β) to investigate how well our model could fit to describe real two-week later follow-up scans. The evaluation function in the grid search was spatial cross-correlation (77) between model deformed and true second exam T1c MRI within outer ellipsoid masks defined by $g_\beta > 0.05$.

Our study returned highest performance of the deformable registration methods for tumor growth projections containing low maximum radial tissue displacement (low mass effect) combined with high infiltration phenotypes. Moreover, displacements were most accurate in contrast-enhanced and edematous lesions when compared to necrotic lesions. Of the investigated deformable registration methods, ANTs SyN with cross-correlation loss metric and Gunnar-Farneback optical flow performed with lowest displacement estimation errors.

The grid search on baseline and real second scans pairs from all 27 patients for the optimal simulation parameters, revealed some interesting aspects of the early treatment regime. Our deformation model was best fit to describe two-week later scans when exhibiting a high infiltration parameter combined with a low maximum radial tissue displacement (low mass effect). An example of optimal parameters illustrating simulated low mass effect and high infiltration ($\hat{\alpha} = 3.4 [mm]$ and $\hat{\beta} = 0.14$) is seen for a single patient in Figure 29 along with the corresponding estimated displacement field from ANTs SyN. Low infiltration was also associated with larger total tumor volume.

Figure 29 here

In summary, this work highlighted the favorable clinical conditions when using deformable image registration to develop prognostic displacement-based analyses to patients with GBM. Our results indicated that high infiltration and low mass effect phenotypes may lead to the highest accuracy of displacement estimates from deformable registration in early and short-interval post-operative longitudinal MRI of GBM. Deformable registration methods may thus accurately quantify small tumoral and peritumoral tissue displacements for use in early treatment response assessment. This work provided empirical evidence for the well-suitedness of using the prognostic deformation biomarkers from deformable registration in the second paper. Furthermore, our deformation model provided robust predictions of future tissue displacements based on few simulation parameters. This led to insights about the typical low mass effect and high infiltration conditions seen on early post-operative longitudinal MRI of GBM.

A complementary grid search on all longitudinal scan interval pairs (not included in the publication) was that many best fit projections also described tissue shrinkage (accomplished with a negative α) early in the treatment (Figure 30).

Figure 30 here

5. Discussion

The general objective of most of the work in this thesis was improving computer aided description of clinically relevant MRI imaging regions and features and thereby accurately describing and improving patient prognosis in brain cancer. This involved accurate characterization of structural brain and cancer regions through manual and automatic segmentation, followed by monitoring the spatial and intensity transformations in and around regions of interest along with the treatment. Segmentation of various brain structures and lesions such as various tumor tissue constitute an important subfield in medical image analysis. The segmentation of brain structures in the first paper was performed using conventional and high-quality software, while the tumor segmentations in all papers were either performed manually (by a neuroradiologist) or based on a deep learning (DL) method. The methods were described in the preprocessing section of the thesis. An important aspect of our results is interpolation. A separate discussion about best practices in interpolation is found in supplementary methods. The main scientific contribution of the thesis was an investigation into various methods for obtaining spatiotemporal tracking of clinical image features.

5.1. Paper 1

EPI correction was performed by specialized spatial and intensity tracking methods which led to more accurate CBV maps. CBV maps captured from DSC-MRI are imaging features with clinical relevance and it is important that CBV is accurately matched with structural MRI for optimal treatment assessment. We investigated how spatial and intensity distortions caused by varying tissue susceptibility in DSC-MRI with stretching EPI distortions affected CBV in multiple cortical and subcortical brain regions, leading recommending distortion correction to ensure improved spatial and intensity consistency of CBV compared with structural MRI in cancer.

Our main findings were that CBV estimated from DSC-MRI risks being underestimated when not performing correction, and that this effect was most prominent together with geometric distortions in cortical areas in the frontal, occipital and temporal lobes (Figure 27). As is discussed in the paper, the location of a tumor affects the survival prognosis. Several studies have associated the survival prediction capabilities of CBV in brain cancer (31,115–117). In our paper we presented evidence that CBV values of a tumor involving multiple brain regions with varying degree of EPI distortion may return an artificial gradient of reduced CBV values even within a tumor, if not corrected for. There are some differences between the correction methods investigated, and in CBV values from SE and GE DSC-MRI. This is discussed in our paper. In general, TOPUP correction of SE EPIs led to the most precise correction and subsequent CBV estimation. A previous study using a 7 Tesla scanner found that when compared to using GE EPIs, TOPUP with SE EPIs led to better correction only in the ventromedial prefrontal cortex (118). This is a region with large signal drop-out on GE EPIs. It is widely known that magnetic susceptibility distortions and drop-out increase with

magnetic field strength. In our study, GE DSC-MRI also led to generally higher CBV values than when estimated from SE DSC-MRI independent of correction method. We hypothesize that this is related to the FID signal in GE EPIs being stronger than the pure T2w signal in SE EPIs..

Another important discussion that affects the impact of correction on CBV is the phase-encode direction in the EPI sequence. Note that in our paper the words “positive” and “negative” for describing phase-encode direction were swapped when compared to the images in the thesis. This was done in order to keep terminology in the thesis more consistent with existing literature (69). Specifically, bottom-up (=positive) and top-down (=negative) phase-encode direction results in compression and stretching distortions, respectively. To avoid confusion, it is suggested to use only the compression and stretching distortion terminology when referring to the two main types of EPI distortion that can occur and which depend only on the phase-encode direction in the EPI sequence. We hypothesize that the results in the first paper could be different if the EPIs in the DSC-MRI had the opposite phase-encode direction (leading to compression distortions). Intuitively, not correcting for these distortions may result in overestimated CBV values and perhaps Dice inconsistency for another set of cortical regions. However, this is only speculation and a separate study with EPIs containing the opposite phase-encode direction in the DSC-MRI sequence would be needed to investigate this further.

The impact of other EPI correction methods on CBV estimates could further identify potential shortcomings of FSL TOPUP and EPIC. Some relevant methods could be the SPM ACID HySCO (119) and DR-BUDDI (120) reverse gradient methods, reverse gradient methods for specific locations in the brain such as the temporal lobe (121), or DL-based (122–124)

methods. Geometric distortions may also be present on structural MRI (125), challenging correct anatomical alignment of EPI and structural MRI. However, these distortions are mostly caused by external factors and corrected for as discussed previously.

5.2. Paper 2

Deformable registration of longitudinal MRI of cancer provided robust spatiotemporal tracking. We developed four biomarkers based on estimated displacement from longitudinal deformable registration. The association of these deformation-based biomarkers with RANO tumor status, and survival prediction and low and high survival stratification capability was investigated. We showed that the biomarkers may have prognostic ability in predicting survival as well as being early markers for assessing cancer recurrence. Compression of peritumoral healthy tissue is known to cause life-threatening neurologic symptoms (126). Moreover, our deformation biomarkers may be especially useful for eloquent areas, since compression in these areas may affect important cognitive functions. The accuracy of these biomarkers highly depends on the accuracy of the deformable registration method. A discussion of deformable registration accuracy is thus warranted.

Our main objective in using deformable registration was to link various locations in the brain that are of interest between MRI scans for a given patient in order to track the underlying biological properties and possible transformation of tissue along with the treatment and cancer progression. On a macroscopic scale this amounted to tracking spatial displacement of voxels between MRI scans (Figure 16). However, deformable registration does not track voxel intensity change. Optimally, tracking both displacement and intensity change should be biologically possible, i.e. the same piece of brain tissue in a patient should be identifiable across MRI scans even when exposed to biological transformation from treatment or cancer

resulting in voxel intensity change on MRI. The voxel tracking problem may then be seen as a multimodal image matching problem (127).

The biological interpretation of a change of voxel intensity on MRI strongly depends on the MRI sequence. An increase in water density would result in a (lower) darker or brighter (higher) intensity value on a T1w or T2w MRI, respectively. Another factor impacting intensity is the use of a contrast agent, which in the context of T1w structural imaging selectively increases the voxel intensity value in regions where it is accumulated. Water density and contrast agent accumulation may depend on cancer phenotype. The T1wc MRIs in Figure 7 clearly showed intensity increase in contrast accumulated tumor regions, while Figure 8 showed intensity decrease in peritumoral regions as a result of an inflammation, an increase in water density resulting from edema, at exams late in the treatment. Different weighting schemes as well as varying contrast agent injections may thus impact the accuracy of deformable registration accuracy and subsequent impact our deformation-based biomarkers. We used T1wc MRI in the second paper.

Quantifying the geometric displacement of tissue and local tissue compression in peritumoral regions as a result of tumor mass effect, as seen in Figure 8, was the focus in this work. No voxel intensity change and only spatial deformation between longitudinal MRIs (i.e. $\Delta I = 0$) may be thus a favorable condition for using deformable registration for voxel displacement tracking of cancers with a strictly pushing phenotype or similar types with little voxel intensity changes. For this case, tracking peritumoral and non-cancerous regions would closer resemble homeomorphic (one-to-one) mapping if no appearance or disappearance of mass (resulting in intensity changes) occurs during the tracking. Since diffeomorphic deformable registration does not shift intensity values, only spatial

deformation between MRIs may result in the highest possible registration accuracy. An example of erroneous use of deformable registration for displacement tracking is when an intensity change $\Delta I \neq 0$ leads to a false displacement estimate $\mathbf{d}$ when no displacement occurred.

Changes in tissue mass with cancer and treatment is another aspect challenging deformable registration accuracy. We hypothesize that with aggressive tumor growth and subsequent intensity change from mass increase, that deformable registration may give most accurate results if the moving image is registered backwards-in-time to a fixed first time-point image. The rationale is that tracking mass that disappears results in more accurate displacement estimates than tracking under the influence of mass appearance. Non-spatial transformation of tissue should preferably be described by an additive intensity term ΔI in the frame of the fixed image to rule out this recording task for deformable registration algorithms.

The time direction of registration, however, may not be crucial for correct tracking of displacement since mass may both disappear and appear in standard treatment of brain cancer as results of successful and unsuccessful treatment. New or decaying mass resulting in image changes are expected in cancer, which challenges the physical accuracy of deformable registration for use in cancer diagnostics. How well a registration method describes the actual tissue displacement highly depends on the mathematical and physical guarantees of the registration method. Some other factors may be the selection of regularization method and loss function for the optimization process of the registration algorithm. If the symmetric property of SyN is not required, Greedy (128) may be a better option since it provides diffeomorphic registration at reduced computational cost.

Previous studies have investigated the use of deformable registration for measuring mass effect in form of lateral ventricle displacement (92) and peritumoral tissue deformation heterogeneity (42,129). However, these studies measured mass effect induced deformations relative to an MNI brain template and did not incorporate longitudinal exams and result in voxel tracking.

5.3. Paper 3

The third paper investigated the geometric accuracy of deformable registration under the influence of synthetic voxel displacements produced by our deformation model. We drew inspiration from longitudinal MRI of GBM to model realistic tissue deformations by a growing tumor exerting a mass effect, by producing a radial voxel displacement field from brain and lesion tissue masks and with simulation parameters for maximum tissue displacement, infiltration and irregularity. We showed that the deformable registration methods had the highest accuracy in estimating the displacement field for simulated low maximum tissue displacement (low mass effect) and high infiltration, and within contrast-enhanced and edematous lesion tissue types. Moreover, we identified ANTs SyN with cross-correlation metric with overall highest registration accuracy. It is generally known that an increase in mass effect is associated with worse survival prognosis in GBM (92,130,131). An important discussion of these results is how realistic the simulated ground truth displacement fields were when varying the parameter configurations for mass effect, infiltration and irregularity. Thus, a general discussion about the anatomical correctness of the deformation model and its application in evaluating deformable registration methods follows.

The main strength of this work was not introducing a highly patient-specific physically and biologically accurate model of brain cancer deformation in treatment of GBM, but introducing a robust and interpretable model with the ability to efficiently generate synthetic deformation examples from binary mask data, including segmentation annotations, of the most typical structural deformations seen in GBM MRI receiving the standard treatment. The model is much more methodically simple and computationally efficient than comparable reaction-diffusion (93,132) and DL (133,134) based models. The most typical deformations include structural compression of surrounding peritumoral tissue as a mass effect (92) from cancer growth (possibly associated with midline shift (131) and poorer survival), or oppositely, shrinkage of lesion areas from response to treatment.

We observed that existing literature were more focused on modeling cancer growth (with a resulting tissue expansion) than shrinkage of tissue areas (93,132–137). Many of these tumor growth models do not incorporate treatment-related changes. Most of our patients experienced a shrinkage of lesion areas in the early stages of treatment (possibly as a response to the radiation treatment), followed by aggressive expansion of old and new lesions areas as a result of cancer recurrence. Our model fitting indicated that tissue shrinkage may be just as common as expansion in the early treatment assessment (Figure 30). As such a further elucidation when modeling mass effect may be whether the patient experienced a mass increase effect or oppositely a mass decrease effect. GBM is a highly complex cancer with large inter- and intra-tumor heterogeneity and analyzing images of patients undergoing treatment makes the data even more complex. A strength of our deformation model is that it can use few simulation parameters and little input data to generate realistic enough tissue displacements for performing parametric evaluations deformable registration methods.

There are limitations in our deformation model. First, intensity shift is not part of our model. An investigation into registration accuracy under the influence of synthetic intensity shifts remains as further work and possible extension of our model. In true infiltrative tumor growth, intensity shift of voxels caused by transforming tissue, may be just as apparent as displacement of voxels. However, incorporating intensity shift would not result in a model of tissue deformation, but in a model of the spatiotemporal transformation of tissue from tumor growth. Deformable registration is only aimed at estimating displacement, thus by also modeling intensity shift it would be more complicated to use our model to perform a parametric evaluation of deformable registration methods (which was our main objective). Moreover, our infiltration parameter controlled the model displacement aspect of infiltrative growth since high infiltration results in cancer in larger regions of the brain compared with low infiltration. Another extension of the model may be to allow for more specialized directions of the cone masks either by random deviations in the directions or possibly by aligning the cone directions with principal diffusion directions from DTI. Or, incorporating perfusion maps such as CBV to guide model parameters such as infiltration β and irregularity γ . The increased complexity of input data, parameters and model may however outweigh a possible benefit of getting a more accurate model from these improvements, and in requiring additional preprocessed data it would also make it less robust against preprocessing errors and noise.

5.4.Future aspects

Below is a summary of outcomes and applications as well as some additional results related to tracking clinically meaningful imaging properties.

5.4.1. EPI correction software

A natural outcome of the first paper could be enabling researchers and clinicians to easily perform EPI correction and optimally having it as a part of the clinical workflow.

Incorporating EPIC into such a workflow was the main objective in a previous Master's thesis (64). In our work, FSL TOPUP was packaged into bash scripts for easier use and shared with other researchers at our hospital. These scripts can be run on Linux virtual machines (e.g. Docker, VirtualBox or VMware) with FSL installed and are available at GitHub (scripts/computetopup.sh and scripts/applytopup.sh).

5.4.2. Alternative uses of deformable registration

There are other potential clinical use cases of deformable registration at our hospital.

Hydrocephalus is a general life-threatening state in which CSF spaces are under pressure and resultingly are enlarged. SyN may be used to provide a quantitative measure of this by measuring overall deformation change when comparing to a normal brain template.

Another used case is midline shift quantification which may be solved similarly using a template.

5.4.3. Standardization and visualization

Substantial efforts were put into organizing and preprocessing data. Better standards for dealing with data (e.g. file types and data structures) could improve reproducibility and cross-collaboration among research groups and significantly alleviate technical dept for common processing and preprocessing tasks in neuroimaging. Most of the work in the thesis drifted towards complying to the brain imaging data structure (BIDS) consensus among researchers. Since working with research data often means continuously discovering

and solving processing errors, while simultaneously consenting to share data that was used in previous publications, updates to a data set should optimally be tracked like code in a software project. For this task, the data version control (DVC) software was used on the BIDS datasets. BIDS and DVC are further described as supplementary material.

Having standards also simplifies visualization and quality control (QC), since necessary assumptions about file types, locations and file organization structure can be made in software and scripts. A summary of the visualization tools used can be found in supplementary methods. For examples of what could be easily automated when having stricter data organization standards, see Figure 31 and Figure 32 and their link to the corresponding time evolution animation, as well some examples for visualization techniques using well-known software.

Figure 31 here

Figure 32 here

BIDS incorporates a way to link raw, minimally processed and processed data without mixing them by having the tree folders sourcedata, rawdata and derivatives with near identical folder structures. This means that it is easier to run processing and visualization scripts on both raw and processed data. For demonstration, we performed radial basis function (RBF) interpolation on the irregular interval examinations to visualize one-day regular interval image approximations to of the overall longitudinal evolution of patients. RBF interpolation is described in supplementary theory.

Figure 33 here

5.4.4. Voxel displacement path tracking and visualization

A natural extension of voxel displacement tracking would be to compute the total displacement path of voxels according to the displacement field from each examination interval in longitudinal MRI. Theoretically, these are pathlines computed from the time-varying voxel displacement vector field describing tissue displacement as described in supplementary theory. The displacement pathlines can then be visualized like DTI fiber lines and thus DTI visualization software can be used.

A demo web site based on the X toolkit (138) was made for easy visualization of tissue displacement paths from our pipeline and is presented in the below figures. In figure 34, the displacements were based on longitudinal backwards-in-time SyN deformable registration, while in Figure 35 the displacements were based on fitting the forward-in-time deformation model using grid search. See supplementary methods for more details.

Figure 34 here

Figure 35 here

An interactive graphical user interface containing the most common viewing settings to be expected in conventional medical viewers, was developed together with some specialized settings related to restricting pathline length visualization (Figure 36).

Figure 36 here

A possible use case of this viewer could be to present a brain cancer treatment tissue response atlas in approximate MNI space. If containing pathlines from many longitudinal patient cases, it could be an interesting way to present and the most typical tissue deformations.

5.4.5. Improving segmentation using the deformation model

Paramount in this thesis was developing methods for longitudinal tracking of macroscopic imaging features of clinical interest. The two most common approaches today are 1) voxel-wise tracking and 2) region-based tracking. The thesis investigated voxel-wise tracking by incorporating both voxel displacement and voxel intensity change along with time and disease progression and treatment. In this ideal case, the spatial location of a piece of tissue and its trajectory and intensity value history from cancer and treatment is described directly.

It was shown that SyN registration as described in section 3.7 can be applied to estimate voxel displacement with high accuracy. By estimating a displacement field from deformable registration, it can then be applied on volumes of interest, for instance tumor masks and target delineation in surgery and radiation therapy, to re-locate the outlined regions of interest in a later time point exam. The methodology for voxel-wise tracking was developed in the second publication and its accuracy was assessed in the third publication. However, voxel-wise displacement estimation may not be required or accurate for the general task of tracking data with clinical relevance. One limitation is the lack of estimating intensity transformations as described in section 3.7.

Traditionally, volumetric or delineated surface changes have been used to for treatment response assessment. As a sparser tracking approach, region-based tracking using segmentations may be used. This tracking approach does not enforce a direct description of voxel transformation and thereby overcomes a possible limitation of requiring voxel-wise tracking in physically difficult scenarios. Such a scenario may be major spatial and intensity transformations from cancer leading to uniform image gradients such as necrotic regions.

The leading medical image segmentation methods are based on DL, which are commonly deep convolutional neural networks trained on large amounts of structural MRI with multi-label segmentation masks as annotations (139,140). Lack of large-scale medical training datasets is the leading factor in many DL brain tumor segmentation algorithms poor performance (140). Data augmentation is a widely accepted solution to the problem of limited data for DL and machine learning model training (141).

Our deformation model could alternatively be utilized as a data augmentation method specifically made for improving longitudinal segmentation performance in brain cancer. The deformation model here would belong to a class of domain-specific local data augmentation methods. It could be further developed for offline and online (test-time) augmentation for use in DL training. In summary, such potential improvements in clinical accuracy of DL segmentations methods may ultimately lead to successful adaptation to tasks such as radiotherapy target volume delineation (142). However, using these advanced computational tools to improve patient care requires adequate crosstalk between computer scientists and oncologists in order to fulfil the needs of the oncologists, and to overcome the technical burden of confusing terminology used by computer scientists.

5.4.6. Non-localized tracking

It is possible to track clinically meaningful imaging properties without defining a ROI. These are exploratory methods capable of categorizing more abstract and high-level patterns in the data and which do not necessarily relate to voxel-wise or region-based properties. They are typically patterns learnt by DL models (and not hand-crafted such as our deformation model parameters), and interpretability techniques are often required to find and make use of the most useful patterns.

A future aspect of longitudinal MRI analysis in brain cancer may be to utilize clustering and unsupervised methods in order to find patterns that correlate well with clinical data such as treatment response, survival and various known medical conditions. An unsupervised DL model such as autoencoder (AE) could for instance be targeted at categorizing disease based on multiple patients analogous to the previously mentioned idea of having a treatment tissue response atlas of displacements. A new patient may then be associated with existing patients with treatment outcome already known by using similarity and interpretability techniques on the DL model.

A simple example of non-localized tracking of structural ventricle change was demonstrated in the thesis. Principal component analysis (PCA) is a widely known and understood statistical dimensionality reduction method. Moreover, the simplest form of a linear AE spans the same subspace as the PCA loading vectors (143). We reproduced this work using our longitudinal volumetric MRI of a patient and identified the second component in PCA to correlated with ventricular expansion as seen in Figure 37.

Figure 37 here

Furthermore, we were able to reproduce the loadings plot in Figure 37 from a linear AE model trained on the same data, by conducting singular value decomposition (SVD) on its decoder weights. Our point was to give an example of identifying a simple high-level pattern in the data correlating with atrophy and that this pattern was indeed captured by the simplest possible linear fully connected three-layer AE. In comparison, the widely successful U-Net (144) for medical segmentation tasks has 23 convolutional layers.

Most of our patients experienced ventricle volume increase during the time they were scanned, which is believed to be a consequence of brain atrophy due to CRT (145,146). This

experiment illustrated that despite the huge dimensional complexity of DL models, that it is possible to build up intuition about their subspace complexity and resulting interpretability analogous to PCA loadings. These methods may enable us to capture and interpret more holistic patterns in data that may be clinically relevant without resorting to ROI-based analyses.

5.4.7. Multivariate analysis of clinical data

Multivariate analysis of structural ventricle changes in GBM led to some additional results that may be worth looking more into. A PCA model was computed on data containing ventricle and tumor volume change, normalized relative CBV change in tumor and sub-ventricular zones, age, overall survival and time from first scan. Two data sets with a total of 41 patients with GBM consisting of 387 scan intervals was used. The non-linear iterative partial least squares (NIPALS) version of PCA (147) was used for this case due to some missing data. Outlier removal according to 95 % confidence intervals according to Hotelling's T^2 statistic (a multivariate generalization of Student's t-statistic) was performed. Figure 38 presents the loadings for the first two components where the overall correlations between the input data variables are seen.

Figure 38 here

Some notable results were the negative correlation of overall survival and CBV increase and ventricle volume increase, as well as of age and CBV increase and ventricle volume increase. An increase in CBV was associated with worse survival prognosis, while younger patients were associated with less ventricle volume increase. A larger tumor volume increase correlated with worse survival prognosis, as expected. However, an older patient was not much associated with tumor volume increase.

6. Conclusion

7. Appendices

7.1. Supplementary theory

7.1.1. Radial basis function interpolation

This is a meshfree in approximation method (148,149) that takes scattered data points in arbitrary dimensions as input and describes them as a weighted linear combination of strictly positive definite (150) radial functions (Figure 39).

Figure 39 here

From <http://shihchinw.github.io/2018/10/data-interpolation-with-radial-basis-functions-rbfs.html>

Assume that the spatial coordinate and time point for a given voxel in linearly registered longitudinal MRI for a patient is $\mathbf{x}_j = [x, y, z, t]$ and its intensity value is y_j . Then, all N $\mathbf{x}_j$ - y_j pairs can be fitted to a linear combination of certain basis functions B_k creating the continuous function

$$\mathcal{P}_f(\mathbf{x}) = \sum_{k=1}^N c_k B_k(\mathbf{x})$$

(7.1)

The number of basis functions B_k is the number of data points N and

$$B_k(\mathbf{x}_j) = \varphi(||\mathbf{x}_j - \mathbf{x}_k||) = \phi(\mathbf{r})$$

(7.2)

is a RBF centered at $\mathbf{x}_k$ where $\mathbf{r} = ||\mathbf{x}_j - \mathbf{x}_k||$ is the radial distance from its center position $\mathbf{x}_k$ to the true data point $\mathbf{x}_j$. B_k is radial because its output value is only dependent on the magnitude of the input vector $\mathbf{r}$ and it is thus symmetric. A common RBF is the Gaussian function $\phi(\mathbf{r}) = e^{-(\epsilon\mathbf{r})^2}$ where ϵ is a positive shape parameter (Figure 40).

Figure 40 here

From (149).

RBF interpolation amounts to finding the appropriate center $\mathbf{x}_k$, shape parameter ϵ_k and weighting c_k for all N RBFs by solving the linear equation system $A\mathbf{c} = \mathbf{y}$ where $A_{jk} = B_k(\mathbf{x}_j)$, $j, k \in [1, N]$, $\mathbf{c} = [c_1 \ \cdots \ c_N]^T$, $\mathbf{y} = [y_1 \ \cdots \ y_N]^T$. An interpolated value y can be obtained by sampling $\mathcal{P}_f$ on any desired input value $\mathbf{x}$.

7.1.2. Voxel displacement path tracking

Correct estimation of longitudinal voxel displacements could result in enough information to describe the whole displacement trajectory of a piece of tissue starting from a given voxel.

The trajectory of a voxel or piece of tissue originating from the first image would then directly follow the pathline computed from the time-varying displacement vector field described by the consecutive displacement transformations $T_1, T_2, \dots, T_N$. If $\mathbf{d}(\mathbf{x}(t), t)$ describes the displacement fields evaluated at voxel coordinate $\mathbf{x}$ for the time duration $t \in [1, N]$, its pathline is computed by solving

$$\frac{dx}{dt}(t) = \mathbf{d}(x(t), t)$$

(7.3)

7.2. *Supplementary methods*

7.2.1. Summary of MRI visualization tools

Different visualization tools were used for different steps in the preprocessing and analysis processing pipelines to QC data and results. Volumetric longitudinal data is much heavier to handle than many other types of data such as text and tabular data. It is suggested that a suited visualization tool is one that is efficient in visualizing a specific stage of the processing. This led to good visualization practices in preprocessing, analysis processing and modeling as summarized below. An example of QC in longitudinal is visual validation of linear registration and longitudinal intensity normalization.

Raw DICOM and NIFTI

nordicICE (nICE) provided fast simultaneous visualization of multiple raw images in both DICOM and NIFTI format. Since images are not overlaid by default, but displayed side-by-side, it was a good solution to get an overview of raw data without preprocessing such as linear registration. If registered, however, synchronized scrolling through slices can be enabled for easy comparison between images. Since being available in our software environment and running on Windows, and most hospital computers with data access run Windows, it was suited for visualizing data close to its source. nICE is paid software but support was recently discounted, making it accessible for free.

Raw and processed DICOM and NIFTI

Aliza was used for efficient volumetric visualization (for instance maximum intensity projection) of longitudinal raw and registered images. Two strengths are its adaptive histogram-based adjustment of image brightness and saturation, and that it reads both DICOM and NIFTI formats. Its volume visualization capabilities are based on the established visualization toolkit (VTK). Aliza was free software at the beginning of the doctoral period, but later versions requires payment. It runs on both Windows and Linux.

Processed NIFTI

ITK-SNAP became the preferred tool to QC linear and non-rigid registered data, since it by default overlays multiple images and synchronizes slice locations across all images. This made it easy to for instance compare structural change for specific anatomical locations across various time steps. It can visualize displacement vector fields both in form of individual components, vector magnitude and deformation grid. It provides no DICOM import but the NIFTI format common for processed images. Like much other NIFTI centric software, ITK-SNAP follows internal file handling conventions according to the insight segmentation and registration toolkit (ITK). For instance, it displays images by applying the provided affine transformation in the NIFTI header (qform and/or sform). This assures that linearly registered (and not necessarily re-sliced) images are correctly overlaid. Other software may contain incomplete handling of sform/qform leading to image flipping problems (like nICE) or requiring additional re-slicing to correctly display registered images (like Aliza). ITK-SNAP is free software and runs on both Windows and Linux.

As an alternative FSleyes provided with FSL was occasionally used to visualize overlaid NIFTI images, for instance for checking T2w-FLAIR and CBV spatial correspondence. It reads in

registered images with affine transformations like ITK-SNAP. This is a great visualizer of registered and longitudinal (functional MRI) NIFTI data since it is based on open software and has extensive documentation. Some strengths of FSLeves are that it integrates well with Python environments (fslpy, pyopengl) and provides off-screen rendering. Rendering here means that a given visualization can be saved (rendered) to a file. Off-screen means that this process does not require a graphical desktop environment, but only access to a terminal. When compared to other viewers, it has good automatic adjustment of image contrast and saturation when opening images. Moreover, the exact visualization settings involving input images, layout and visualization parameters, can be saved and re-produced as a large terminal command. These properties of FSLeves made it suited for being automated in shell scripts. FSLeves is most easily run in Linux environments.

At last, Matlab with the well-known statistical parametric software (96) provided good visualization tools for verification of Matlab centric processing results in the first paper. Some useful but relevant alternative viewers not used frequently in the theses are FreeSurfer's FreeView, Chris Rorden's MRICron and MRICroGL and Kitware's paraview.

Processed numpy arrays

Through experimental image processing in the Python programming language developed a need for visualizing images directly from numpy arrays. Python is the most popular free programming language in data science and competes with high-level languages such as Matlab. Luckily, Python has good support for both DICOM and NIFTI file import using the pydicom and nibabel packages, which reads the images into numpy arrays.

Jupyter notebook and Jupyter lab are popular cross-platform client-server web-based interactive frameworks for rapid prototyping of Python code, which was done in the

preliminary work of the first publication. For these cases, the easiest visualization of two-dimensional images was accomplished with the Matplotlib package.

Three-dimensional volumetric visualization within the Jupyter frameworks (such as ipyvolume) quickly showed suboptimal performance for full-resolution MRI data on a conventional computer, when compared with established NIFTI MRI image viewers. An example of sub-optimal volumetric visualization performance is “lagging” when interactively using the mouse to rotate a visualized MRI volume. For this task, the Python software spimagine, using OpenGL hardware accelerated volume rendering with pyopengl, proved efficient in visualizing full-resolution MRI. It also supports longitudinal (four-dimensional) numpy arrays. Napari is a similar software and is suggested over spimagine since it has more functionality. Both spimagine and Napari can be used from the Jupyter frameworks if the Jupyter server is run on a computer with graphical interface, from standard Python scripts, or as standalone programs.

7.2.2. Interpolation practices

Many of the pre-processing steps carried out in this work involved interpolating data. This is common when working with multi-resolution data (like combined analysis of functional and structural MRI). For instance, when re-slicing an image after registration it is important to decide whether to downscale or upscale the image resolution as well as decide which interpolation method to use for this task. Downscaling may lead to losing important data, while on the other hand, upscaling may create false data. Interpolation method (such as k-nearest neighbor, linear, spline/polynomial, etc.) may also affect the severity of data loss or creation of false data points.

It is suggested that k-nearest neighbor (k-NN) interpolation is the method that provides the least amount of data modification and is favored when downscaling resolutions. An advantage of k-NN interpolation is that it preserves binary values which is important for segmentation masks. On the other hand, k-NN interpolation leads to a common artifact when performed after linear registration and re-slicing, seen for instance as diagonal line artifacts in axial images. This comes as a result of the combination of having a non-smooth interpolation method and rotating a volume.

Since CBV from functional MRI is created natively in a low resolution, it was natural to perform the analysis in the first paper in this low-resolution space (since it was deemed important to preserve the integrity and original values of CBV). Thus, we used k-NN interpolation to downscale corresponding images to this native CBV resolution.

In the second and third paper, we used linear interpolation to re-slice images to a common isotropic high resolution, thereby avoiding the k-NN artifact described previously. Linear interpolation was preferred over any polynomial interpolation of higher degree (than one) for simplicity and interpretability. Linear interpolation is simply making straight lines between points, and possible data loss and false data from re-slicing are likely minimized when compared to methods of higher degrees.

As an ad-hoc method for visualizing and understanding high-resolution longitudinal MRI, interpolation with RBFs (for more than three dimensions) was investigated. Neither of the software for the other interpolation methods utilized were implemented for more than three dimensions, and thus this method was investigated. RBF interpolation is a form of Gaussian process regression (“kriging”), or interpolation with Gaussian kernels. A Gaussian process may be described as an infinite dimensional generalization of a multivariate normal

distribution. Although somewhat computationally demanding, a parallelized version of this method was implemented, and an example is shown later in this supplementary part of the thesis.

7.2.3. Scripting

Efficiently scripting and task automation was perhaps one of the most important practical skills during the doctoral fellowship period. Since most research software run natively on Unix/Linux platforms and earlier studies and work, as well as personal interest, had made me comfortable in working in such environments, it laid good conditions for testing out most of the relevant research software.

The bash scripting language was by far the most useful tool in automating processing tasks in the thesis. This made it possible to automate the running of both established and in-house software (such as Python code). Bash may be considered a “glue” systems language enabling automating the execution of a wide variety of tools and is thus a software-agnostic tool. Moreover, parallel execution through various tools such as xargs with the -P option, GNU parallels, or using the ampersand (&) for asynchronous execution of multiple commands, made processing efficient on commodity hardware.

7.2.4. Computation infrastructure

Substantial time and effort were spent in installing and making accessible various research computing servers at our hospital (Miniserver 1 & 2, gpu-fys), both for use in the thesis and for use by others in our environment. This especially gained students in the computational radiology and artificial intelligence (CRAI) research group in fulfilling their Master’s and PhD degrees (by for instance providing working graphics accelerated training environments and

software for DL), but also physicians and others employed at department of diagnostic physics in learning to use research software in Linux environments (now department of physics and computational radiology). The much-needed knowledge and competence in hardware and software maintenance, such as user management, remote proxy access for home-office during Covid, and assistance in file and data handling over the network, was offered by the candidate in good faith as contributions and improvements to the environment.

7.2.5. Brain imaging data structure

Keeping conventions on file and folder organization of the research data became an important requirement when running various scripting tasks for improving the quality and adding new data to existing datasets. This involved most of the preprocessing and analysis methods described in the thesis.

BIDS (108) is a cross-institutional effort for establishing a bare-bones standard for organizing and sharing data in neuroimaging experiments. It is supported by a large number of neuroscientists and also comes with useful tools such as the BIDS-Validator (151) for minimally processed rawdata. Most importantly, BIDS contains folder and file naming suggestions for how to organize and link unprocessed and processed longitudinal DICOM and NIFTI files as well as code as illustrated in Figure 41. BIDS guidelines on longitudinal MRI for fMRI was used as a baseline for organizing and processing the research data.

Figure 41 here

7.2.6. Data version control

Tracking of changes in the BIDS datasets was enabled by using Data version control (DVC) (107). DVC is a Python-installable package that runs on top of Git to enable Git commit-based tracking of dataset changes. This means for instance, that the exact state of a dataset (the files, folders and code) that was used in a publication, can be recovered (in BIDS form) in the same way as recovering an earlier version a code file in a Git software project.

The information needed to get a specific version of the dataset, is having access to the Git repository for the DVC project, the self-hosted storage backend and knowing the commit string describing specific dataset version.

Modifications and improvements in datasets is logged/tracked by DVC in form of re-computing and summarizing MD5 hash sums from files, which is then tracked by Git. DVC is privacy oriented since the actual data is tracked using a storage backend which can be hosted locally. Such a storage backend can be a local storage server providing SSH access or scalable self-hosted object storage such as MinIO. A local SSH backend was used in the thesis.

7.2.7. Scriptable longitudinal visualization

Aliza, ITK-SNAP and FSLeves also supports being started from the command line interface (CLI). By utilizing the well-organized preprocessed data structure, CLI visualization tools and conventional Unix shell scripting and tools, it became possible to automate the process of visualizing longitudinal data. A Unix shell is a scripting language for natively running commands in text-based terminals. Bash is among the most common shells and proved as a useful tool throughout the thesis.

For instance, the following commands will open all T1wc images into the same visualizing window of Aliza, for a first patient organized into the BIDS derivatives structure (Figure 42):

```
aliza $(find sub-01 -type f -name T1c-icor.nii.gz | sort -V)
```

Figure 42 here

The corresponding commands for ITK-SNAP could be (Figure 43):

```
readarray -t files < <(find sub-01 -type f -name T1c-icor.nii.gz | sort -V)
```

```
itksnap -g ${files[0]} -o ${files[*]:1:${#files[*]}}
```

Figure 43 here

Linear registration (involving re-slicing) as well as longitudinal intensity normalization ensure that the images are properly aligned and have comparable intensity values. FSLEyes was utilized similarly from the command line with multiple MRIs to create the animations in Figure 32, Figure 32, and Figure 33, which is described in the next section.

7.2.8. Animating longitudinal images with FSLEyes render and ffmpeg

It was discovered that FSLEyes has CLI-based off-screen rendering capability. This means that an exact visualization could be re-produced and automated for multiple images and saved to .png files. The ImageMagick CLI tool was then used to draw text and a progress bar line on each .png file, before inputted to the ffmpeg processing tool to create PowerPoint friendly .mp4 and .gif animations of the time evolution of treatment images.

The lightbox view of FSLEyes provided a quick overview of volumes using a certain axial slice gap. Since the longitudinal data was linearly registered and in approximate MNI space, assumptions on image orientation and voxel size enabled automatic longitudinal

visualization with minimal intervention. The whole process was automated in bash scripts resulting in animations as illustrated by maximum intensity values in Figure 31.

Automatic longitudinal visualization quickly uncovered preprocessing errors such as incorrect linear registration. This is seen in Figure 32 for many of the T2w images. Incorrect spatial alignment is a real-world example of a consequence of having erroneous data and should be uncovered early in the analysis from good visualization tools. If not, inclusion of these images in processing could possibly result in erroneous results.

7.2.9. Estimating voxel displacement paths

The information necessary to compute voxel displacement paths are displacement fields of voxels from the longitudinal consecutive MRI pairs, as well as a mask defining the voxels to track. The fields could be computed from deformable registration, or from fitting the deformation model to the data by grid search. The voxel displacement pathlines can then be computed as described in supplementary theory.

The optimal case would be to track tissues with constant intensity values during tracking. Candidates of tissue keeping constant intensity values over time may be voxels within the contrast enhancement ring of the longitudinal intensity normalized T1w MRIs. Here, pathlines may correctly describe the true voxel displacement resulting from the cancer and treatment related deformations (Figure 34). A ROI of the contrast enhancement may thus be used for defining the starting voxels for which to compute pathlines.

By deformable registration

If ignoring intensity changes ($\Delta I = 0$), Equation (3.17) is a general formulation of (non-rigid) deformable registration as described in section 3.7. For this case, I_{t+1} and I_t in Equation

(3.17) is equivalent to the moving and fixed image Equation (3.29). Moreover, tracking only the displacements of voxels and assuming that intensity values are preserved over time, reduces the voxel tracking task to an optical flow problem (152).

By fitted deformation model

Alternative method for estimating voxel displacement paths may be fitting the deformation model to consecutive time intervals by grid search. This would result in less accurate displacement estimations, but it would be a more robust method of describing the overall displacement trend between images.

7.2.10. Web-based displacement path tracking visualization

Through working on deformable registration displacement-based voxel tracking and the deformation model was a need for visualizing displacement of voxels along with longitudinal cancer and treatment-induced deformations. If only focusing on tracking displacement between a pair of images (like for distortion correction in the first paper), voxel displacement may be presented directly in form of a displacement vector for each voxel, in form of a vector magnitude map, or as a deformation grid of the displacement field. The former visualization task was accomplished using FreeView or custom Python scripts, while the latter two were accomplished with ITK-SNAP.

For presenting voxel displacement over multiple consecutive longitudinal displacement fields, however, a more advanced visualization method was needed. It was discovered that nervous system fiber tractography software could be utilized for this task. In diffusion tensor imaging (DTI), principal direction vectors of anisotropic diffusion may be described as a bidirectional vector field. From this data, a fiber tract may be found by defining a specific

anatomical location and traversing along a principal diffusion direction from this location by integrating spatial coordinates along a given direction of the principal diffusion vectors. This results in a path that is generally known as a streamline. The corresponding displacement path that is found by integrating coordinates according to a time-varying displacement vector field is known as a pathline. A positive result was that after being computed, both streamlines and pathlines could be stored identically and visualized with the same software.

A python script with the dipy package was developed to compute approximate pathlines from time-varying displacement vector fields. A binary mask (for instance contrast-enhancing lesion) was used for selection of voxels for tracking displacement paths, then a subset of the computed pathlines were stored to a conventional fiber tractography format. Since no satisfying visualization tools for displacement pathlines were found, a web-based single slice and volumetric visualizer was developed for displaying displacement pathlines. It was based on the X toolkit (XTK), which may be regarded a lightweight version of VTK that is written in JavaScript. It is noted that a JavaScript version of VTK exists; VTK.js. This was not used. Since being a full web site, it was a multiple programming language effort involving both hypertext markup language (HTML), JavaScript, cascading style sheets (CSS) and hosting with Python's SimpleHTTPserver and netlify. The visualizer was hosted both locally (intranet) enabling quick visualization of results from processing and globally on the cancer-sim.com web domain (internet) for demonstration on example data (Figure 36).

7.2.11. Creating fixed time-interval longitudinal MRI with radial basis function interpolation

Longitudinal MRI of a single patient (with anisotropic voxel dimensions and/or irregular amount of days between the scans) may be regarded as scattered data in four dimensions.

RBF interpolation was applied as a method for visualizing and understanding the main imaging features in the longitudinal patient data. Specifically, it was used to create an approximate MRI volume for each day estimating the general cancer and treatment patterns and is illustrated for a patient in Figure 33.

7.3.Source Code and Pseudocode

7.3.1. Source Code

Paper 1

https://github.com/ivartz/epi_corrections

Paper 2

Contact corresponding author.

Paper 3

<https://github.com/ivartz/cancer-sim>

<https://github.com/ivartz/cancer-sim-search>

<https://github.com/ivartz/ants-bcond>

<https://github.com/ivartz/opticalflow-bcond>

Voxel displacement path tracking

<https://github.com/ivartz/cancer-sim-search/blob/main/make-pathlines.py>

Radial basis function interpolation

<https://github.com/ivartz/mri-rbf-time>

Displacement path tracking visualization (web site/server code)

<https://cancer-sim.com/>

<https://github.com/ivartz/cancer-sim-viz>

7.3.2. Pseudocode

TODO: This subsection is also in supplementary material for the third publication. Could remove.

Deformation model (paper 3)

Pseudocode 1: Maximum spread normal vectors by maximizing mean starting distances.

```
algorithm max-spread-vectors is
    input: Normal vectors  $V$ 
           Starting positions  $P$  of the normal vectors
           Number of vectors to return  $N_s$ 
    output: Selection lists containing the subset  $V_s$  and  $P_s$  of the normal vectors and positions
    1      initialize empty lists for selected vectors and positions
    2      append to the selection lists the first input vector and position
    3      remove the selected vector and position from input lists
    4      for each selected vector 2 to  $N_s$  do
    5          for each selected vector position(s), compute the Euclidean distance to non-selected vector position(s)
    6          append to the selection lists the input vector and position with the position that makes up the largest mean
    7          Euclidean distance from the selected vector position(s)
    8          remove the selected vector and position from the input lists
    9      return  $V_s$  and  $P_s$ 
```

Pseudocode 2: Directional cone masks.

```
algorithm max-spread-cones is
    input: Normal vectors  $V_s$ 
           Displacement field  $d$ 
           Deviation in degrees  $\theta$ 
    output: Cone masks  $M_c$ 

    1      initialize empty list  $M_c$  for storing cone masks
    2      for each vector  $v$  in  $V_s$  do
    3          let  $\omega$  be the angle difference in degrees between  $v$  and all other displacement vectors in  $d$ 
    4          let  $c$  be the cone mask defined by  $\omega \leq \theta$ 
    5          append to  $M_c$  the cone mask for vector  $v$ :  $c$ 
    6      return  $M_c$ 
```

Pseudocode 3: Infiltrative deformation of displacement field $\mathbf{d}$.

```

algorithm infiltration is
    input: Normal vectors  $V_s$ 
           Normal vector starting positions  $P_s$ 
           Displacement field  $\mathbf{d}$ 
           Cone masks  $M_c$ 
           Brain mask  $M_b$ 
           Infiltration  $\beta$ 

    output: Infiltrative displacement field  $\mathbf{d}_\beta$ 

1       let dnorm be  $|\mathbf{d}|$ 
2       let displacements be a list containing one interpolated part of  $\mathbf{d}$  for each spatial direction in  $s$ 
3       for each spatial direction  $i$  in  $s$  do
4           let nvd, nvc, bmi be  $V_s[i]$ ,  $P_s[i]$ ,  $M_c[i]$  respectively
5           let p_max_bmi be the point furthest away nvc along nvd and within bmi
6           let disp_max_bmi be the length between nvc and p_max_bmi
7           let p_max_brain be the point furthest away nvc along nvd and within  $M_b$ 
8           let disp_max_brain be the length between nvc and p_max_brain
9           let dnormcone be dnorm within bmi
10          let dxcone, dycone, dzcone be the components of  $\mathbf{d}$  within bmi
11          (the following scales all displacement components to unit norm such that their starting coordinates can be displaced equally far)
12          let dxcone, dycone, dzcone be  $\frac{dxcone}{dnormcone}$ ,  $\frac{dycone}{dnormcone}$ ,  $\frac{dzcone}{dnormcone}$  respectively with element wise fraction
13          if  $\beta > 0$  then
14              let mask_pts be the points within bmi
15              let extension be  $\beta * (\text{disp\_max\_brain} - \text{disp\_max\_bmi})$ 
16              (the following displaces mask_pts according to the extension length)
17              displace the mask_pts x, y, z coordinates extension*dxcone, extension*dycone, extension*dzcone length respectively
18              let bmi_copy be a copy of bmi
19              add displaced mask_pts to bmi_copy
20              let bm_geom_center and bm_widths be the geometric center coordinates and dimensions of bmi_copy containing displaced points
21          else
22              let bm_geom_center and bm_widths be the geometric center coordinates and dimensions of bmi
23              let bmi_copy be a copy of bmi
24              let mask_pts be the points within bmi
25              let extension be  $\text{disp\_max\_brain} - \text{disp\_max\_bmi}$ 
26              displace the mask_pts x, y, z coordinates extension*dxcone, extension*dycone, extension*dzcone length respectively
27              add displaced mask_pts to bmi_copy
28              let bm_geom_center_interp and bm_widths_interp be the geometric center coordinates and dimensions of bmi_copy containing displaced points
29              deform  $\mathbf{d}$  by re-mapping components within bm_geom_center and bm_widths to be within bm_geom_center_interp and bm_widths_interp
30              using trilinear interpolation
31              append to displacements the deformed components of  $\mathbf{d}$  for the spatial direction  $i$ 
32          let  $\mathbf{d}_\beta$  be the mean of displacements over  $s$  for interpolated component data
33          return  $\mathbf{d}_\beta$ 

```

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9. Papers

The final part of the thesis contains the three publications appended along with their submitted supplementary information.