Visualization of Fiber Tract Uncertainty during Neurosurgery

by

Sjors Peterse

to obtain the degree of

MASTER OF SCIENCE

in

COMPUTER SCIENCE

at the Delft University of Technology,

to be defended publicly on Thursday September 8, 2022 at 15:00.

Student number:	4342208
Project duration:	August 1, 2021 – September 8, 2022
Thesis committee:	Prof. Anna Vilanova,
	Dr. Thomas Höllt, and
	Dr. Nergis Tömen

This thesis is confidential and cannot be made public until September 8, 2022.

TU Delft

Abstract

In modern neurosurgical practice, a surgeon can see a patient's fiber tracts (nerve tracts) on a monitor in the operating room. This design study investigates the benefit of adding the uncertainty of the tracts and aims to improve the surgeon's orientation while reducing visual clutter.

Based on an interview with a neurosurgeon and our experience during a surgery visit, we designed, implemented, and evaluated a new visualization method for intraoperative use. We present two new visualization techniques: a partial hull that appears when a surgeon approaches it and a distance meter that serves as a warning tool.

We conclude that there is a need for the intraoperative visualization of fiber uncertainty and recommend doing clinical trials using these methods.

Preface

Dear reader,

The thesis that you are about to read is the result of a one-year project at the Computer Graphics and Visualization group of the TU Delft. My original plan was to graduate on my machine learning internship on nuclear fusion in France, but unfortunately the university did not allow foreign projects at the time due to the COVID-19 pandemic. On my return home I realized that the courses I did 'because I liked them' where on Computer Graphics, so I contacted Anna Vilanova and Thomas Höllt, asking them if there was a medical visualization project available. There was!

This project was done in collaboration with the Elisabeth-Tweesteden Ziekenhuis (ETZ) in Tilburg, which has been an amazing experience for me. It has allowed me to watch a radiologist perform fiber tracking, to learn the ins and outs of neuronavigation from Medtronic employees, to interview a neurosurgeon twice and even to visit an actual tumor resection surgery. If some of these terms sound unfamiliar, they will become clear in Chapter 1.

I would like to recognize the invaluable assistance of my daily supervisor, Faizan Siddiqui. At one point he even went to the hospital without me in order to get the systems up and running. He helped me steer my project back on track while I was going down rabbit holes. Anna and Thomas were there every step of the way. We had a meeting every week, which is something many of my fellow students were jealous of. I am very grateful to Geert-Jan Rutten, the neurosurgeon who has taken the time to answer all my questions and to be my research subject for the evaluation. I should also appreciate Maud Landers (surgeon in training) and Bart Brouwers (neurosurgeon) for arranging the surgery visit. I'd like to thank Maikel Brands (Radiology) for explaining the preoperative workflow, and Jan de Haan and Jacob Swart for making sure the neuronavigation device was there when we needed it. Jacob drove across half the country just to bring me a phantom head for the evaluation. Finally, I'm grateful to my brother for making some of the hand-drawn figures, and my parents for their incredible emotional support.

Sjors Peterse
Delft, August 22^{nd}*, 2022*

Contents

List of Figures

1
Introduction

When a neurosurgeon removes a brain tumor, the preservation of brain function is of paramount importance. Fiber tracts, which are bundles of nerve fibers, connect the different areas in the brain. Some of these tracts are essential for primary functions such as movement or speech. Damaging these tracts will cause severe irrecoverable neurological deficits, so surgeons avoid them at all costs. The main problem is that these critical tracts look identical to ones that are not so essential. Visualizing fiber tracts in the operating room allows surgeons to take them into account while operating.

Although the fiber tracts are invisible to the naked eye, they are computable with the data from an MRI scan. This computation, called fiber tracking, allows surgeons to see the fiber tracts on a monitor in the operating room. Unfortunately, many factors limit the accuracy of fiber tracking, causing the image in the operating room to give a false sense of precision. When surgeons need to operate very close to a critical fiber tract, they keep the patient awake and apply electrical stimulation to verify the tract position. Otherwise, they consider safety margins around these critical brain structures [5].

Considerable research focuses on either the uncertainty estimation or its visualization. For the uncertainty estimation, bootstrap methods [71] are popular because they only require making a single volume scan, saving time and money. There is also ongoing research in fiber tract uncertainty visualization. Uncertainty visualization is a big topic by itself and covers a wide range of fields, going from ocean forecasts [22] to fluid dynamics [38] to fiber tracking. Of particular interest are illustrative methods that show different levels of uncertainty [23]. Even though fiber tract uncertainty visualization is well studied in the literature, it only focuses on preoperative planning. Often it is developed from a technical perspective, rarely evaluated in the field, and lacks consideration of the constraints of the operating room [28]. This work bridges the gap between intraoperative visualization and uncertainty visualization.

Apart from the lack of uncertainty data, the current clinical intraoperative visualization has two main problems. First, the visualization uses three orthogonal planes called sagittal, coronal, and axial, as shown in Figure 1.1. Often, the surgeon looks at the patient from a different angle, as in Figure 1.2a. The surgeon then makes a mental reconstruction of the anatomy, which takes a long period of practice. The second problem is visual clutter in the fiber visualization. The tracts are visualized as an opaque spaghetti plot, causing parts of the slice to become invisible, as evident from Figure 1.2b.

This study has three design goals to improve intraoperative visualization in neurosurgery. The first goal is to improve the surgeon's orientation by changing the plane to be visualized. The second goal is to show the fiber uncertainty, and the last goal is to reduce the visual clutter. In the process, we do an initial interview with a neurosurgeon, visit a surgery, connect our visualization to a neuronavigation device and finally evaluate the design with the surgeon.

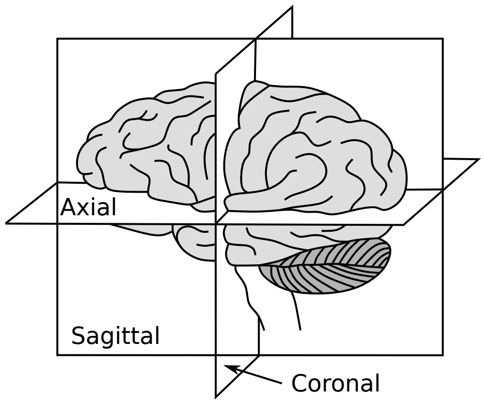
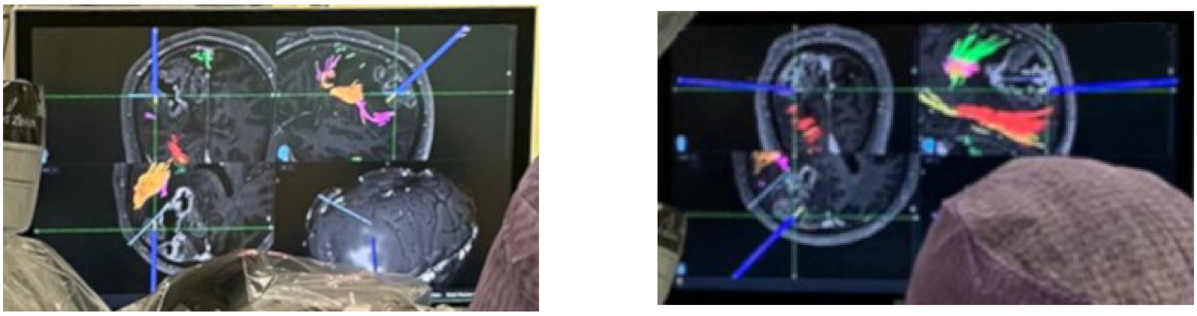


Figure 1.1: The three orthogonal anatomical planes (adapted from [65]).



(a) The bottom-right view shows the brain surface in 3D.

(b) The cluttering is apparent from the top-right view.

Figure 1.2: Fiber tracts in the operating room. The blue rod represents the surgical tool, the colored blobs represent the fiber tracts.

Our research questions are as follows:

1. Does showing an alternative viewing surface, as opposed to the orthogonal planes, help with the surgeon's orientation?
2. How does showing the fiber tract uncertainty help surgeons in the neurosurgical workflow?
3. Will showing only select illustrative features be sufficient in conveying spatial information?

The rest of the thesis is structured as follows. Chapter 2 gives the required medical background and the more technical aspects of fiber tracking and uncertainty estimation. Chapter 3 analyzes the input data and surgeon tasks, while Chapter 4 explores the related work in the visualization domain. In Chapter 5, the design is explained and Chapter 6 contains a neurosurgeon's evaluation of the visualization. Chapter 7 closes off with some concluding remarks and suggestions for future work.

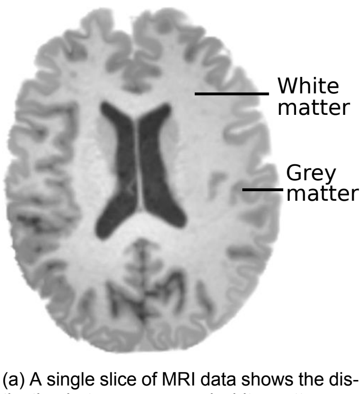
2

Background

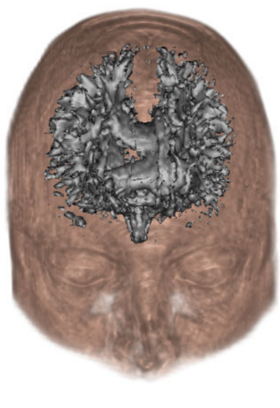
The main topic of this thesis is uncertainty visualization in fiber tracking, but in order to understand the visualization requirements it is necessary to have some background knowledge of the medical domain. When a patient is diagnosed with a brain tumor or glioma, a physician may decide decision to perform surgery. Before surgery, a patient has to take an MRI scan, which is then used to calculate the location of important fiber tracts. The related imaging techniques required for fiber tracking will be introduced in Section 2.1. The process of fiber tracking is described in Section 2.2. During surgery, a surgeon uses a device called a neuronavigator (Section 2.3) to navigate through the brain.

2.1. Diffusion Imaging

The human brain is largely composed of two substances: grey matter and white matter (Figure 2.1). The surface consists of grey matter: neurons that are essential for movement, memory, emotion and many other functions. White matter can be seen as the infrastructure that connects many of the grey matter areas: they are elongated tracts consisting of axons and transmit electrical signals to the grey matter.



(a) A single slice of MRI data shows the distinction between grey and white matter.



(b) White matter is a complex interconnection network of fiber tracts.

Figure 2.1: Grey matter and white matter make up a large portion of the human brain. Fiber tracts are bundles of white matter.

In medical imaging, there are multiple ways of making a 3D image of the body. CT and MRI dominate due to their high resolution and their good signal-to-noise-ratio [51]. Computed Tomography (CT) is essentially a rotating X-ray scanner that uses ionizing radiation to create an image [47]. Magnetic Resonance Imaging (MRI) does not use radiation, but uses a magnetic field to create the image. It is better for imaging soft tissue, such as the brain. Fiber tracking is done based on Diffusion Tensor

Imaging (DTI), which in turn is based on Diffusion Weighted Imaging (DWI). The next subsections will go into each of these. Figure 2.2 summarizes the relationship between MRI, DWI and DTI.

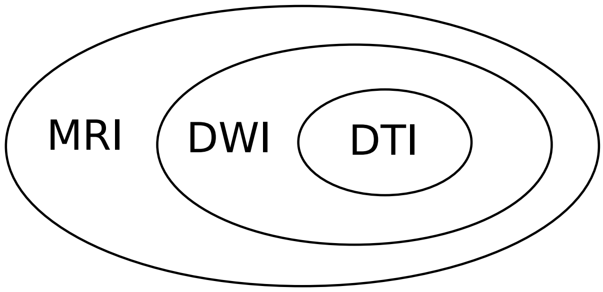


Figure 2.2: Relationship of MRI, DWI and DTI. Diffusion Tensor Imaging is a specific method for modelling a Diffusion Weighted Image, which falls in the class of Magnetic Resonance Imaging.

2.1.1. Magnetic Resonance Imaging

In order to understand why the computed fiber tracts such as the ones shown in Figure 2.8 will always include some form of uncertainty, it is first necessary to understand the basics of how an MRI scanner works. An MRI scanner consists of three layers, as illustrated in Figure 2.3. The outer layer is the main magnetic coil, and produces a constant homogenous magnetic field $\vec{B}$ in the order of teslas. The middle layer consists of gradient coils that allow to alter this $\vec{B}$ field in $\hat{x}$, $\hat{y}$ and $\hat{z}$ directions, in the order of mT. Finally, the inner layer contains the radio frequency (RF) coils that send and receive RF signals to and from the tissue. The signal affects the quantum spin of the hydrogen nuclei in the tissue, resulting in a detectable response frequency. The gradient coils allow locating where the signals came from, allowing for a 3D volume reconstruction with a resolution in the order of millimeters. How exactly this spin excitation works is a complex topic that is outside the scope of this thesis, but two parameters that are controlled by the technician are the Repetition time (TR) and the Time to Echo (TE). TR is the time between different excitations, and TE is the time between sending the RF signals and receiving the response, as shown in Figure 2.4. Varying the parameters results in different outputs, such as a T1-weighted image (short TR and short TE), a T2-weighted image (long TR, long TE) or a Fluid Attenuated Inversion Recovery or FLAIR (Very long TR and TE). Each one has different characteristics and is better at contrasting different types of tissue. See Figure 2.5 for a comparison.

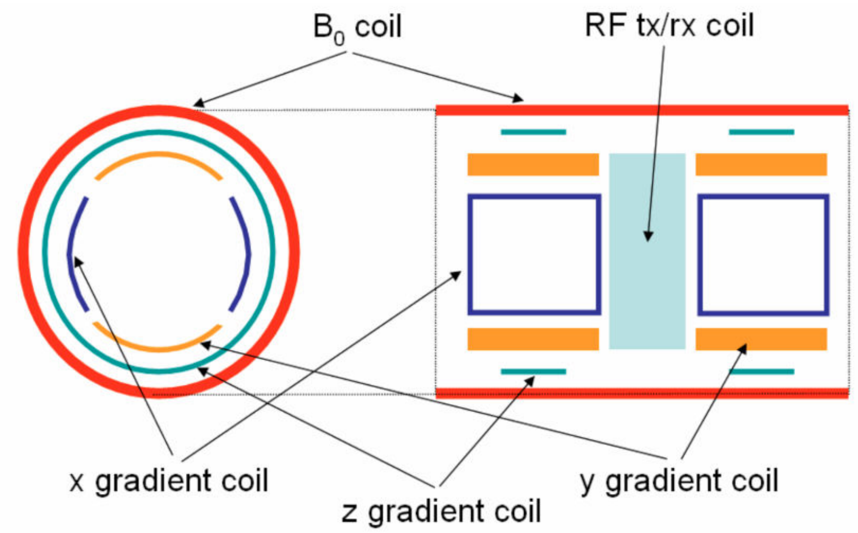


Figure 2.3: The different coils from an MRI scanner [49].

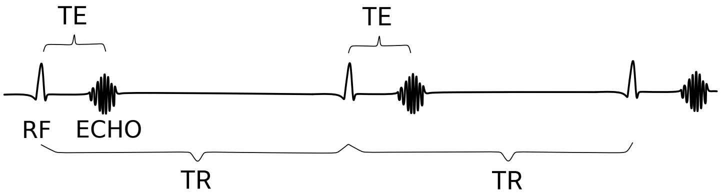


Figure 2.4: TR is the time between different excitations, TE is the time between sending and receiving.

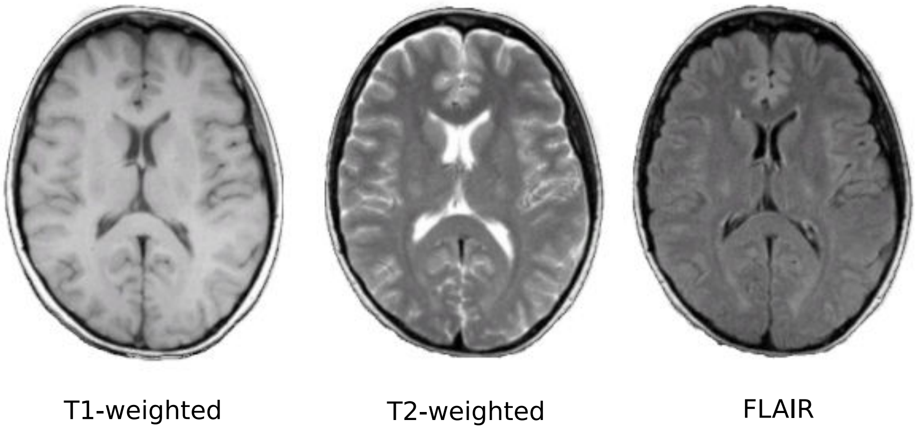


Figure 2.5: T1-weighted, T2-weighted and FLAIR images. Depending on what information is required, a different image is used (adapted from [12]).

2.1.2. Diffusion Weighted Imaging

Images such as T1-weighted, T2-weighted and FLAIR are examples of scalar volumes. They are essentially the three-dimensional analog of grayscale images. This means that instead of only having the x– and y-coordinates of a regular image, there is also a z-coordinate. The value at each voxel (volume element) is scalar, hence the term scalar volume. Although theses scalar volumes are clinically very useful, their resolution too low for showing fiber tracts. To compute the tracts, Diffusion Weighted Imaging (DWI) is used.

DWI works by measuring how well water molecules diffuse through the tissue, and in what directions. This is done by starting with synchronized hydrogen atoms, applying a small magnetic gradient in a single direction, and then applying the same gradient in the opposite direction. If the water was not able to move in the direction of the gradient, the effect of the two gradients cancel out each other, and the result is that the hydrogen atoms are still synchronized. If the water *was* able to move during the first gradient, the effects do not cancel out and the hydrogen atoms are not synchronized any more. By performing this sequence in multiple directions (at least six, but using more gives better results [14]), the diffusivity can be calculated in all those directions. The result is a 4D scalar image, with the fourth dimension being all the different diffusion directions that have been used.

When diffusivity is equal in all directions is called isotropic diffusion, but when diffusion is only possible in certain directions because of movement restriction, it is anisotropic. Figure 2.6 illustrates an example of anisotropic diffusion. Fiber tracts consist of axons and their insulating myelin sheaths, which restricts water movement. If the bundles of axons are sufficiently large, one can measure the diffusivity along their length. In order follow the trajectory of these tracts, this 4D diffusion image is turned into a 3D second-order tensor image.

2.1.3. Diffusion Tensor Imaging

Diffusion Tensor Imaging (DTI) was introduced in 1992 as a way of modeling the orientation of muscle fiber [1][2]. After that, it gained wide clinical application in brain tumors, spinal cord diseases, epilepsy, diffuse axonal injury, multiple sclerosis, Alzheimer disease, and ischemic stroke [43]. Here, it is used

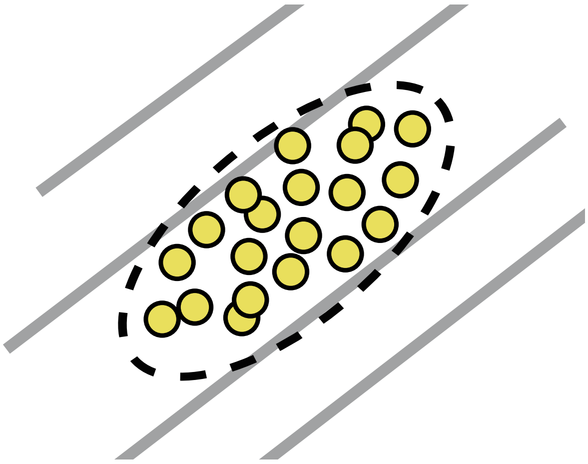


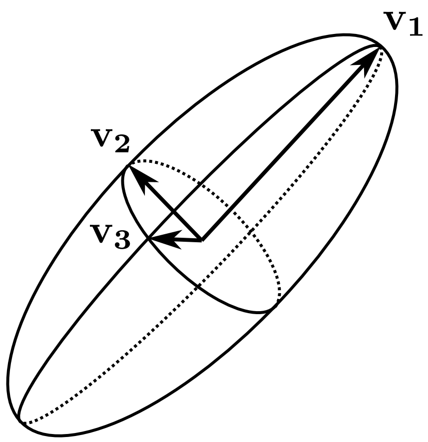
Figure 2.6: In anisotropic diffusion, the diffusion of the water molecules is restricted by the shape of the tissue. Adapted from [4].

to calculate fiber tracts. A tensor is the mathematical extension of a vector: a scalar is a tensor of order 0, and a vector is a tensor of order 1. We are interested in the diffusion tensors which are of order 2 and can be represented by a matrix. More specifically, a 3x3 matrix since we use it in 3D-space.

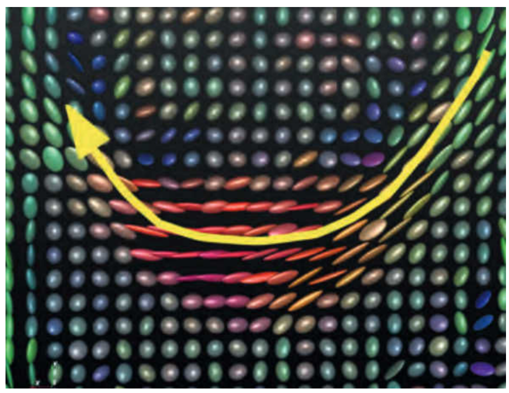
$$\mathcal{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \tag{2.1}$$

The three diagonal elements (D_{xx}, D_{yy} and D_{zz}) are proportional to the diffusion along the three coordinate axes. The off-diagonal entries are proportional to the covariances of displacements along these axes. By doing an eigen decomposition of this tensor matrix we obtain the eigenvectors ($\mathbf{v_1}$, $\mathbf{v_2}$, $\mathbf{v_3}$) and eigenvalues (λ_2, λ_2 and λ_3).

Just as vectors (first order tensors) with three elements can be visualized as a 3D arrows, so can 3x3 matrices (second order tensors) with a 3D ellipsoids [69]. This is done by computing the eigenvectors and aligning them with the axes of the ellipsoid, as in Figure 2.7a. In fact, this is exactly how tensor fields are commonly visualized, as in Figure 2.7b.



(a) $\mathbf{v_1}$, $\mathbf{v_2}$ and $\mathbf{v_3}$ represent the ellipsoid axes.



(b) One slice of a diffusion tensor volume [4]. Each tensor is represented with an ellipsoid. By following the main direction of the tensors, one can extract the fiber shape.

Figure 2.7: Tensors represented as ellipsoids. The long side of the ellipsoid coincides with the main diffusion direction.

The DTI volume is essentially a simplified model of the full DWI dataset, and calculating it requires a least-squares fit of the DWI volume. DTI is not only useful for calculating fiber tracts, but also for the study of the heart muscle [64].

A drawback of DTI is that it does not deal well with regions of crossing fibers [43], as the diffusion tensor will try to average them together. One option is to use spherical deconvolution to estimate the fiber orientation distribution function [62][50]. However, because DTI is still so wide-spread in the industry and because of its simplicity, it is the method of choice here.

2.2. Fiber tracking

The goal of fiber tracking or tractography is to compute the location of the fiber tracts, based on the available data. Figure 2.7b illustrates the main concept of fiber tracking. One starts with an initial point called a seed point, and follows the diffusion direction until certain stopping criteria are met. There are two categories of fiber tracking algorithms: deterministic and probabilistic [43]. The main difference between the two is that the probabilistic approach attempts to form a probability distribution instead of a “best fit” estimate. This does not make probabilistic fiber tracking more accurate than the deterministic counterpart, but it is better at conveying the uncertainty. Fiber tracking is usually performed by radiologists, and is currently quite a labour-intensive task. The reason for this is that a fiber tracking algorithm typically only considers diffusion data, not the actual anatomy. Tweaking the parameters such a the seeding region, ending region and/or stopping criteria are essential for obtaining good results [43][54].

2.2.1. Four important tracts

There are many different fiber tracts that all vary in shape, size, and function. Figure 2.8 shows ten different ones. It is important to note that during surgery, it is not possible to visually distinguish the different tracts from each other. For this reason, the tracts have to be visualized on the navigational monitor. Our collaborators currently use four different tracts in their neurosurgical workflow and plan to add more in the future. The ones they use are: [54]

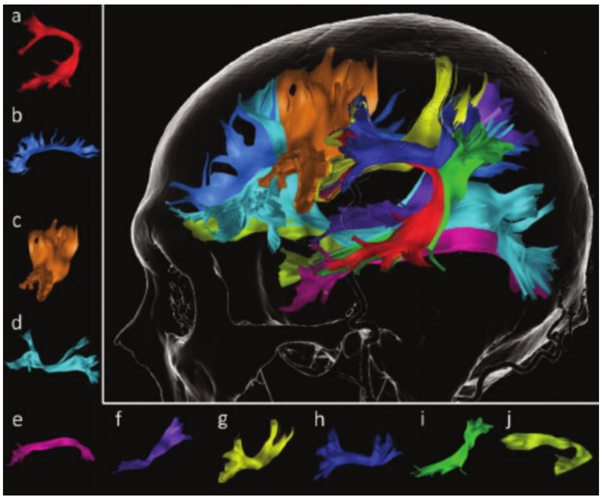


Figure 2.8: Ten different fiber tracts [33]. Although clearly distinguishable here, during surgery they look like one large mass of white matter.

- The Tractus Corticospinalis (CST), also called the pyramidal tract, is responsible for transmitting movement signal to the muscles of the body (motor function).
- The Arcuate Fasciculus (AF) is concerned with phonology (how words and sentences sound) and articulation (pronouncing those words).
- The Inferior Fronto-Occipitale Fasciculus (IFOF) deals with the semantics of language.
- The Radiatio Optica (OR) connects parts of the brain related to vision.

The pyramidal tract was the first tract that was used in neurosurgery, since it represents the largest tract system, is traceable most easily and that is most robust against tracking errors [43].

2.2.2. Uncertainty modelling

The pipeline going from MRI to visualization has four main stages: data acquisition, diffusion modelling, fiber tracking and visualization [60]. Each of the stages adds uncertainty to the pipeline. For instance, the data acquisition stage adds uncertainty due to noise, distortion, or moving patients. The diffusion modelling stage adds modelling errors, as the measurements from the different gradient directions are fitted into a single tensor. The fiber tracking process is very sensitive to user parameters, such as the seed region definition, the stopping criteria or the integration scheme. Finally, the visualization parameters such lighting add further variability to the results. The pipeline and their associated sources of uncertainty are shown in Figure 2.9.

[redacted]

Figure 2.9: Visualization pipeline with the associated uncertainties [5].

Various approaches have been done to model this uncertainty [60]. One method in particular is called Wild Bootstrapping [27]. In this technique, the residuals that remain after fitting the diffusion tensors are randomly multiplied by –1 or +1. Every time this process is repeated results in a unique tensor volume on which deterministic fiber tracking can be applied. This saves having to do multiple acquisitions which is important in a clinical setting as these acquisitions cost time and money.

2.2.3. Validation

When using the fiber tracking data in a clinical setting, especially during an intraoperative setting, it is essential that the information can be trusted. Validation of the results is therefore a crucial factor. Unfortunately, validating fiber tracking results is far from trivial. In the past, it has mainly been validated by a qualitative comparison with data obtained from dissection [43]. In fact, our knowledge of human neuroanatomy comes primarily from postmortem investigation using techniques such as the Klingler dissection [56].

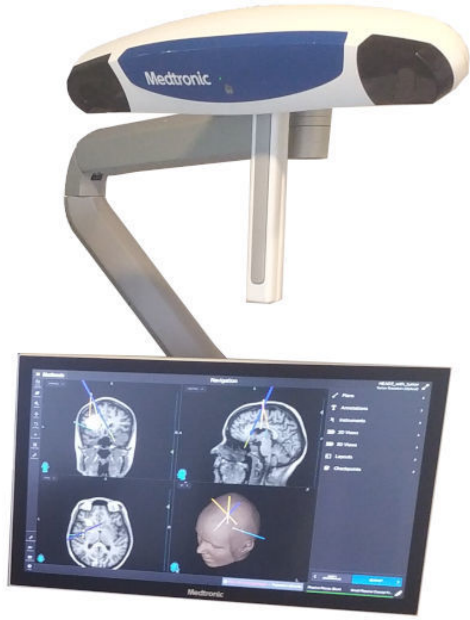
Actual validation can be done postoperatively or intraoperatively. Postoperative validation is an indirect clinical validation that is done by evaluating the motor, language or visual deficits after the surgery. Intraoperative validation is done by applying electrical stimulation to areas which are believed to contain certain tracts. The first attempts correlating the DTI fiber tracking findings to intraoperative electrophysiological measurements showed quite some discrepancies, amongst others because of the shifting of major white matter tracts during a neurosurgical procedure. This was which demonstrated by comparing pre– and intraoperative fiber tracking, acquired by an MRI applied during surgery [42]. Intraoperative imaging is uncommon, because the operating room has to be completely adapted to include an MRI scanner, and accessability to the patient is reduced. It is more common to apply electrical stimulation to identify the major white matter tracts intraoperatively. During surgery, the patient is kept awake and asked to perform task related to motor, language or visual function. If, for instance, the patient notices a visual deficit during an electrical stimulation, the precise location of the optic radiation fiber tract has been found [43]. Motor function can be validated by measuring muscle activity [11].

2.3. Neuronavigation

A neuronavigation system allows a surgeon to navigate inside the brain [66]. The system consists of a tracker and monitor (Figure 2.10b), the surgical instrument (Figure 2.10d), and a head clamp reference (Figure 2.10a). By relating the position of the surgical instrument with respect to the head clamp reference, the system can calculate the position of surgical instrument up to an accuracy of around 1 mm, according to our collaborators. The monitor displays the current position of the surgical tool, and the three anatomical slices that intersect the instrument tip. Figure 2.11 shows them being used during neurosurgery.

Registration The neuronavigation system only keeps track of the locations of the head clamp reference and that of the surgical instrument, so in order to calculate the position of the surgical instrument with respect to the MRI image, a registration step is performed at the start of the surgery [47]. This is essentially determining the location of the MRI image with respect to the head clamp reference. The surgeon uses the pointer tool (Figure 2.10c) to trace the skin of the patient. When a large enough surface area of the skin has been traced, the system tries to fit the skin data points to the MRI image. This never results in an exact fit, but a registration accuracy of around 1 mm can be achieved.

(a) Head clamp and reference. It is essential that the head remains still during surgery, and by rigidly attaching the reference to the head clamp, it serves as a reference for the head position.



(b) Tracker and surgical monitor. The tracker localizes the head clamp reference and the surgical instrument. The monitor shows MRI slices at the location of the surgical instrument.

(c) The pointer tool is used amongst others for registering the patient. The small reflective balls allow the tracker to locate the tool.

(d) The tumor resection device is used to suck up the tumor. The reflective balls are not shown here.

Figure 2.10: Elements of a neuronavigation system. When using optical tracking, there must be a line of sight between the tracker, the head clamp reference and the surgical instrument. Throughout the text, the word ‘pointer’ is used to refer to any surgical instrument.

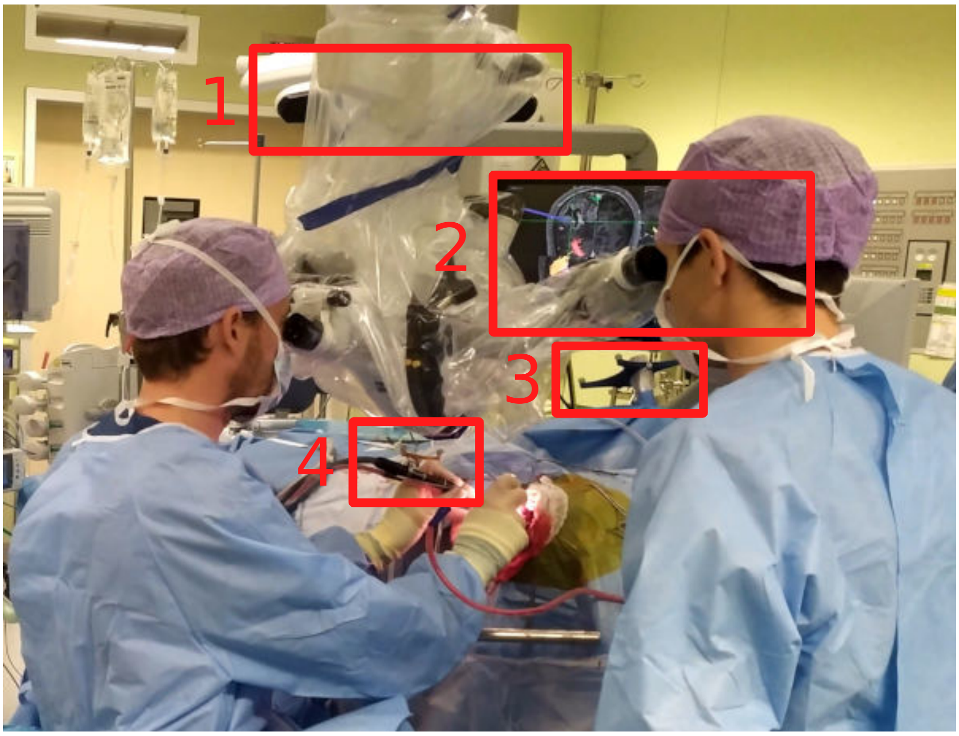


Figure 2.11: Neuronavigation setup during surgery. 1. Tracker that locates both the surgical instrument and the head clamp reference. 2. Navigational monitor showing slice views. 3. Head clamp reference. 4. Surgical instrument.

3

Design process

Any visualization task can be analyzed using three questions [39]:

- **What** data does the user see?
- **Why** does the user use the visualization tool?
- **How** are the visual encoding and interaction idioms constructed in terms of design choices?

Answering these three questions gives an abstraction of the visualization problem and makes it possible to design a visualization without having in-depth domain knowledge. This chapter deals with the first two questions, the last one is addressed in Chapter 5.

3.1. What: Data abstraction

The basis of medical imaging is covered in Section 2.1, but it is useful to have a concrete list of (derived) data that can be used in a visualization. A summary of how it all fits together is shown in Figure 3.3.

Anatomical (scalar) data The basis of neuronavigation lies in the anatomical data: a 3D scalar field. Multiple imaging techniques are possible, such as T1-weighted imaging, T2-weighted imaging or FLAIR. It is the anatomical data that allows the surgeons to recognize structures and orient themselves in the brain. This data comes directly from an MRI device. See Figure 3.1a.

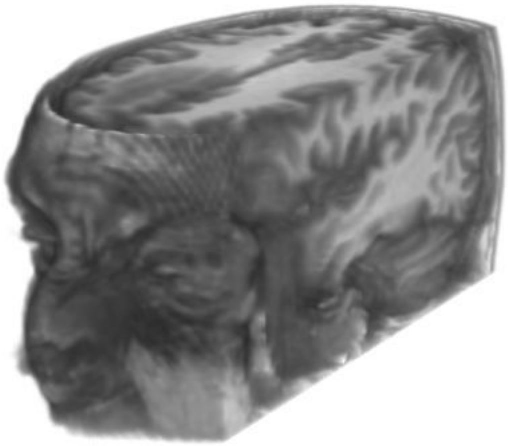
Segmentations Certain anatomical structures are best visualized by showing them separately. For instance, a tumor can be segmented from an MRI scan by taking an isosurface. When there is no clean tumor boundary, this segmentation can be done manually as well. This derived data is a 3D geometry and forms a closed surface. A segmentation of the entire head is shown in Figure 3.1b.

Fiber tracts These are calculated by applying fiber tracking on the 3D tensor field as explained in Section 2.2. The result is a 3D geometry that is composed of a set of streamlines. See Figure 3.2a.

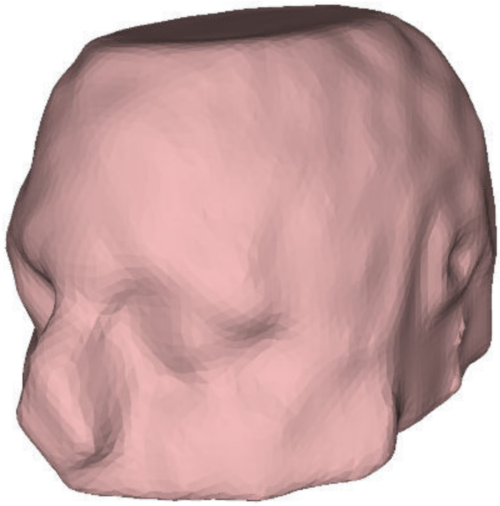
Fiber tract uncertainty This is data that is derived on the fiber tracking process. It is a 3D scalar field that gives an indication of the likelihood of the presence of a fiber tract. See Figure 3.2b.

Pointer This is a surgical instrument that is tracked by the neuronavigation system. After the proper transformations have been applied, it gives the position and orientation of the tip in 3D space. A physical pointer is shown in Figure 2.10c, but it is usually visualized as a simple cylinder.

Foot switch This is not a data element but rather an input device for the surgeon. It is commonly used to freeze the neuronavigation monitor.



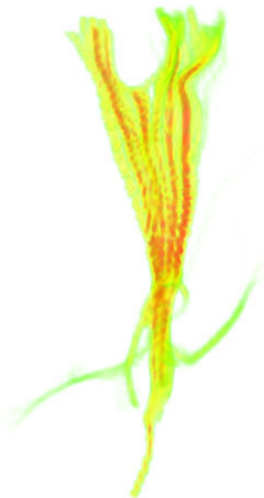
(a) Volume render of a clipped T1 volume. This data is referred to as ‘anatomical data’.



(b) Segmentation of the head. This is a geometrical model and contains no volumetric data.

Figure 3.1: Two data types representing the head: volumetric (left) and geometric (right).

(a) Fiber tract streamlines are the result of a fiber tracking algorithm. This does not contain uncertainty data.



(b) Fiber tract uncertainty is a scalar volume like the anatomical data. Here, more certain fibers are colored red while more uncertain fibers are colored green.

Figure 3.2: Two data types representing the tracts: volumetric (right) and geometric (left).

3.2. Why: Surgeon tasks

From a high level, the tasks of the surgeon during a tumor resection are easy to understand:

- Remove as much of the tumor as possible.
- Damage as little healthy tissue as possible, specifically the important fiber tracts.

These tasks are especially difficult because often there is no clean boundary between the fiber tracts and the glioma, and doing damage to the tracts will lead to lasting neurological deficits. The tasks are often also conflicting with each other when there is no clear tumor border. It is the responsibility of the surgeon to make a judgement of how much tumor can safely be removed in the presence of fiber tracts. In order to get a good understanding of the problems a surgeon faces during surgery, we visited a real surgery.

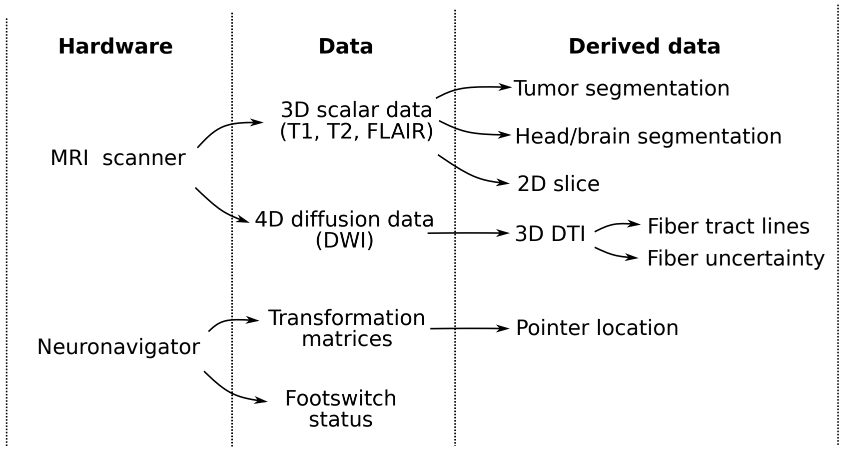


Figure 3.3: Overview of the data flows. The MRI scan is done preoperatively, the neuronavigator provides live data and is the only direct way for the surgeon to interact with the visualization.

3.2.1. Surgery visit

Brain surgery can be done both under anesthesia and awake. The advantage of doing an awake surgery is that the patient can provide important feedback by reporting loss of sight or sensation. Cognitive function and speech is continuously monitored, and electrical stimulation of the brain areas can be used to find the fiber tracts. The disadvantage of awake surgery is that it requires more personnel for the patient communication, and the experience could be traumatizing for the patient. During the visit, the surgery was done under anesthesia.

Registration The first step is making sure that the patient's body and head are in the correct position. In order to prevent the head from moving during the surgery, the patient's skull is clamped using a head clamp (Figure 2.10a). As explained in Section 2.3, the location of the head is then registered to the neuronavigation system by tracing the pointer along the skin of the patient. See Figure 3.4.

OR sterilization When the registration is complete, the room has to be made sterile. This means that the patient is almost entirely covered up, the medical equipment is covered in plastic and the surgeons wear paper over their clothing. This is necessary to minimize that chance of an infection in the brain.

Skull opening Next, the head is partly shaved, a skin flap of about 10x10 cm is cut and held in place using clamps. Three holes are drilled in the skull, and a bone flap is sawn out. The remnants of bone and the flap are saved. Finally, the meninges (tissue between the skull and the brain) are carefully cut open and held in place with the skin.

Tumor resection The resection itself took a couple of hours to complete. A tumor resection device (Figure 2.10d) is used to suck away the tumor, one small piece at a time. Two surgeons are working very closely together, both looking through the microscope or at the navigational monitor (Figure 6.1). Once the tumor is gone, the healthy brain tissue moves towards the newly available space, causing a registration offset. For this reason, the tumor boundary is removed first, causing the least amount of brain shift.

Closing up Once the tumor has been removed as much as possible, the head can be closed again. The meninges are stitched, the bone flap is put back in place using screws, the drill remnants are glued back and the skin is stitched as well.

3.2.2. Surgeon interview

The full transcript of the interview can be found in Appendix A, but the most important findings are summarized here.

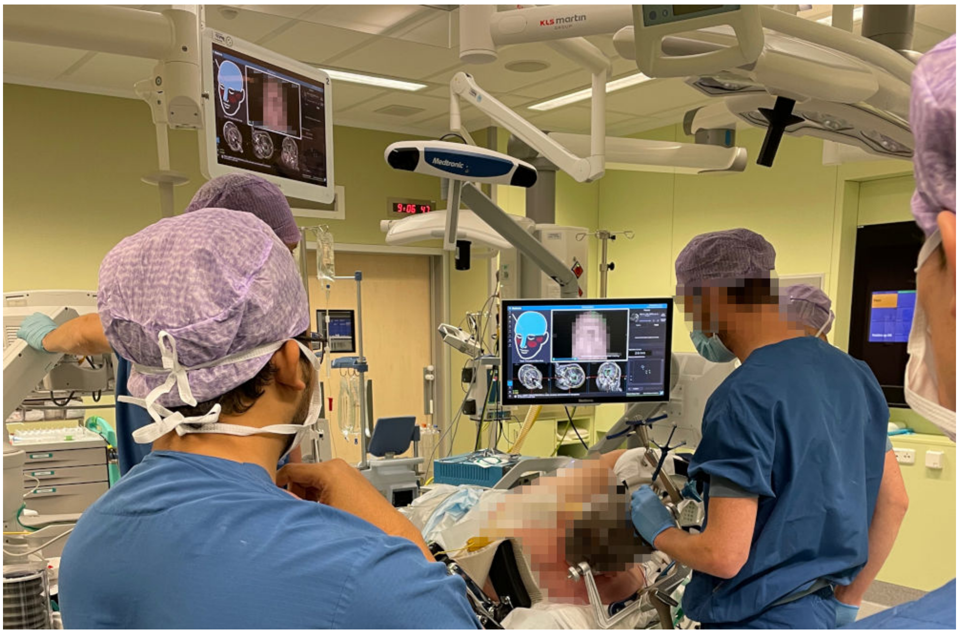


Figure 3.4: The registration step is performed before the OR is made sterile, because a fair amount of skin needs to be traced to complete the registration.

Figure 3.5: Full (sterile) neurosurgical setup in the operating room. The monitor on the left shows the microscope image. The nurse in the back is carrying out supportive tasks, amongst which is changing settings on the navigation monitor.

Uncertainty The surgeon is activity participating in fiber tracking research and is well aware of the uncertainties it brings. He has ten years of experience verifying its accuracy, and is still adding new fiber tracts to the neurosurgical workflow. Less experienced surgeons however, should also be able to get of sense of how large the uncertainty can be without having to do years of research themselves. When the tumor and fiber tracts are within one centimeter of each other, they choose to do the surgery awake, and use electrical stimulation to verify the location of the fiber tracts. While operating in critical areas, one surgeon is continuously watching the navigation monitor and informing the main surgeon of potential dangers.

Point of view According to the surgeon, a big flaw in the usability is the way the slices are visualized on the navigational monitor. Their directions are always the same anatomically (Figure 1.1), but this does not coincide with the angle from which the surgeon is looking. A mental reconstruction of the anatomy has to be done, which can be quite difficult. In the ideal system, the brain is shown in 3D from the perspective of the surgeon, and you can see which tracts you are going to approach in the depth.

Clutter The current system uses streamlines to visualize the fiber tracts, and all fibers within a certain distance of the slice are shown. This results in a large area of the navigational monitor being blocked from view because of these fibers (Figure 1.2b). When that happens, a nurse is asked to remove the fibers from the visualization to regain the regular navigational function.

Brain shift While it is true that that brain shift will always increase the registration error, this does not make neuronavigation useless. The general shift is always in the same direction, but the surgeon does have to account for this offset. Anatomical landmarks such as the tumor border, a ventricle, or the gyri and sulci of the brain surface can be used to verify how much the brain has shifted. This is done by holding the pointer on one of these landmarks and looking at where the neuronavigation system the pointer is. Especially the current 3D view can be used for this check.

4

Related Work

Every design process starts with an investigation of the current possibilities. This chapter deals with the related work in the visualization field, and its goal is to show as many visualization techniques as possible without going into much detail on each one. We will begin by showing ways to visualize the input tensor field data directly without the use of fiber tracking (Section 4.1). As we will be visualizing fiber tract uncertainty intraoperatively, the main visualizations of interest will be those of fiber tracts (Section 4.2) and uncertainty (Section 4.3). The chapter will conclude with how the tracts should be placed in context — as without any anatomical context, the fibers would float in mid-air (Section 4.4).

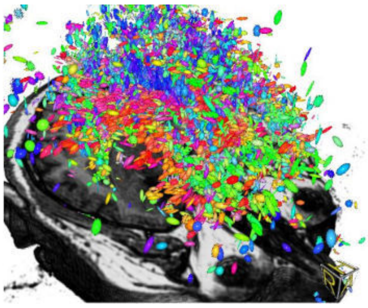
4.1. Tensor field visualization

Before considering visualization techniques for fiber tracking, we will first look at possibilities of visualizing the input tensor field directly. This is important for two reasons. One is to start off this literature survey as broadly as possible, as it might give rise to inspiration for the design phase. The second reason is that by omitting the fiber tracking step, we remove a stage in the visualization pipeline (Figure 2.9), resulting in less overall uncertainty.

The first option we consider are glyphs, mainly because of the sheer amount of available research. The most basic visual representation of a tensor is an ellipsoid, as was illustrated by Figure 2.7a. A popular alternative to ellipsoids are superquadrics, which improve the shape and orientation perception [31]. More advanced glyphs make use of an orientation density function [57], such as Qball glyphs [63] or HARDI glyphs [46]. The obvious downsides to using tensor glyphs intraoperatively is that they are difficult to interpret. It does not provide any global connectivity information about major white matter structures [40]. They can also lead to information overflow, distracting the surgeon from the task of removing a tumor [43]. An example of a highly cluttered glyph representation is shown in Figure 4.1a.

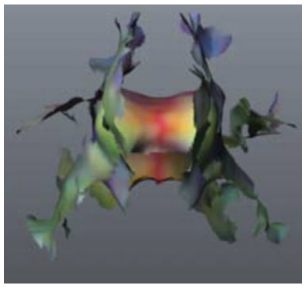
Another approach to show the full tensor data is by means of volume rendering. Direct volume rendering works by shooting rays through the volume and combining the data it encounters into a single pixel color. The transfer function determines how the data points should be combined. Designing the transfer function properly is nontrivial for scalar fields, but even harder for tensor fields. A possibility is to create a colormap from tensor to RGB, such as hue-balls [30]. See Figure 4.1b for an example of this technique.

The last tractography alternative we consider is extracting the white matter surfaces from the anisotropy in the data. Anisotropy is a measures of how non-isotropic the diffusion tensor is. Water that can move freely has an anisotropy of 0, while water that that can strictly only move in one direction has an anisotropy of 1. Using this metric, you can create surfaces from the volume data either by calculating isosurfaces [58] or by using the derivatives to calculate creases [32]. An example is shown in Figure 4.1c.



(a) Volume of glyphs [15].

(b) Volume rendering using hue-ball coloring [30].



(c) Anisotropy creases [32].

Figure 4.1: Tensor field visualization methods provide an alternative to fiber tracking.

4.2. Fiber tract visualization

The previous section shows that it is possible to show the white matter structure even without fiber tracking. However, it gives very little control over which tracts are shown. By doing the fiber tracking one has more control over which fibers are shown by setting the seed region. Moreover, uncertainty estimation is easier when the tracts have been computed. The techniques that will be considered in this section are streamlines, hulls, contours and illustrative methods.

Streamlines The most basic form of streamlines is a simple polyline without any shading, as was shown in Figure 3.2a. More common types are colored polylines (Figure 4.2a) and cylindrical tubes (Figure 4.6e) [57]. Streamtubes [72] go one step further as they encode specific information such as anisotropy from the diffusion tensor on each point (Figure 4.10a). The main advantage of streamlines is are that they are very straightforward; it clearly shows the results of the tractography process. The main disadvantage is that too many fibers will still lead to visual clutter.

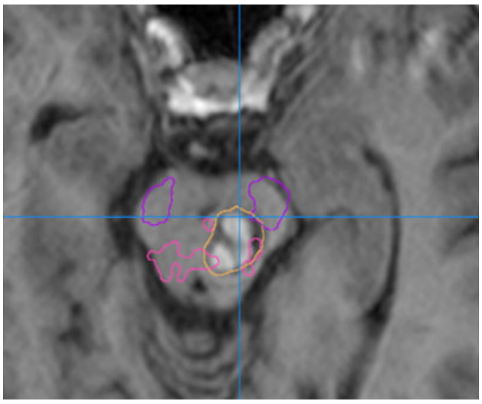
Hulls In order to reduce the visual clutter of the streamlines, the streamlines can be wrapped up in a hull, such as in Figure 4.2. Most of the time, this will also lead to a better spatial perception because there is a larger surface area that can be shaded [8][16]. The advantage of wrapping the fibers in a hull is the intuitive visualization. The results look like flexible tubes which are closely related to the expected appearance of a major white matter bundle [40]. The major downside is that the generation of surfaces that wrap the fibers is error prone for complex cluster shapes [44][57].

(a) Streamlines using color to encode the local direction.

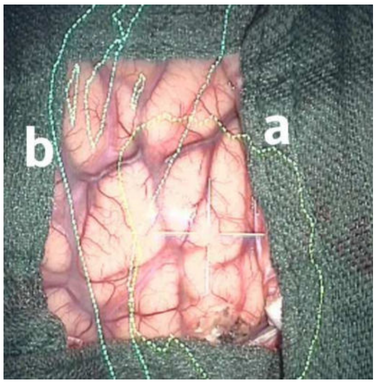
(b) Tightly wrapped hull around the streamlines.

Figure 4.2: Hull wrapping improves the spatial perception of the tracts [35].

Contours When viewing anatomical data, this is commonly done using slices of the volume. Although it is possible to show a 3D hull through a 2D slice, sometimes it is preferable to show only the intersection of the hull with the slice. Sometimes showing a contour is the only option, such as when overlaying the data on the surgical microscope [41]. Figure 4.3 shows examples of fiber contours. An advantage of using contours is that is has the minimal amount of clutter and is easy to understand. A disadvantage is the lack of spatial information.



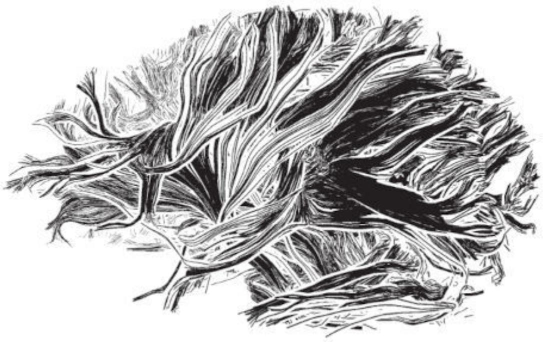
(a) Fiber tracts (pink and purple) and a tumor (orange) intersecting an axial slice of a T1-weighted image [9].



(b) Tumor (a) and the pyramidal tract (b) intersecting the focal plane of a surgical microscope [36].

Figure 4.3: Contours show the intersection of a 3D shape with a plane.

Illustrative These techniques do not attempt to provide a photorealistic image, but instead focus on conveying as much information as possible with the smallest amount of visual complexity. Most commonly they try to mimic hand-drawn images by only using lines. For instance, Figure 4.4a manages to convey an excellent spatial perception by adjusting only the margin (halo) around the lines. Figure 4.4b manages to do the same thing by leaving only a small subset of hint lines and internal contours instead of the full fiber tracking data. An advantage of illustrative techniques is their low visual complexity, a disadvantage is their implementation difficulty, especially in interactive applications.



(a) With depth-dependent halos, the width of the margin around the lines is dependent on the depth [17].

(b) Hint lines, outline and internal contours of a single tract [44].

Figure 4.4: Illustrative techniques showing fiber tracts.

4.3. Uncertainty visualization

The techniques presented in the previous section do not show any uncertainty, giving the illusion that there is none which may result in a dangerous assumption when used in surgery [21]. In current clinical practice, a safety margin between 5 mm and 1 cm is used around the tracts [43]. When a fiber tract is located close to the tumor, taking a safety margin that is too large means that a part of the tumor should be left in. In general, a greater extent of resection is associated with improved survival [45], so the goal is to get a more accurate visualization of the uncertainty than just a fixed safety margin. Ways to show this uncertainty include glyphs, hulls, volume rendering, illustrative techniques, animation and point displacement.

Uncertainty glyphs Glyphs are included here mostly for the sake of completeness, as showing it intraoperatively would result in an extremely high visual complexity. It is similar to Figure 4.1a, with the additional information of the uncertainty of each tensor. The tensors themselves are not certain either, as they are a best-fit of many MRI images taken from different directions. One way to show this, is using uncertainty cones [26] such as in Figure 4.5.

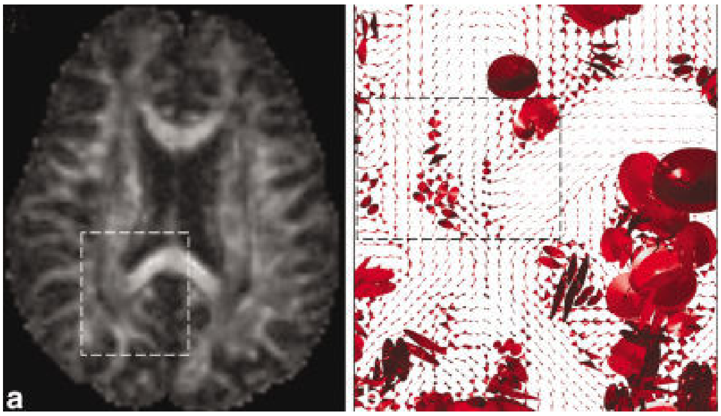


Figure 4.5: Uncertainty glyphs. The cones of uncertainty show a 90% confidence angle [26].

Uncertainty hulls This is the most common method of showing fiber tract uncertainty. In case of noisy unreliable data, a thick hull could be added, while in highly reliable data, the hull would be thinner [43]. An even more sophisticated visualization is adding layers to the hulls to show different levels of uncertainty [40]. There are many variations possible, but two important categories are those that are based on isosurfaces, and those that are based on hull wrapping. Isosurfaces can be used when an uncertainty volume is available, for instance in the form of a visitation map [7]. Figure 4.6a shows an example of an isosurface-based visualization.

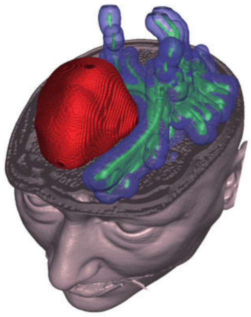
When using hull wrapping, as selection of the fibers is made on a certain metric, for instance the distance to the central streamline [59]. Here, a smooth wrapping of all fibers of interest is very important [40]. Figure 4.6b and Figure 4.6c show possible visualizations.

Another approach of modeling the hull is using Principal Component Analysis for modeling the streamlines [18]. By making a distribution of points in the PCA-space, a median and confidence interval can be defined. Figure 4.6d shows an example using weather data, but it should also be possible using fiber tract streamlines.

A non-parametric way of showing the distribution of streamlines is using contour boxplot [70] or a curve boxplot [38], as shown in Figure 4.6e. Like a regular boxplot, a contour boxplot allows showing a mean line, a median line, multiple hulls corresponding to a certain percentage, and outliers.

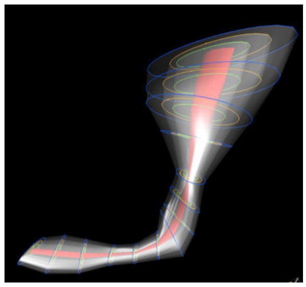
Direct volume rendering Showing (multiple) hull is a good way of showing the tract uncertainty, but another possibility is using direct volume rendering [68]. This allows showing the uncertainty in more detail without the restriction of having discrete layers, but it does require designing a transfer function. Figure 4.7 shows two examples using this approach.

Illustrative Just like it is possible to show the deterministic fiber tracts using illustrative techniques, it is also possible to show the uncertainty in that way. Figure 4.8a shows multiple contours and silhouettes of fibers. This differs mainly from the uncertainty hulls in that it uses flat shading, which reduces visual complexity but also reduces depth perception. Figure 4.8b shows an uncertainty lens which only displays the illustrative uncertainty in a selected region of focus. Other channels of showing the uncertainty include saturation and textures [21].

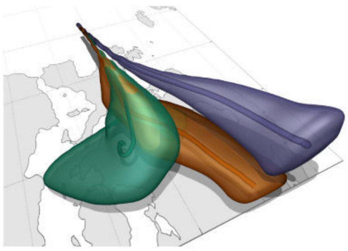


(a) Isosurface: Uncertainty hull based on a visitation map, with an additional safety margin [7]

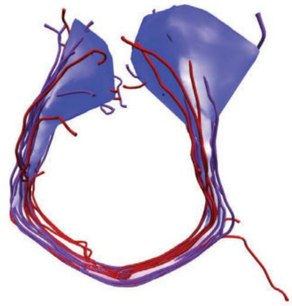
(b) Wrapping: multiple transparent hulls showing different levels of streamline coverage [19].



(c) Wrapping: multiple transparent hulls and uncertainty rings [16].

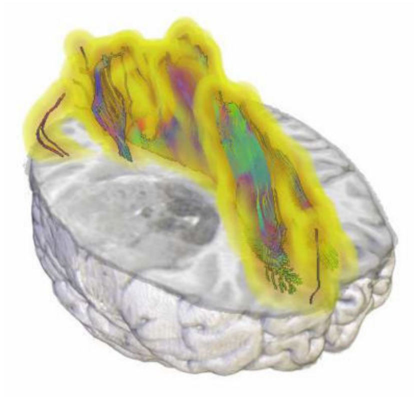


(d) Confidence lobes together with a center line. The center line is based on the streamline-median The lobes are based on the distribution of the streamlines in PCA-space [18].

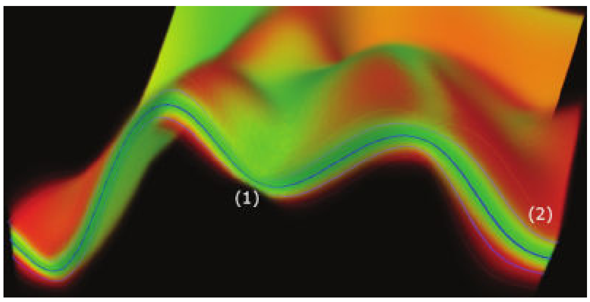


(e) A curve boxplot that shows a 50% confidence interval together with the outliers [38].

Figure 4.6: Different hull visualizations used for showing streamline uncertainty.



(a) Volume render based on an uncertainty volume [67].

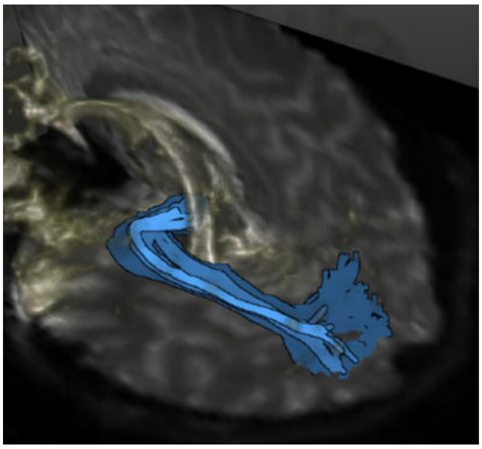


(b) Using volume rendering and hue for encoding the uncertainty in the thickness of a surface. (1) is green and more certain, while (2) is red and thicker [48].

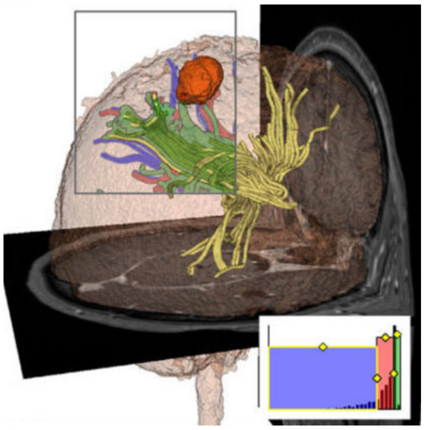
Figure 4.7: Volume rendering for showing surface uncertainty.

Animation Although less common, animation can be used to draw attention to the (un)certainty of tracts. Oscillations have been used to show uncertainty in fluid flow [34] and vibrations have been used for showing surface uncertainty [6]. Another option is to show a moving pattern on the more certain fibers to focus the attention on those levels. The speed of this animation increases as the fiber certainty increases [21].

Point displacement Finally, Figure 4.9 shows how points on a surface can be displaced in order to show surface uncertainty. The more uncertain the surface, the farther the points are displaced. This has a similar effect as using vibrations on the surface, except that the image is static which makes it easier to look at.



(a) Multiple silhouettes based on uncertainty level.



(b) Uncertainty lens displaying streamlines color-coded to their uncertainty level.

Figure 4.8: Illustrative methods showing fiber uncertainty [5].

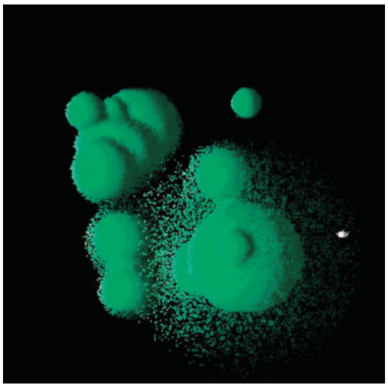


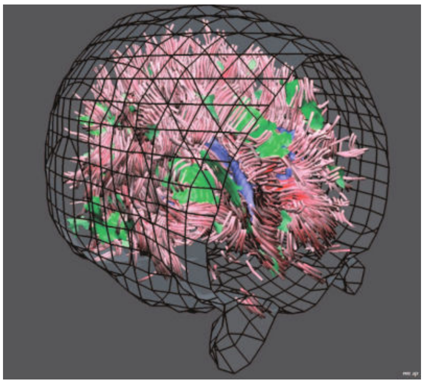
Figure 4.9: Surface uncertainty through point displacement. Uncertain surfaces appear as point clouds [20].

4.4. Anatomical context visualization

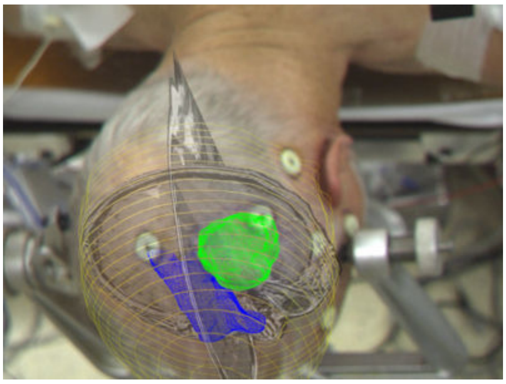
Some examples from the previous section show fibers in their anatomical context, others show isolated fibers without any context. For intraoperative visualization, and especially for neuronavigation, it is important to show this context. Before surgery, a radiologist creates an MRI image of the patient, and this image is shown during neuronavigation. It allows the surgeon to orient him or herself in the brain, and also helps to avoid damaging other important structures such as blood vessels. In current neuronavigation systems, the anatomical data is shown using three orthogonal slices that intersect each other on the pointer tip. In this section, we explore alternative ways of showing this context. This can be basic (Figure 4.10a) or advanced using AR [10] such as in Figure 4.10b. Here, we will discuss the current clinical technique using slices, using a 3D model, illustrative techniques and alternative surfaces for showing the anatomical context.

Slices In the current neuronavigation systems, navigation is done by showing one slice from every direction [41][9][73]. These directions are coronal, sagittal and axial, as shown in Figure 1.1. Two examples of such systems are shown in Figure 4.13.

3D One option that is sometimes shown as a fourth view in a neuronavigation system is using a 3D-model of the head, or of the cortex surface. This does not show the T1-weighted image such as the slices do, but it much easier to relate spatial estimations. A user study has also shown that showing the tumor in 3D was considered helpful [73]. Figure 4.11a shows an example of showing the structures in 3D. Instead of a model, one can also use direct volume rendering. This has the advantage of not having to segment individual structures, but the disadvantage that a separate transfer functions needs to be designed for each type of image. Figure 4.11b shows an example.

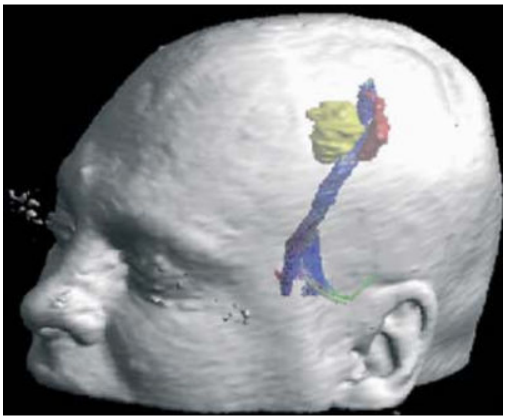


(a) A wireframe of the skull is a very basic context visualization [72].

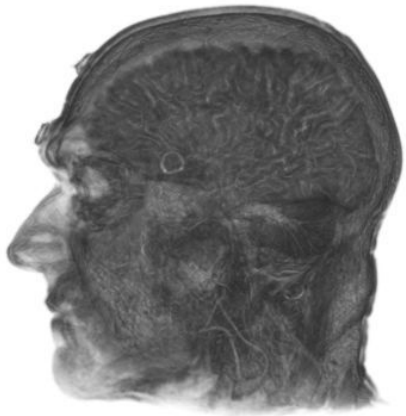


(b) Augmented reality as seen by a surgeon wearing a head-mounted display [47].

Figure 4.10: Two extreme cases of anatomical context visualization.



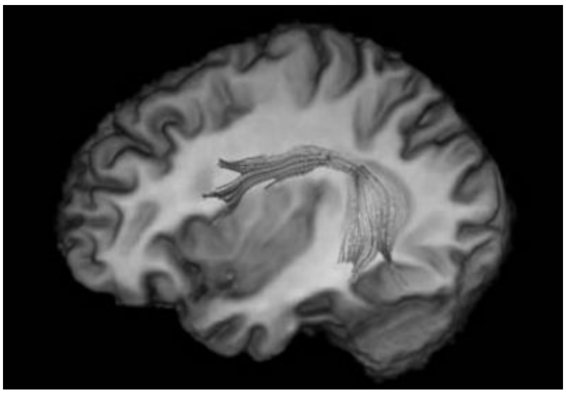
(a) A model of the patient's head being used as frame of reference [41].



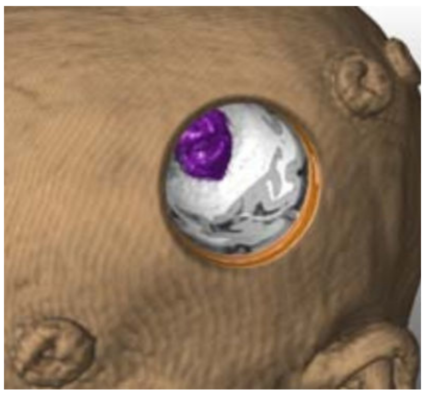
(b) Direct volume rendering of a T1-weighted image, not showing fibers. Generated using 3D Slicer [29].

Figure 4.11: Showing the head as context in 3D.

Alternative surface Instead of showing the anatomical data using the orthogonal slices, another option is to choose a different surface. For instance, a slice plane that is angled differently with respect to the head, or a different surface shape altogether. Figure 4.12a shows fibers in a context called a Virtual Klingler Dissection, which aims to mimic an actual dissection of the brain. Figure 4.12b shows the surface in a cylindrical shape between the viewer and the tumor.



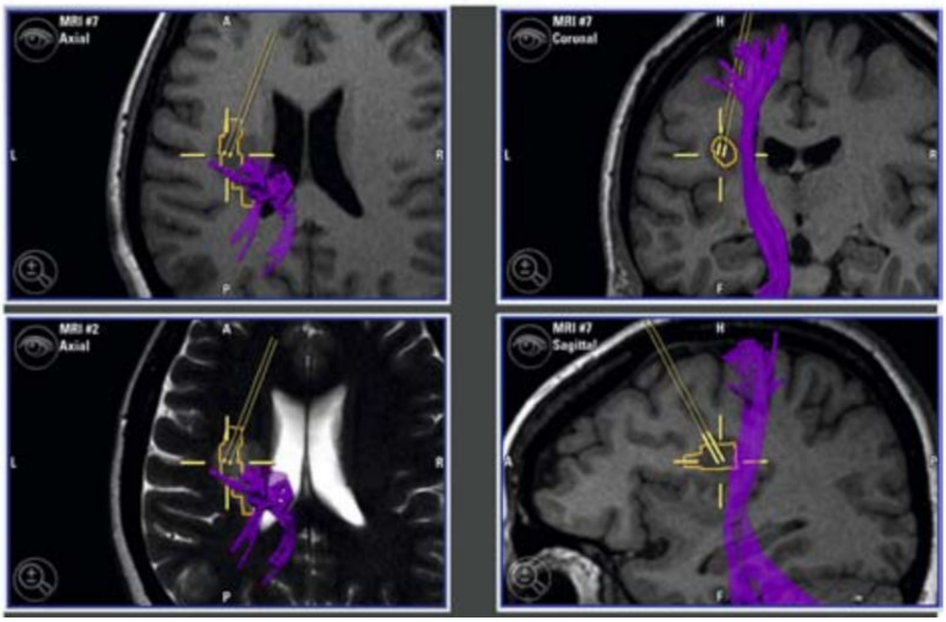
(a) The Virtual Klingler Dissection mimics the actual Klingler dissection [56].



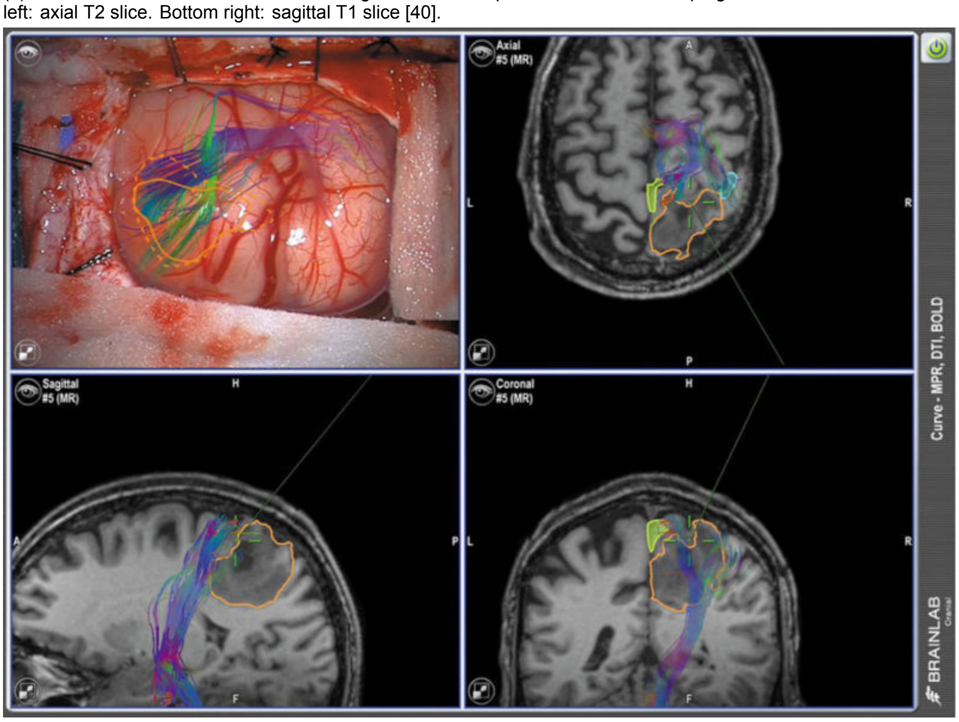
(b) Cylinder surface opening the way to the tumor [53].

Figure 4.12: Alternative surfaces showing anatomical context in a non-conventional way.

Illustrative For anatomical context there are also illustrative examples, although these can not be found in current navigational systems yet. A shaded model like Figure 4.11a could for instance be simplified by using suggestive contours [24], or replaced by just the outline of the brain [24]. Figure 4.14a shows an example of using the outline for context. Figure 4.14b shows another pen-and-ink style visualization. This one might not be useful intraoperatively, but it does show how much detail is possible using illustrative methods.

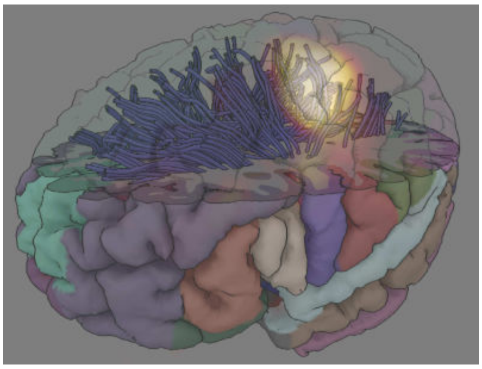


(a) Fiber tracts are shown as 3D hulls through the slices. Top left: Axial T1 slice. Top right: coronal T1 slice. Bottom left: axial T2 slice. Bottom right: sagittal T1 slice [40].

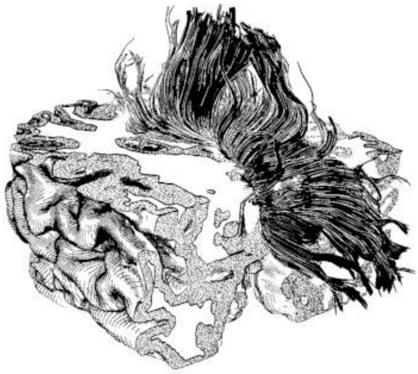


(b) Tracts are shown as streamlines and the tumor as an outline. Top left: a surgical microscope overlay. Top right: Axial view. Bottom left: sagittal view. Bottom right: coronal view [37].

Figure 4.13: Actual neuronavigation images from Brainlab. The slices that are shown always intersection with the surgical instrument, so whenever the surgeon moves the instrument, all three slices are updated.



(a) Multimodal visualization using the cortex outline for context [3].



(b) Pen-and-ink rendering of fiber tract in situ [61]. It is so detailed that it almost appears shaded.

Figure 4.14: Illustrative methods of showing anatomical context.

5

Design

The objective of this thesis is to design, implement and test a visualization that informs a neurosurgeon of the uncertainty in the calculated fiber tracts. This visualization is to be integrated in a neuronavigation setup so that it can be used during tumor resection. This chapter explains the design in a linear fashion, although in reality making any kind of design is a highly iterative process.

Section 5.1 starts by establishing our design goals. In addition, we have set up some desirable features in Section 5.2, which we will use to compare potential visualization solutions. The visualization is then divided into two distinct parts. The anatomical context, which is everything apart from the fiber tracts is discussed in Section 5.3. Then, in Section 5.4, the fiber tracts and their uncertainty are considered. Section 5.5 introduces some possibilities of improving the shape and the depth, and Section 5.6 concludes with ways that the user can interact with the system.

5.1. Design goals

After having interviewed a neurosurgeon, three main design goals have been set in order to improve the intraoperative visualization in neurosurgery. These goals are showing fiber tract uncertainty, improving the surgeon orientation, and reducing clutter.

G1: Show fiber tract uncertainty The process of tractography introduces many sources of error and uncertainty, but without showing that uncertainty it looks like the location of the fiber tracts is perfectly clear. During awake surgery, surgeons use electrical stimulation to find a fiber tract if they think they are close to one, but this can be very time-consuming. Showing the tracts intraoperatively already helps, but showing the uncertainty gives the surgeon an even better indicator on when to start stimulating.

G2: Improve surgeon orientation In standard clinical practice, the surgeon sees three orthogonal cross-sections of the brain, called slices (Figure 1.1). From our initial interview with a neurosurgeon, we know that it is difficult to mentally translate the three slices to a three-dimensional anatomy. The purpose of medical-image-data visualization is to explore patient data rapidly and accurately with minimal cognitive effort [52]. Making the visualization more intuitive would allow surgeons to use the system more easily, in particular surgeons that have little experience.

G3: Reduce visual clutter Typically, the fibers are shown as opaque streamlines which are a direct result of the tractography. If there are too many streamlines this approach can lead to highly cluttered visualizations [5]. When that happens, the underlying anatomical context becomes invisible and the surgeon needs to ask an assistant to turn the fiber tracts off in order to see it. Using a different representation of the fibers could help seeing both the fibers and the anatomical context at the same time.

The main design challenge lies in the combination of adding information (the uncertainty) and at the same time reducing clutter, as these goals are partially conflicting. A careful balance needs to be found between these goals. In addition, we have to fulfill a number of technical requirements, which are as follows:

- Interactive framerates are required, because a fast response time is essential during surgery.
- The software should be implemented in VTK, ideally as a 3DSlicer module [29], in order to make the results reproducible.
- The navigation interaction should be done using the neuronavigator as supplied by our collaborators.

5.2. Desirable features

Neuronavigation is not a trivial task from a visualization point of view. There are multiple structures that need to be visualized simultaneously, and often, improving the perception of one structure reduces that of another. After an analysis of the available visualization options from Chapter 4 and putting them in context for the surgeon tasks, we came to the following list of desirable features. These features have then been used to choose suitable visualizations.

Point of view Because the standard anatomical slices give the surgeon an extra mental reconstruction step, it is difficult to navigate. In order to improve the surgeon orientation, we propose that a potential visualization is done from the point of view of the surgeon [55].

Navigation Although we are looking at fiber tracts in particular, the visualization functions first and foremost as a navigational software. This means that the surgeon needs to be able to orient him/herself in the brain by being able to recognize anatomical structures in the data. It is very important that the visualization tool is able to show the anatomical context well.

Reference In order to relate the 3D position of the fibers to the pointer position, the surgeon should be able to see the location of important structures with respect to the surgical instrument (pointer). For instance, by showing the intersection of the fibers with the slice.

Locality The closer to the pointer, the more important the information is. A good visualization should place extra emphasis on structures that are close by, and less emphasis on structures that are further away.

Decision The decision that the surgeon needs to make is binary: either enter an area or not. Everything that is shown should directly relate to this decision. This means that knowing ‘where there is fiber’ is more important than the exact shape of the fibers. For clinical intraoperative use, the actual border of a major white matter tract is of main interest [43], and a good visualization should aid the surgeon in making this decision.

Operating direction The surgeon wants to know what is ‘behind’ (in extension of) the pointer, as that is the region where the surgeon has to decide to go to. For this reason, fibers ‘in the back’ are at least as important as the fibers ‘in the front’.

5.3. Context visualization

Before going into the fiber tracts themselves, it is first necessary to determine how the rest of the brain is going to be shown. Missing the context would mean that the fibers are simply floating in space, which would score very low on the *Navigation* and *Reference* criteria. For this reason a context, or frame of reference, for all other parts of the visualization should therefore be visible at all times [24]. The ideal context would be a single 3D view in which all relevant structures are clearly visible. An obvious candidate would be to use volume rendering for the context. With a properly designed transfer function, all relevant structures would be visible. However, knowing which exact structures are important and how to design the transfer function to show them requires a lot of medical knowledge and is beyond the scope of this project. Moreover, this transfer function would be dependent on what type of imaging data is available, which can be T1-weighted, T2-weighted, or FLAIR.

Another option that also uses a single 3D view, but does not require the design of a transfer function, is a surface-based approach. This involves segmenting the important structures before surgery, and tweaking the opacities of the structures so that everything is visible. The downsides to this approach are that again, it is necessary to exactly know what structures the surgeon should know about, and manually segmenting many structures for each patient is very labour-intensive.

To avoid these downsides, an alternative is to not show the entire volume of data, but showing a surface by making a cut through the volume. This surface would need to move along with the pointer, because of the *Navigation*, *Reference* and *Locality* criteria. Having this surface at the pointer however, would mean that it becomes much harder to show something that is behind the pointer (*Operating direction*). Showing multiple surfaces from different angles simultaneously could alleviate this problem, which is exactly why the three orthogonal slice-based visualizations dominate in the field of radiological diagnosis [52][51]. We will consider three slice-based visualization options, and three alternative surface options.

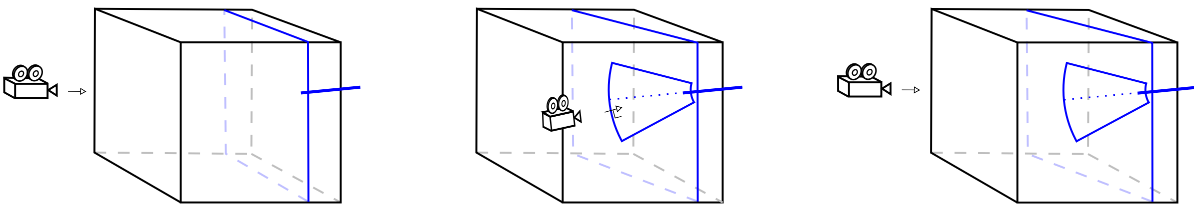
5.3.1. Slice-based

A slice-based approach uses several views simultaneously. These could be the anatomical (coronal, sagittal, axial) planes, but this is what we are trying to avoid in order to improve the *Point of view*. The alternatives to be considered are Surgeon-oriented views, Pointer-oriented views, and a combination of the two.

Surgeon-oriented views One of our proposals is setting a virtual camera from the point of view of the surgeon. Moving the pointer up, down, left and right from the surgeon's perspective moves the main view accordingly. For the other two views, we define a top view and a side view, which are all rotated by 90 degrees with respect to the main view. The advantage of this approach is that it scores best on *Point of view*, as it is exactly from the point of view of the surgeon. However, it scores a little less on *Operating direction*, as there is no view that shows what is directly behind the pointer. A side view is shown in Figure 5.1a.

Pointer-oriented views This proposal moves the main camera along the with pointer direction, and sets the top and side views relative to that. The advantage here is that both the top view and the side view show (by definition) what lies behind the pointer, but then scores a little less on *Point of View*. A side view is shown in Figure 5.1b.

Combination Finally, a combination is also possible which sets the cameras based on the Surgeon-oriented view, but the top and side view slices based on the *Pointer-oriented view*. See Figure 5.1c.



(a) Surgeon-oriented side view: fixed camera, slice orthogonal to the camera.

(b) Pointer-oriented side view: slice is along the pointer, the camera remain orthogonal.

(c) Combination: slice is along the pointer but the camera remains fixed.

Figure 5.1: Different configurations for side views. The corresponding front views would be from the point of view of the surgeon, and from the point of view of the pointer respectively.

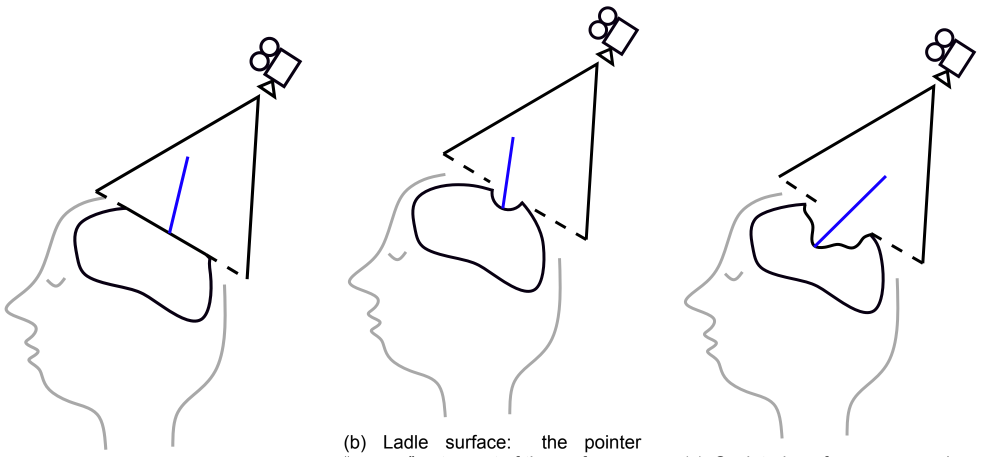
5.3.2. Alternative surfaces

Slice images are the simplest way to put fiber tracts into context. However, they do not convey the three-dimensional shape of structures in the T1-data [56]. We will consider three alternatives: the ladle surface, the sculpted surface and the Virtual Klingler Dissection.

Ladle surface The basic idea of the ladle surface is shown in Figure 5.2b. This places more emphasis on the fact that we are actually dealing with a 3D structure than the sliced-based visualizations do. It scores well on the *Locality* criterion, because the more context close the pointer is shown. A disadvantage is that depth perception is hindered (*Reference*), and it is not possible to see what is in the extension of the pointer (*Operating direction*).

Sculpted surface One way of reasoning about the ideal surface to visualize, is to show the surface that the surgeon is most likely to go next. This surfaces changes over the course of the surgery; as more tumor is removed, different areas of the brain are reached. An option is to start the surgery by only showing the skin surface, and make holes in the surface when the surgeon starts to reach deeper areas. Ideally, this would make the visualization look similar to the actual state of the surgery. A downside is that the *Operating direction* is not visible.

Virtual Klingler Dissection The Virtual Klingler Dissection [56] tries to follow the anatomical structure of the data instead of the geometrical surfaces discussed above. This places extra emphasis on the 3-dimensional nature of the data, and makes it easier for the surgeon to recognize structures. The downside is that this is a very difficult solution implementation-wise, and it is not certain that this would work well in a navigational context.



(a) Slice-based surface: the tip of the pointer moves along with the slice.

(b) Ladle surface: the pointer "scoops" out a part of the surface as if it were a ladle. When the pointer moves, the spherical hole moves along.

(c) Sculpted surface: every place the pointer visits is permanently cut away.

Figure 5.2: Slice-based surface and its alternatives.

5.3.3. Selection

Table 5.1 summarizes the context surfaces that have been considered. The scoring is based on our own judgement. The surgeon-pointer combined views are considered to be the best option for visualizing the anatomical context around the fiber tracts, so this solution has been chosen. An impression of what that looks like is shown in Figure 5.3. The actual implementation is shown in Figure 5.4.

	Point of View	Navigation	Reference	Locality	Operating direction
Anatomy-oriented slices	- -	+	+	+/-	-
Pointer-oriented slices	+	+	+	+/-	++
Surgeon-oriented slices	++	+	+	+/-	+
Surgeon-pointer combination	++	+	+	+/-	++
Ladle surface	+	+/-	-	++	- -
Sculpted surface	+	++	+	+	- -
Virtual Klingler	+	-	-	+/-	-

Table 5.1: The different context visualization options that have been considered. The *Decision* criterion is not relevant for the context visualization. The surgeon-pointer combination is selected as the most suitable one.

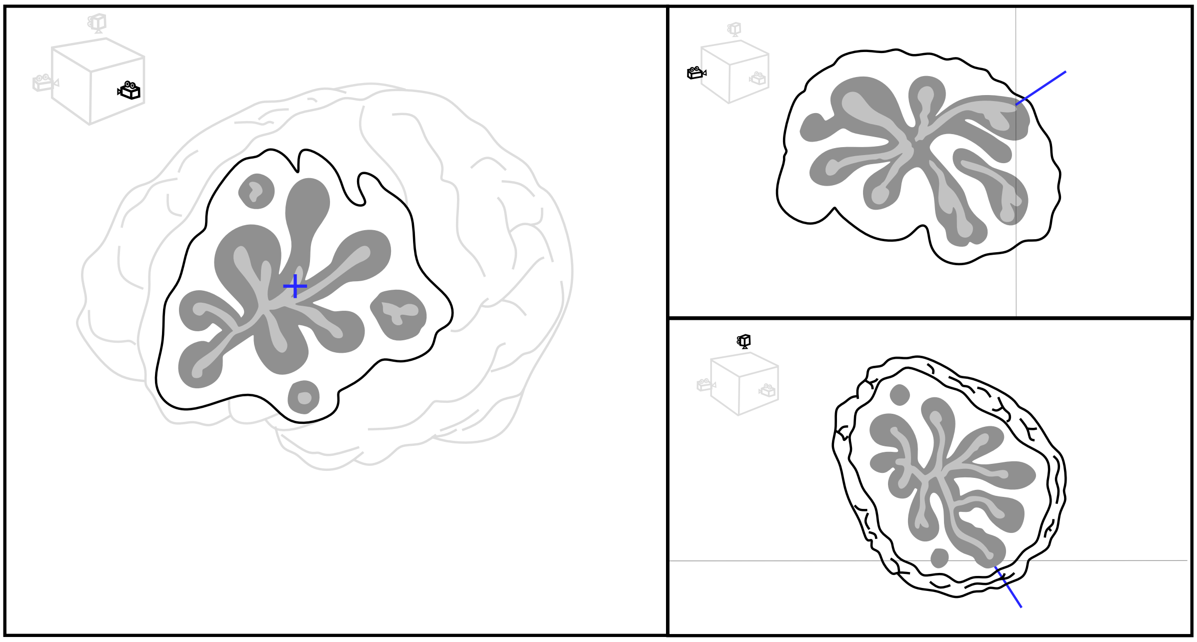


Figure 5.3: Impression of how the context should be shown. The main view is set to the surgeon's perspective, then the side and top views are automatically calculated. The cortex surface is shown for extra context.

5.4. Uncertainty visualization

As discussed in Chapter 4, there is a large class of different techniques for uncertainty visualization. The candidates that will be discussed are streamlines, transparent hulls, volume rendering, intersection only, silhouettes/outlines, the curve box plot, point displacement and animation.

5.4.1. Geometrical models

Streamlines Using streamlines or spaghetti plots is the most basic option in deterministic fiber tracking, as it simply shows the tracts exactly how they are calculated. There are different rendering options such as plain polylines, shaded lines or the little more sophisticated streamtubes [72]. All of them have the same disadvantage though, which is that they add a lot of clutter to the visualization.

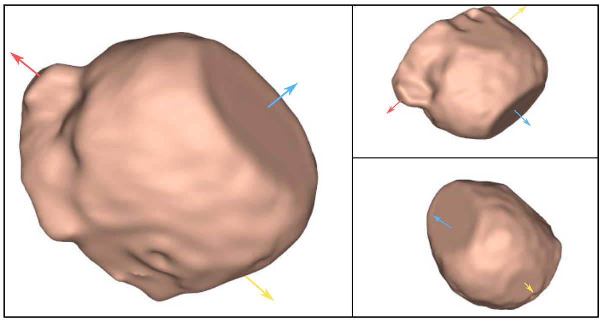
Hull / Curve Box Plot Users are often not interested in individual fibers but rather in fiber bundles [5]. By creating a hull around a fiber bundle, you get a much simpler geometric object that causes less clutter than the individual fibers. Alternatively, a 'Curve Box Plot' [38], can be created by wrapping 50% of the fibers in a hull, and showing the outliers as streamlines.

Multiple hulls An alternative to the Curve Box Plot is to show multiple hulls, each corresponding to a different uncertainty level. In order to see these multiple hulls, they need to be partially transparent. Needless to say, the more hulls are added, the more complex the visualization becomes.

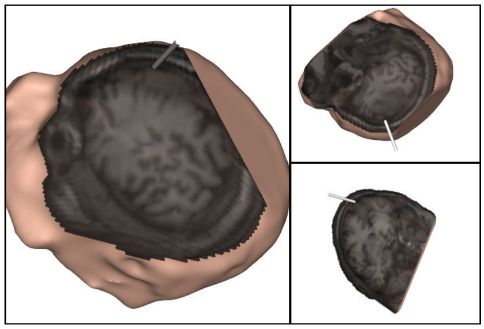
5.4.2. Illustrative techniques

The idea of using illustrative techniques to visualize the fiber tract uncertainty is to show them using a sparse visual representation. This is a promising alternative to a semi-transparent display, where the ordinal depth cues, such as occlusion and shading are hardly recognizable for a transparent surface [52].

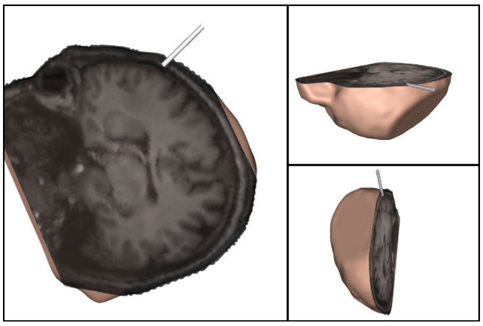
Silhouette/Outline A lot of visual complexity can be removed from a hull by only showing a silhouette or an outline of the fiber. For instance, multiple fiber silhouettes can be used to indicate different categories of uncertainty [5]. This is very good for showing the general shape of the fiber [21], but a downside is the reduced depth perception.



(a) Main view from the point of view of the surgeon (left), top view (top right) and side view (bottom right). The top and side view are obtained by rotating the main view by 90 degrees.



(b) Views after entering the skull. The main view slice is always perpendicular to the viewer, the other two are in line with the pointer. When moving deeper, the pointer always moves upward in the top view and rightward in the side view.



(c) Holding the pointer at an extreme angle shows that the top and side view slices are in line with the pointer. In practice the surgeon will not hold a tool like this.

Figure 5.4: Implementation of the context visualization. All slices intersect the pointer tip at all times.

Intersection only (2D) Another way to reduce complexity is to limit the scope to 2D: only show the uncertainty at the slice itself. This is a good example of the *Decision* and *Locality* criteria, as the surgeon can see that there is fiber close by, without having to know where that fiber goes off to in the distance. When used in combination with the pointer-oriented top and side views, it also show exactly how far off the fiber is in the *Operating Direction*.

5.4.3. Other techniques

Volume rendering Volume rendering is also a valid option for uncertainty visualization. This does require having an uncertainty volume, which is an assumed input in this thesis. It must be noted that the quality of a volumetric representation depends on the data resolution, and, depending on the transfer function, can lead to visual clutter [5].

Point displacement Another possibility is to render the fiber surface as a collection of points, and displace the points along the surface normal by an amount proportional to the uncertainty at that point [20]. The downside is that it creates a very noisy-looking image with a lot of visual complexity.

Animation Finally, animation can be used to show the uncertainty. For instance, using vibration [6] or animated textures [21]. The downside of this is that it can be quite distracting for a surgeon.

5.4.4. Use of color and transparency

For showing the uncertainty in fiber tracts, one option is to use light-to-dark coloring with a constant (low) opacity [5]. On the other hand, it is known that saturated colors attract the attention to a higher level than unsaturated colors [21], so it makes sense to color more certain regions with a more saturated color. If the fibers are more certain, then it also makes sense to have a higher opacity. In particular, the intersection of the inner fibers with the slice do not need to show MRI data as the fiber is the most important anatomical feature at that point (*Decision*).

5.4.5. Selection

Table 5.2 summarizes the uncertainty visualization techniques that have been considered above. Interestingly, the 2D intersection with the context plane scores high on many of the criteria, despite its simplicity. For this reason it has been chosen as the main encoding for uncertainty. Since this does not show the general direction and shape of the fiber, the outline is chosen to be visualized as well. See Figure 5.5 for an impression, and Figure 5.6 for the implementation.

	Navigation	Reference	Locality	Decision	Operating Direction
Streamlines	- -	- -	+/-	- -	+/-
Hull / Curve Box plot	-	+	+/-	+	+/-
Multiple hulls	-	+	+/-	+	+/-
Silhouette/Outline	++	+	+/-	+/-	+/-
Intersection only (2D)	++	++	++	++	++*
Volume rendering	+/-	+	+/-	+	+/-
Point displacement	-	-	+/-	- -	+/-
Animation	- -	+/-	+/-	-	+/-

Table 5.2: Different uncertainty visualization options that have been considered. The *Point of View* criterion is not relevant for uncertainty visualization. The intersection with the surface has been chosen for uncertainty visualization, and and outline is chosen to indicate the general fiber direction. *Only in combination with the pointer-oriented side/top view.

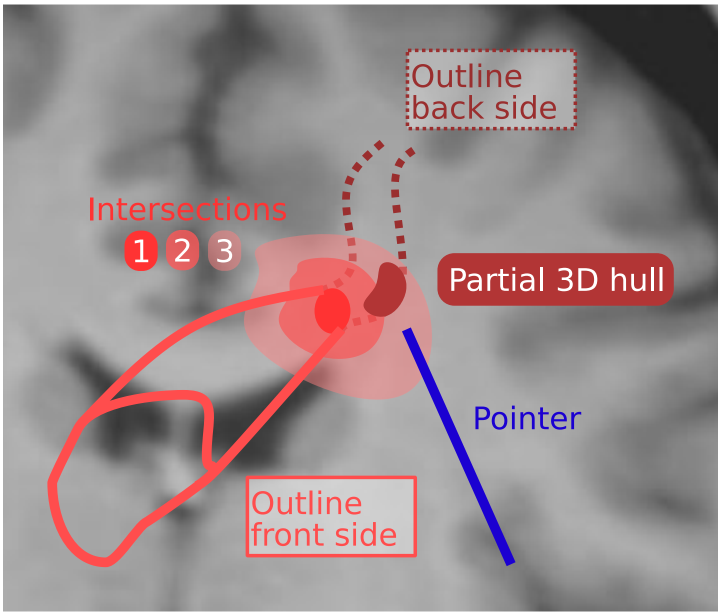
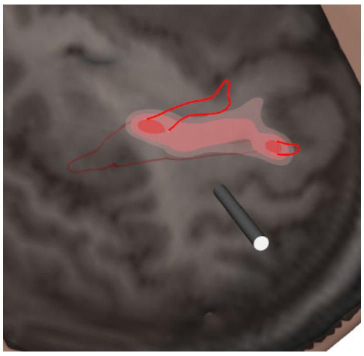


Figure 5.5: Impression of the uncertainty visualization. The uncertainty is shown for three levels, at the slice plane. The central level is also shown as an outline with a solid color at the front side of the slice, and dotted on the back side. The only 3D surface is the partial 3D hull, close to the pointer. This surface is shaded in the actual implementation.

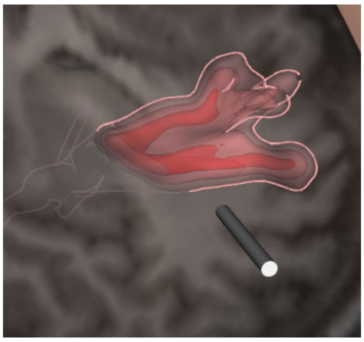
5.5. Shape and depth cues

A potential problem with the current visualization is the very limited amount of shape and depth queues. There are multiple ways to improve depth perception without changing the entire visualization strategy. The ones discussed below are either line-based, surface-based or motion-based.

Line-based The shape perception of the fiber can be improved by not only showing the contour of the fiber, but some sharp interior edges as well. Examples on how to do this is by using interior contours [44] or suggestive contours [13]. A way to improve depth perception using lines only could be done setting halos around the lines, and adjusting the width of these halos as a function of distance [17]. That does require dense line data, which is undesirable in this case.



(a) Three levels of intersections with the slice and the outline of level 1.

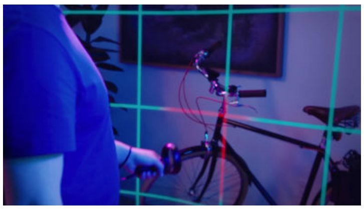


(b) Transparent hulls together with the outline of level 3.

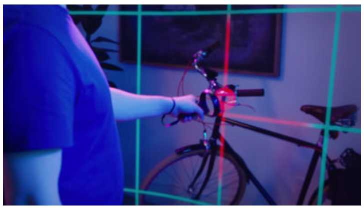
Figure 5.6: Implementations of the uncertainty visualization. The opacities of the intersections and hulls may be adjusted.

Surface-based Surface-based cues include shadows and shading. Shadows are difficult in this case because of the lack of a suitable surface to cast the shadows on. Shading, such as Phong shading can be used to improve the depth and shape perception of the fibers [16]. As a trade-off between showing the full shaded fiber hull and not showing it at all, it is also possible to show a partial surface hull. The idea of using this comes from a VR-setting (Figure 5.7), in which a user is also warned when nearing a dangerous area. In our context, instead of rendering the full hull, we clip the fibers using a sphere centered at the pointer tip. This also has the advantage of only showing the fibers that are close by (*Locality*). An example of showing multiple partial hulls simultaneously is shown in Figure 5.8.

Motion-based Finally, a lot of shape and depth cues can be achieved using motion. In particular, the motion parallax, the kinetic depth effect, and the perspective projection while in motion [52]. This advocates the use of pointer-oriented views, as that brings a moving camera for free.



(a) When nearing a dangerous area, a part of the virtual grid lights up in red.



(b) When moving closer, the potential area of impact is shown using a circle.

(c) When moving even closer, the circle widens.

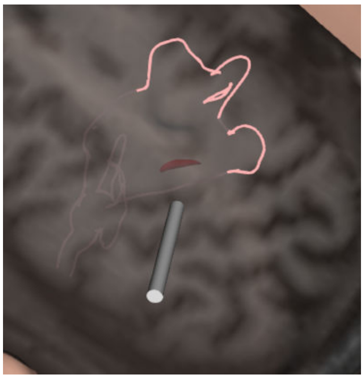
Figure 5.7: The inspiration of the partial surface hull comes from the 'Guardian' feature of the Oculus Quest VR glasses. It works very well for showing the location of a dangerous area.

Distance meter As a final tool to help the surgeon see the current distant to the tracts, an additional view is added which shows exactly that. Since the 'distance to the tract' is not exactly defined because of the uncertainty, the distance to each individual level is shown. Figure 5.9 shows the initial design, and the result is shown in Figure 5.10.

5.6. Interaction

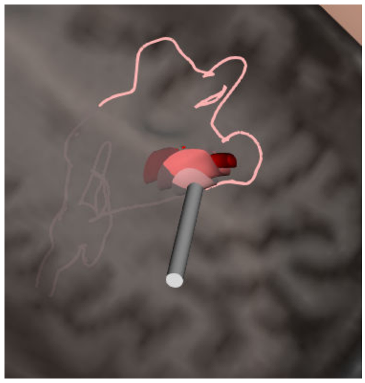
User interaction is an important aspect of this visualization, as the surgeon is not able to use a mouse and keyboard while operating. Different interaction configurations are discussed below.

Neuronavigation system The main way to interact with the system is to connect to the neuronavigation device and move the pointer. This is the most straightforward method, and results in the views as shown in this chapter.



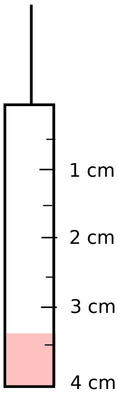
(a) When moving close to a tract, the inner-most hull is shown first.

(b) Moving closer, the center hull becomes visible too.

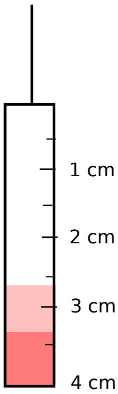


(c) Moving even closer, all three levels are shown.

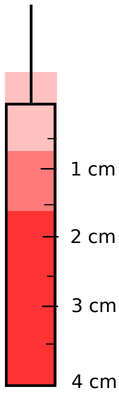
Figure 5.8: The partial surface hulls only show when the pointer comes close to the tract. This is done both to avoid cluttering the views, and to give interactive hints on where the hulls are located with respect to the pointer. Which levels are shown, as well as the size of each of them may be adjusted.



(a) The pointer is about 3.5 cm away from the low-risk region.



(b) Moving closer, the low-risk region is at 2.5 cm while the mid-risk region is still at 3.5 cm.



(c) Moving closer still, the pointer has entered the low-risk region, while the mid-risk and high-risk areas are at 0.5 and 1.5 cm respectively.

Figure 5.9: The distance meter shows the current distance to a tract. The saturated color corresponds to the high-risk region, where the fibers are most certain. The line at the top of the meters represents the pointer.

Camera mode This is an alternative viewing mode which does not fix the position of the camera from the main view. In this case, the virtual camera is place right behind the pointer in the main view and moves along with it. In practice this means that the physical surgeon instrument becomes a virtual camera. This is a useful feature to have at the start of the surgery, to set up main view by pointing at the patient's head from the surgeon's point of view.

Record and replay Apart from using the system in a live environment (which requires a neuronavigation device), it is also possible to record the location of the pointer so that it can be played back at a later stage.

Mouse and keyboard This is the mode we used most during the development of the tool, and is useful for anyone wishing to try it out. The mouse can be moved around in the main view, and the pointer follows along. Moving deeper is done by scrolling up, and moving out by scrolling down. The 'W', 'A', 'S' and 'D' keys are for rotating the pointer upward, leftward, downward and rightward respectively. The 'Q' and 'E' buttons can be used to rotate the pointer along its own axis and is only used in camera mode. Although mouse and keyboard is not as intuitive as using the neuronavigator, it does allow putting the pointer in all possible positions.

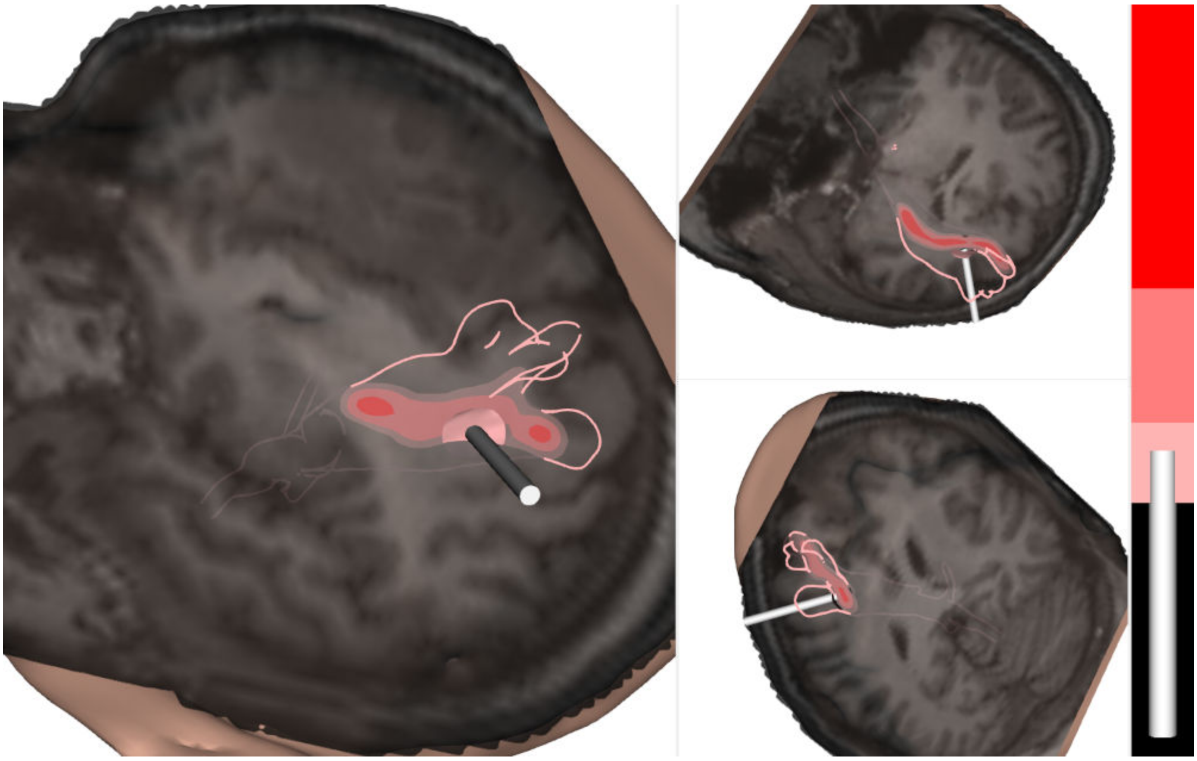


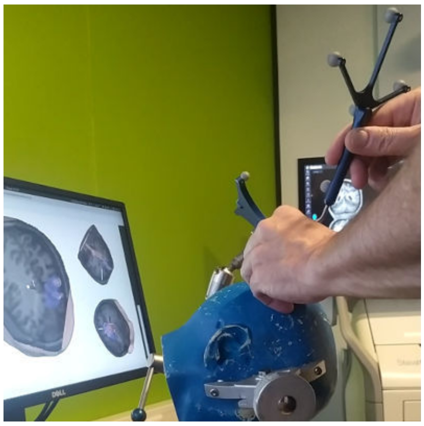
Figure 5.10: Full user interface including distance meter on the right. The intersections are shown of all levels, the outline and partial hull of the third level only. The distance meter can be a considered a simplified version of the top view, with the pointer just entering the level 3 zone. The pointer at the bottom of the distance meter remains stationary while the three uncertainty levels vary according to their distance.

6

Evaluation and discussion

In order to evaluate the effectiveness of the design, a neurosurgeon is asked to try out the system. The anatomical and fiber tract data from an anonymous person was used and registered to a phantom head. The setup is shown in Figure 6.1. First, the system was demonstrated and the possible configuration options were shown. After that, the surgeon got some time to familiarize himself with the system. Then, the surgeon carried out a task using different visualization options, and finally we conducted an interview to assess the effectiveness of the visualizations. The whole session was video-recorded, the navigation monitor was recorded, and location of the surgeon pointer as well.

(a) StealthStation running the stock software.



(b) Surgeon performing a task using an external monitor.

Figure 6.1: Setup for the evaluation. The Medtronic StealthStation S8 was used for tracking the pointer.

6.1. Task

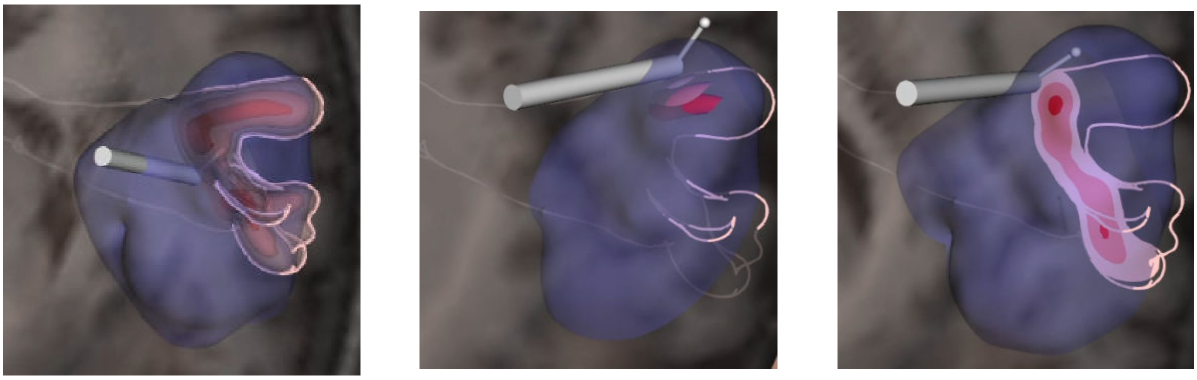
In a real tumor surgery, the main objective is to maximize the extent of resection while minimizing morbidity [45]. During an awake surgery, electrical stimulation is used to verify the existence of fiber tracts. In this task, a phantom head is used instead of a real patient, so electrical stimulation is not possible. For this reason, the following risk-regions have been defined for the fiber tracts:

- The high-risk region (level 1) must be avoided at all cost, as entering that region is certain to cause neurological deficits.
- The mid-risk region (level 2) has a chance to cause neurological deficit, and should be avoided if possible.
- The low-risk region (level 3) is considered safe and may be entered. It serves as a warning area for the mid– and high risk regions.

The task of the surgeon is then to reach as many areas of the virtual tumor as possible, without touching the mid– and high-risk fiber regions. This task is repeated a number of times, with the following visual configurations:

- With the transparent hulls enabled (Figure 6.2a)
- With the partial hulls enabled (Figure 6.2b)
- With the intersections enabled (Figure 6.2c)

The low-risk fiber outline is shown at all times.



(a) Transparent hulls. (b) Partial hulls. (c) Intersections.

Figure 6.2: Three different visualizations in which the surgeon had to perform the same task.

6.2. Design validation

After doing the task, we conducted an interview with the surgeon. He was most surprised with the new views and liked the fact that the main view was now aligned with his own point of view: *'I think it is a very good approach towards a new view on where the structures are'*. About the top and side views he was a little less enthusiastic. This was partially because he had difficulty recognizing the anatomical structures with the different orientations, and partially because he had to look at the different views sequentially. He put this in contrast to how he looks at the conventional neuronavigation system, which also has multiple views, but which he perceives as a single image. In cognitive psychology, this process is known as chunking [25], and is gained with years of experience. He anticipated a long training period for others to get used to this system, but admitted that the same holds for the conventional system. *'With some training, yours might be preferable'*. For making the system more intuitive, he suggested using a single view in which the fibers were visible in the depth.

Overall, the surgeon was happy with the uncertainty visualization, but he suggested using two levels of uncertainty instead of three. This would still make surgeons aware that the uncertainty exists, but is easier to interpret. Especially the distance meter was a helpful tool in performing the task, as it serves as a warning system that they are currently lacking. An improvement to the distance meter could be integrating it more closely with the main view, as he had to shift his attention between them. One suggestion was to let the pointer serve as a distance meter.

From the three visualization options that he tried, he found that the task was easiest using the intersections as the location of the tracts was very clear. With that came two footnotes: he had already practiced with the other two before that, so he was more familiar with the system. Furthermore, he noted that for clinical use, having the tracts in 3D would be more beneficial. He preferred using the full hulls over the partial hulls, but only because the partial hulls were too small. Especially when multiple fibers are visualized, having the partial hull(s) would make sense: *'You don't want to visualize them all at the same time. I think that it is a very good approach'*. The outlines were effective in showing the general shape of the fiber, but he was not sure how well it would work using multiple fibers. A potential solution for this is having a partial outline similar to the partial hull, by only showing the outline that is near the pointer. When asked about possible other applications for the system, he suggested anatomy training for medical students. The full interview can be found in Appendix B.

6.3. Discussion

The design goals for this visualization as stated in Section 5.1 have largely been achieved. Fiber uncertainty is shown successfully using different methods (G1), and clutter has been reduced using only outlines and partial hulls instead of streamlines (G3). Whether the surgeon orientation has been improved with respect to the classical system (G2) can only be said for certain after more practice and by having the visualization side-by-side with the classical system during a surgery.

That being said, during the evaluation the surgeon mentioned multiple times that he would rather have a single view in 3D that contained all the relevant data. A single 3D view was considered during the literature study (Section 4.4), but it makes context visualization much harder. One option is direct volume rendering, which casts rays through the data volume and gives some weight to each of the data points it encounters. These weights, or the transfer function, must be designed in such a way that all the relevant structures are visible. That would be a very interesting project by itself, but out of scope for this one. Anther option is indirect volume rendering. In this approach, all the relevant structures have to be segmented and shown as 3D surfaces. This is a time-consuming task that would have to be done for every patient, but if in can be automated it is a viable option. In either case, the ideal visualization would not need to use any slices.

Another limitation is the fact that the evaluation has only been done by showing the corticospinal tract while during surgery multiple tracts are shown. The assumption is that by clipping the fibers locally using the partial hulls or a similar technique, the overall visual complexity does not increase significantly, but this is yet to be evaluated. As for the partial hulls themselves, we recommend only showing one or two single uncertainty levels using this technique, and with a bigger radius. Three levels did result in some visual clutter and did not improve the overall experience.

Finally, the task was carried out using a phantom instead of a real person. Even though this did not matter for the visualization, it is completely different from a real surgery. The surgeon could freely move the pointer through the hollow head, which would be impossible with a person. In order to get a better understanding of the intraoperative benefits, the system should also be tested intraoperatively.

7

Conclusion

In this design study, we created a new visualization that allows neurosurgeons to see the uncertainty in fiber tract data during surgery. Knowing this uncertainty is relevant because it will influence a surgeon's decision to enter certain regions. We started by first obtaining relevant medical background, after which we conducted an interview with a neurosurgeon and visited a surgery. When we had a clear picture of what tasks a surgeon has to perform, we reviewed relevant literature in the fields of fiber tract visualization, uncertainty visualization and context visualization. This is a unique combination, as intraoperative uncertainty visualization of fiber tracts has not been done yet in the current literature. In the design process, we weighed desirable features of existing visualization techniques and also added two new ones. We implemented the design and integrated it with a neuronavigation device. Finally, we evaluated the effectiveness of the visualization with a neurosurgeon.

What made the design challenging was incorporating our limited knowledge of the medical domain. The brain is a highly complex organ and we were tasked with showing the relevant parts of it to a surgeon. In the process, we had to learn about MRI scanners, surgical practice, neuronavigation, and the visualization platforms 3D Slicer and VTK.

Our three design goals were showing the fiber tract uncertainty, improving the surgeon's orientation and reducing visual clutter. We have successfully shown fiber tract uncertainty to a neurosurgeon using (partial) hulls, intersections and a distance meter. For improving the surgeon's orientation we showed the anatomical data from the surgeon's point of view, as well as adding top and side views. For reducing the visual clutter we have chosen to show a fiber outline to indicate the general shape, and partial hulls to indicate the position of the tracts.

Our main contribution is creating awareness for the need of fiber uncertainty visualization in the operating room, by opening up a new area for research. Furthermore, we created two new visualization techniques that may be used intraoperatively: a partial hull that is only shown when a surgeon gets close, and a distance meter that serves as a warning tool. Finally, our implementation is made as a module in 3D Slicer, which allows others to try it out as well.

In Chapter 1, we introduced the following three research questions:

Does showing an alternative viewing surface, as opposed to the orthogonal planes, help with the surgeon's orientation?
The surgeon confirmed that the new point-of-view was definitely an improvement. However, having top– and sideviews proved to be less intuitive than anticipated. Our suggestion is to move away from surface-based representations altogether and focus on volume rendering. This is challenging, but will likely lead to better results.

How does the fiber tract visualization along with uncertainty information help surgeons in the neurosurgical workflow?
In the words of the neurosurgeon: '*you need to raise awareness among surgeons that it is just visualization of statistics*'. By showing uncertainty information, surgeons become aware that position of the fiber tracts is not known exactly. Moreover, the fiber tract uncertainty is larger in some areas than in others. Knowing this allows surgeons to make better decisions on when to start electrical stimulation, or in which areas to operate. This can save time during surgery.

Will only showing select illustrative features be sufficient in conveying spatial information?
Neuronavigation needs a complex visualization because the brain is a complex organ. Using illustrative features simplifies fiber tract information while still showing enough to be useful. In our case, the surgeon perceived general shape of the fiber using the outline only.

The next step is to try out our visualization using different measures of uncertainty data in order to establish the generalizablilty of our work. Our focus has been on uncertainty visualization, not uncertainty estimation, so it is important to verify that it also works for other inputs. Then, an extensive clinical trial should be held. The safest way to go about it is to show the new visualization alongside the commercial one and see what features surgeons really like. Finally, a collaboration with a medical technology company will allow incorporating the new visualization into their system so that everybody can benefit from it. Another way society can benefit from this work is by including it in the educational program of medical students, allowing them to learn the anatomy interactively.

We found that there is a need for the visualization the of fiber tract uncertainty during neurosurgery. Adding this uncertainty is important because ultimately, it will help surgeons to save lives.

A

Surgeon interview

Below is a full transcript of the neurosurgeon interview. The interview was conducted on December 13th 2021 at the ETZ hospital in Tilburg.

What means do you have to interact with the the fiber tract visualization during the operation (e.g. mouse, foot pedal switch, other people)? I would ask the nurse to use the mouse. Although sometimes, we have a mouse in a sterile package so that I can use the mouse myself. We can also track the CUSA, the system with which we remove the tumor. That interacts with the software and is the most important one. If we want to change the settings, we have to ask the nurse. *How about the foot switch?* You can use the foot switch to freeze the screen. Normally you are using the pointer, and you can then press the foot switch so that you have all the time to examine the screen. *What kind of settings can the nurse change?* It is mostly very basic things, like changing the contrast or the brightness of the screen, and adding new tracts to it. We have multiple tracts, like the AF or corticospinal tract, and you can visualize them or not. Sometimes all of these tracts overlay over the tumor so you can't see the tumor any more, so then I ask the nurse to remove it.

Actually, the Stealth system has a tracker which is rigidly fixed to the patient. On that tracker there are some options to steer the navigational system, to zoom in and to zoom out. You have to point to these controls and then you can zoom in and zoom out, but actually we never use them. So it is possible to use the pointer to have some basic functionality.

In which situations during the surgery do you need information from the navigation monitor? Let me ask the question back to you. You saw us interacting with the navigational machine during surgery. What was your observation on how we used it? *I had the feeling that the important tracts are not visible in the microscope, as they look indistinguishable from the other white matter.* (There is no information in the microscope, correct). *So the idea that I got was that you have your tool, you see where it is with respect to the fibers on the screen, and then you relate it to what you see on the microscope, so you now that a certain location is close to the tract.* We continuously look at the screen to see where we are in the brain in relation to the tumor, and all other sorts of critical structures like blood vessels. So even without the fibers you are continuously updating yourself in knowing where you are, and we are virtually extending the pointer so that we know in what direction we are moving. So that is the information that we get from the screen, and on top of that we can add the fibers. *You are mentioning blood vessels as well?* A normal MRI is with contrast, for instance, so you see the large blood vessels, and you see the tumor border. You have to know where in the brain you are, and where you are moving towards. That is the most important information that we get from the navigational system. On top of that, we add functionality by adding these fiber tracts, which are important functional structures. Because as you said, you can't see the difference in the microscope.

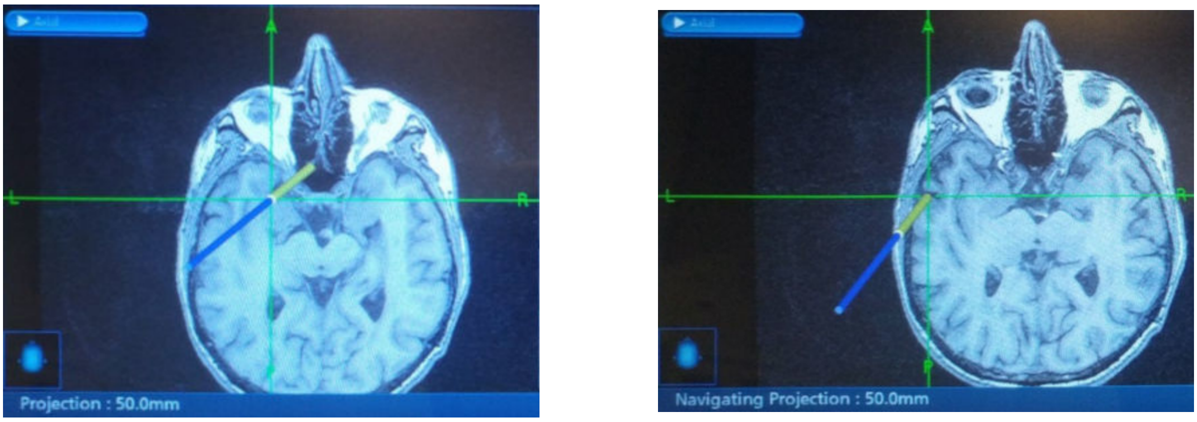
How often do you look at the monitor? I don't really know myself, but why is this a relevant question? *This question is related to what you said about freezing the screen, as you are not able to see the microscope and the screen at the same time, even though you might wish to.* Sometimes you are with two people, so one is operating and the other is also looking at the microscope, but also continuously looking at the monitor, telling the other which structures he or she is approaching. So that is also a possibility. So I don't know exactly, but in our case we are looking very frequently. *Is there a specific scenario in which you need to have a second person to continuously monitor the screen?* That is when we are moving towards certain structures that we know we should avoid. The more you approach them, the more you want to have feedback.

What do you need to setup in advance to achieve the visualizations you want? Think of things like registration. Registration is the only step we need to start navigation. *How about settings?* We have fairly standard settings, which are actually very old-fashioned, because these three orthogonal planes which are not the three planes which you are thinking in anatomically, because you are viewing the brain from a different angle. So you have to look at three orthogonal planes which is actually very strange, because at least you want to have a plane that is the plane in which you are looking, but we don't see that. We always look at the standard manner that you visualize your MRI scan. *Do you ever use the 3D view?* For planning the trajectory we also have another view, the 3D view, that we do use. We use it when we open the skull. When you look at the brain, you see the sulci and the gyri. Then we look in 3D to the same position, and then you can recognize the same structures. It is sort of a check. You then put your navigational pointer to a certain structure, for instance a gyrus or a sulcus, at the surface, you can see that also in the 3D view. That is a reassuring step that you know at least that you don't have too large of an error. There is always the possibility of an error in the system, so I always check whether this matches with my expectations. *How do you get the system to render the outside of the brain?* You have to make a 3D model of it. So our personnel does the tractography, import the tracts, and also do us a favor by making a 3D model of the brain. It is a module within the Stealth, you can best use the FLAIR, and then go to models. You have your 2D and 3D options. If you look at 3D, you can make your own model of your FLAIR. Then it automatically strips the skull. I think this 3D view is very helpful, as a check.

What are the limitations of using the orthogonal views? If I am looking from a certain angle towards the brain while removing the tumor, then it would be perfect if I would have a 3D view with in the depth the fiber tracts that are coming up. I think that would be very intuitive for us because now, I virtually extend the pointer so I know at least the direction I'm looking in, but I have to infer that from these three orthogonal planes. Sometimes during surgery, it is very difficult to see what exact angle you are facing. So in 3D, transparent with in the depth the fiber tracts that you are going to approach, or some other critical structures, I think that would be very valuable.

About the projection that you mentioned, do you prefer to navigate the instrument tip, or navigate the projection? (Figure A.1) I navigate the instrument tip. If you don't extend the pointer, you get a cross, and you see at what point you are. Not everybody is doing this, but I extend it because I want to know the direction I'm going. You have to look out with navigate projection, because then you are extending your pointer with, say, four centimeters, and you navigate your projections. We use this for instance when we want to insert a drain in the ventricle. You can image that if you point towards it, you don't know if you end up in the ventricle. So you virtually extend this, and then you point to the skull, you can see where you end up. So for some situations this is very useful, but for seeing where you are, this is very very tricky. *How do you use the navigate projection during a ventricle drain?* In that case, you are not very interested in where the tip is, but you want to know where the tip ends up. Then you can use the virtual extension. *So you just use it to determine the insertion angle?* Yes, for that it can be useful. For tumor resection where you want to know where you are, that is not useful.

How much do you trust the fibers' accuracy? I have to tell you a story to give you a sense of why we sometimes trust it. There is anatomical knowledge about certain fiber systems that we know the function of. Mainly these are fiber systems that connect what we call primary cortical areas, such as the motor cortex. Obviously a large part of the brain is involved in the motor function, but the primary motor cortex is like the end-zone from where projections go to your muscles. We know that if there is damage to this fiber tract, coming from the primary motor cortex, we know that the damage will probably be permanent. This is opposed to other tracts that you can damage without any clinical deficits. So



(a) When using navigate tip, the slice that intersects the pointer tip is shown.

(b) When using navigate projection, the slice that intersects the virtual extension of the tip is shown.

Figure A.1: Navigate tip and navigate projection. The blue rod represents the physical pointer, the yellow rod represents a virtual extension.

there is the motor fiber tract, the optical radiation, and there are two fiber tracts for language for which there is evidence that if you lesion them, you get severe deficits. So what we did in the beginning when we had this new tool, tractography, with an unspecified error, was to get some experience with cases. We started with these four fiber tracts, of which we know that we could find them in the OR. We can find the motor tracts, so we have a form of validation. You can stimulate the motor tract. Same for vision and language, they can be found during awake surgery. So what we did over the years, we have done it for about eight or ten years now, is that we started putting these in the navigational machine, using them in awake surgery. You have to know that awake surgery is also a procedure which in itself has errors. But if you stimulate some part of the brain, and someone gets motor deficits or language deficits, you at least know that you are in the vicinity of important areas. Over the years we have built the experience that we can find these tracts within a certain margin. We got some reassurance that this really meant something real. We don't trust it to the millimeter, because of uncertainties with diffusion MRI and tractography, and also because the navigational error adds up to that. So anywhere within one centimeter of such a tract, we will start stimulating. But in our experience, if the tract is about a centimeter away from the border of the tumor, we trust it now, at least for the four tracts, and we don't do it awake any more. So we have some level of confidence. *So one centimeter?* Yes, that is sort of a guideline. That can vary, obviously, if tumors have a lot of mass effect or if we don't see the tract because it is very difficult to image. Then you know if patient has no deficits while perhaps the tract is there (false negative). Then again, in most cases it will work. So what we did, is we implemented these four tracts into a clinical protocol and we have people that will do the analysis. And now we try to automate this, and are adding new fiber tracts to it. We are currently interested in a fifth tract and are now building up experience with it in the same way that we did with the other four. So just imaging a tract, putting it in a navigational system and saying to a surgeon 'OK, this is a tract', I think that is fairly useless. You have to have some a priori knowledge of the tract, of the anatomy, and preferably also experience in awake mapping. And that is gaining more and more evidence.

So you decide to operate under anesthesia when the tumor is sufficiently far away from the fiber tracts? Yes. Here I have a case where the border of the tumor is more or less a centimeter away from the corticospinal tract, so the motor tract. In this case we did the surgery not awake, because it was fairly distant from the tumor border, within the margin of error. Here is another case of how you can use tractography. Here are three glioma patients before surgery. All of them are low-grade gliomas, but in two of the cases the tract is running through the tumor, and in the third case the tract is displaced. So you see that the tumors have different behavior. Sometimes there is predominantly mass effect that are pushing away the tumor. Sometimes there is no mass effect, but the tract is just running through the tumor. Pathologically they are all the same tumors, low grade gliomas, but they have a different meaning. The one where the tract is running through the tumor you can't get out. When we stimulated the tumor in that case, we found that the tract indeed did run through the tumor. So it has a predictive value before surgery as well. In the other two cases we could take it all of the tumor out. So fiber tracking gives you additional information about the patient, and you can decide to leave a remnant of the tumor in. We have a number of cases where we confirmed this. That is another way of using tractography data, not during surgery but before. During surgery, when you are approaching a certain tract, you start stimulating.

Can you describe a recent situation in which neuronavigation influenced your decision-making during surgery? We dare to operate cases under anesthesia, so not awake, because of our experience with tractography. On the other hand, it gives us information during surgery so we can speed up the procedure and know when we have to stimulate. *Can you explain why it is sped up during surgery?* Because you have to remove this part of the tumor, and it is a very big tumor, and only when you are here in the depth, when the tumor is out, then you know that there is a tract running underneath this tumor. So you can remove a big part of the tumor and then start stimulating where the tract is. It gives you directions that in the other part you don't have to worry because there is no tract there that is relevant for surgery. It is like navigation with extra information regarding the surroundings. When you talk to other surgeons, they will say that they know the tract is there because of anatomical principles, they should run through this and that corridor. That could be, people that have all the anatomy in their head. Still, I think for most surgeons, it would be very beneficial to have as an add-on this information available because it is just anatomy which is very useful to you.

During the surgery, how do you validate that the navigation is still correct? Sometimes you have a tumor border that is clearly visible. If you are working along the tumor border, and you see on the navigation system that you are still along the tumor border, you know there is not much shift. Sometimes you enter the ventricle. Then, too, you check with the navigation system if you are indeed in the ventricle. There are some known anatomical landmarks that you can check with your navigation. Not always, but they are there sometimes. You can use them to check, at that moment, how accurate the system is. It is not always possible though. *And say there has been a big shift, how do you compensate for that?* Some people say that if you want to use tractography during surgery and you have shift, it is useless. I think that that is not true, because if you have shift, still you know in what direction you are working. And you still know that you are going to approach a tract. And if there is reasonable evidence that there is a big shift of about a centimeter, then you start stimulating a centimeter or one and a half centimeter before, but you are still orientated. This is because it is fairly predictable in which direction the brain will shift. The directional error is not too much, so you always now what you are going to approach. Whether or not is has shifted a bit, you can correct for that in your head, by just stimulating earlier than you might do if there is no shift.

Are there situations in which you would like to look at the monitor but are unable to do so? Yes, I would like to have all the information in my ocular, like a heads-up display, but we don't have that. Actually, if you want you can display some information within your ocular, but then you have to segment structures. So you have the focus of the microscope, and within the plane of the microscope you can project contours with a laser. But that is not in 3D, so I would never use it. I don't think it is very useful. Ideally you would have a heads-up display so that you don't have to look at the navigational system, you can see it in your live view. You can have some information in the microscope. If you segment the tumor, you can see the segmented tumor in the focus of the microscope. Ideally I would have through the microscope an option, like a switch, and see the 3D surroundings as augmented information in the system. Then I don't have to look at the screen. But that is not there yet.

Are there situations in which you would like to know where the pointer has been previously? That is an interesting question. Not for the resection itself, I guess. No, because why do you use the pointer, you use it to pinpoint the markers, the snapshots of the markers. If we would have coordinates of these markers, that would be very interesting for us. *The markers?* For our research, if we stimulate the language tracts, and if we have the coordinates in the MRI space of the patient, we can then quantify the relationship between the pointing device and the actual tract. For research purposes you can imagine that would be very helpful for us. *You can already do that, right?* We don't have the coordinates for that. We'll have that, perhaps with the SteathLink. What we do now, is that we take snapshots, and are busy writing an algorithm that matches the snapshots to the actual coordinates of the MRI. *How about where the pointer has been, in a more short term, like 30 seconds?* I don't see any benefit in that.

What would the ideal system look like for you? You have two different types of users for the system. There is me, I'm a bit experienced, because I use this tractography, I do research with it, and I know what these tracts mean. But many colleagues of mine don't have this experience and I still want them to use this system. So ideally, that should be a completely automatized system with the tracts imported in it. And also, which is the difficult part, some kind of warning that it is not 'what you see is what you get'. It is the result of a complex mathematical procedure, these nice fiber tracts. It is not like a dissection of anatomy. Ideally they are both the same, but they are not actually. There should be some visualization measure that people automatically realize that there is a margin of error around it, could be false negative, false positive etc. but still I think the information is beneficial for them. So the ideal system would be a system where the user would not have to do the analysis. If you now buy a commercial system, like the Medtronic, you have to get the MRI from their Philips scanner, you have to import it with the diffusion MRI, and then do the tracking yourself and import it in their system. Then everybody does his or her own tracking, but most people don't have the knowledge to do it properly. I think that for these users, and that is 90 to 95 percent of them, it should be a completely automatized system, with also some sort of a warning (about the uncertainty). Then you have the expert user, who always wants to push further, who is able to tweak the results. That would be the ideal situation.

What kind of tweaks are you thinking about? Well, you know that the tracts are not always correct, for instance in the case of edema. You have to manipulate the FA value or the parameters of the system. So you can imagine that if you don't get what you expect, then you want to see for yourself whether or not you can do better. But basic stuff, like the basic four or five tracts that we have experience with, these should be automatized, and for new ones that we want to gain experience with, you need to have some options that we can do the analysis ourselves. It would be good for you to visit our radiology people to see how they do the tractography. You see that they have to push all sorts of buttons, like first doing registration, then select the region of interest, and so on. We have a protocol, but sometimes, for example in the optical radiation, they know they have to tweak some parameters to get a better result. *And in terms of visualization?* I would like to have a visualization in which I do not only see the tracts on the orthogonal planes, but I would like to have the brains transparent, with the tracts in 3D, so that if I navigate and I'm looking in a certain direction that I can see what kind of tracts I am approaching. That would be very beneficial to me, because that helps us enormously in anticipating where in the depth these tracts are coming up. *Do you think that would save time during surgery?* I think that would make my life easier, perhaps that saves time too. But I sometimes find it difficult from the orthogonal planes, and would be easier with a 3D view. That would be beneficial to us. Perhaps the Stealth also has a 3D mode because you can also see the tracts in 3D. I actually never used it, because this mode is not so good. You should look at what they are offering now. *What is not good about it?* They have this spaghetti mode, but it does not blend. It is either on or off so if you have three tracts it all adds up and you can't see anything anymore.

B

Evaluation interview

Imagine having no practice with either the standard system or with this one. Would you prefer having the main, side and top views, or would you prefer the standard anatomical slices? In your visualization, the side and top views are also depending on the surgical view. That means that with every patient, and every time you change the microscope, your view changes. With the old system, the view stays more or less the same every time you change the microscope. I don't know what the best solution should be as that also depends on other factors, but my guess is that the new system has a long learning curve. It is really difficult for me to say right now.

Is the difficult part that the anatomy looks different? Yes. Your immediate orientation towards known anatomical structures is more difficult in your setup than in the setup that we are used to because we have looked at that for ages. So it is not to say that your version is "less", but I think it needs a learning curve and training to see what people would prefer. Right now I really cannot say what the best method is. Before surgery, we can see when a tumor is close to a certain structure, and we have that same view intraoperatively. Your visualization would change every time I change the microscope, and all the screens would look different. Having one 3D view that never changes could help.

You can compare it to a car navigation. One possible view is having north always up, and another one is having the driving direction to be always up. When you are used to navigating on one of these, it might be difficult to navigate using the other one. These things should be tested in practice. I think it would be a good idea to have two screens in the OR. The classical screen, and when we have time, we do ten minutes in your setup. This would get you new feedback, and perhaps there are a lot of advantages in this new view. That is, if you provide enough anatomical orientations, because the difficult thing is having a different orientation every time. When I look towards the classical screen, I see myself approaching the tumor because that screen is not changing and my pointer is the only variable. In your system there are two variables: the orientation of the anatomy, and the pointer. Perhaps it is better that the views are automatically aligned with the surgical microscope. You did some great visualizations, but it needs practice.

Compared to what you are used to, was navigation easier or more difficult? In both methods, it can be difficult to orientate yourself. The relation of the old system towards the anatomy is not one-to-one. The benefit of your system is that once we get used to it, it aligns with the view that you actually see. In the end, this could be very beneficial, but it depends on the situation and how we experience it in surgery. There is not one answer, but I think it is a very good approach towards a new view on where structures are.

Which task had your preference? The one which only showed the intersections. It could that that one was easiest because I had already practiced with the other two before that. The one with the partial hulls was the most difficult one. *Why was it most difficult using the partial hulls?* Because you see less of the tract.

When using the tract intersections, was the location of the tracts clear? Yes, they were clear.

Did the transparent hulls give a good perception of the location of the tracts? Yes, but just as with the other tasks, I also peeked on the other two views. I was continuously going around on these screens. For some reason, when we are looking at the old system, we take in the image as a whole. I'm not used to your visualization, so I have to sequentially look at the different views. That is what makes it difficult right now, but with some training yours might be preferable.

Would you prefer to have the transparent hulls or the streamlines? I think the hulls are a very good visualization, because they show the uncertainty. Perhaps in two colors instead of three, because this is just one fiber tract, and normally we have four or five.

Would you prefer the intersections or the transparent hulls? The intersections make the task easier, but in real life, I guess you need the hulls. I want to see this 3D structure emerge when you approach something. In the end I would prefer a 3D view in which you see the fibers come up in the depth. These hulls would be important for that, not just the intersections. Perhaps they made the task easier for me because I'm not practiced with your system, but in the end you need them in 3D.

Do the intersections show the fiber uncertainty at the most important location? Not necessarily, because it could still be very far away from the pointer. When the fiber curves below the pointer, it shows up at the sides of the intersection, but could run right below the pointer.

In that case, you would also see it in the other views as those are also intersections. If the tract is in line with the pointer, you would see the tract coming up on the other two views. For some reason I think we have to move towards an implementation with one view that is most important, and perhaps some side views. Now I have to pinpoint between all of these views.

Was the outline effective for the shape perception of the fiber? Yes, but I'm not sure if it would work if there were more fibers.

Would you prefer to see all the streamlines, or only the outline? In that case I would prefer all the streamlines, because this shape would imply that if there are one or two outliers, this shape would include them, right? *No, the outline comes from one of the uncertainty hulls, so if the hull does not include the outlier, then neither does the outline.* The other one might have too much information, because you want to also have information on where the true fiber tract is running. This is also giving you the uncertainty, so it is actually an overestimation of where you want to be. Just the outline would not be good for me, I think.

Did the partial surface hulls give you a good perception of the location of the tract? It is difficult to give a definite answer on that after such a short period of practice. It could be a nice method to visualize when you approach something, but then again, we have to see it in real life. It has potential, in particular when there are a lot of tracts, and you don't want to visualize them all at the same time, so you don't get distracted. When I'm working in a certain area, I could choose to only visualize the fiber when I'm coming up to it. I think that it is a very good approach.

Would you prefer the streamlines or the partial hulls intraoperatively? I do not really know. Perhaps as an option, because it is so much information all the time, and when you concentrate on removing the tumor, you could have an option to only see the tract when I'm approaching it. Then I can concentrate on the task of removing the tumor, why not?

Did the distance meter help you in performing the task, and would it be helpful in real surgery? Yes, it did help me in the task. I don't know about real surgery, but I do think you need to have some warning system. We don't have a warning system now. The downside is that you have to keep track of four screens: three screens and you distance meter. That is a lot.

How about another way such as auditory or haptic feedback? Or maybe just change the color of the background. Now I have to move my attention to another system, and I am not looking at the anatomy any more. Maybe the pointer could change color or something.

Was the task representative for a surgery? No. Well, you did a great job, but representative is a large word. It would be great if we could test parts of this in an actual surgery. You have a lot of hypotheses, A lot of ideas, a lot of good things, but we have to test all this in the OR. There you would get real answers.

Would this visualization make a less experienced surgeon aware of the uncertainty? Yes.

Should fiber uncertainty be shown intraoperatively? Yes.

Are these methods a good way of showing that uncertainty? Yes. I'm not saying it is the final system, but it is a good first step to visualize uncertainty. I think it is important.

What did you like about the visualization? It is a new approach. I told you about the focus, so looking along the microscope, and then moving your instrument as a pointer. So your approach is all right, the uncertainty visualization is very nice, it is a new approach towards navigation.

Does the visualization give a good impression of the uncertainty? Yes, I think so, with all the colors and the distance meter.

Does three levels of uncertainty make sense? I think it is always best to have two categories: yes, no, low, high, left, right. Perhaps you should start with two levels of uncertainty. Or one level of uncertainty and one fiber tract. That is easy to understand for users.

Would a safe zone make sense? The problem is that you need to raise awareness among surgeons that this is just visualization of statistics. That is the difficult part. You should see it as a warning system, and I would start with two levels.

Which new features of the visualization would be useful during surgery right now? Although complex, we should work out how to use the different angle towards the anatomy. The 3D-like visualizations of the uncertainty would be great. I still have difficulty doing the task, it is not intuitive enough, so something should be done about that. If less experienced surgeons have to work with your system in this state, I don't think many surgeons will opt for it. It is a huge step from the classical system.

You could also keep the planes the same but only add the partial hulls, for instance. Right now we have four windows, you could start with taking one window and replacing it with a view of your own.

Do you see other applications for this system? Anatomy training. Using a phantom could be a good way of getting people acquainted with the anatomy.

Do you have any last remarks? No, great work! I did not expect this, so I think you have made great progress. I am really impressed. It gives us a platform to build on and to move further. That is really great.

Bibliography

[1] P.J. Basser, J. Mattiello, and D. Lebihan. Estimation of the effective self-diffusion tensor from the nmr spin echo. *Journal of Magnetic Resonance, Series B*, 103(3):247–254, 1994. ISSN 1064-1866. doi:https://doi.org/10.1006/jmrb.1994.1037. URL https://www.sciencedirect.com/science/article/pii/S1064186684710375.

[2] P.J. Basser, J. Mattiello, and D. LeBihan. Mr diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66(1):259–267, 1994. ISSN 0006-3495. doi:https://doi.org/10.1016/S0006-3495(94)80775-1. URL https://www.sciencedirect.com/science/article/pii/S0006349594807751.

[3] Silvia Born, Werner Jainek, Mario Hlawitschka, Gerik Scheuermann, Christos Trantakis, Jürgen Meixensberger, and Dirk Bartz. Multimodal visualization of dti and fmri data using illustrative methods. In Hans-Peter Meinzer, Thomas Martin Deserno, Heinz Handels, and Thomas Tolxdorff, editors, *Bildverarbeitung für die Medizin 2009*, pages 6–10, Berlin, Heidelberg, 2009. Springer Berlin Heidelberg. ISBN 978-3-540-93860-6.

[4] R. Brecheisen. *Visualization of uncertainty in fiber tracking based on diffusion tensor imaging*. PhD thesis, Biomedical Engineering, 2012.

[5] R. Brecheisen, B. Platel, B. M. ter Haar Romeny, and A. Vilanova. Illustrative uncertainty visualization of dti fiber pathways. *The Visual Computer*, 29(4):297–309, Apr 2013. ISSN 1432-2315. doi:10.1007/s00371-012-0733-9. URL https://doi.org/10.1007/s00371-012-0733-9.

[6] Ross Brown. Animated visual vibrations as an uncertainty visualisation technique. In *Proceedings of the 2nd International Conference on Computer Graphics and Interactive Techniques in Australasia and South East Asia*, GRAPHITE '04, page 84–89, New York, NY, USA, 2004. Association for Computing Machinery. ISBN 1581138830. doi:10.1145/988834.988849. URL https://doi.org/10.1145/988834.988849.

[7] Kai Bürger, Roland Fraedrich, Dorit Merhof, and Rüdiger Westermann. Instant visitation maps for interactive visualization of uncertain particle trajectories. In Pak Chung Wong, David L. Kao, Ming C. Hao, Chaomei Chen, Robert Kosara, Mark A. Livingston, Jinah Park, and Ian Roberts, editors, *Visualization and Data Analysis 2012*, volume 8294, pages 262 – 273. International Society for Optics and Photonics, SPIE, 2012. doi:10.1117/12.906872. URL https://doi.org/10.1117/12.906872.

[8] Weri Chen, Song Zhang, Stephfan Correia, and David S. Ebert. Abstractive representation and exploration of hierarchically clustered diffusion tensor fiber tracts. *Computer Graphics Forum*, 27(3):1071–1078, 2008. doi:https://doi.org/10.1111/j.1467-8659.2008.01244.x. URL https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-8659.2008.01244.x.

[9] Xiaolei Chen, Daniel Weigel, Oliver Ganslandt, Rudolf Fahlbusch, Michael Buchfelder, and Christopher Nimsky. Diffusion tensor–based fiber tracking and intraoperative neuronavigation for the resection of a brainstem cavernous angioma. *Surgical Neurology*, 68(3):285–291, 2007. ISSN 0090-3019. doi:https://doi.org/10.1016/j.surneu.2007.05.005. URL https://www.sciencedirect.com/science/article/pii/S009030190700537X.

[10] Swathi Chidambaram, Vito Stifano, Michelle Demetres, Mariano Teyssandier, Maria Chiara Palumbo, Alberto Redaelli, Alessandro Olivi, Michael L.J. Apuzzo, and Susan C. Pannullo. Applications of augmented reality in the neurosurgical operating room: A systematic review of the literature. *Journal of Clinical Neuroscience*, 91:43–61, 2021. ISSN 0967-5868. doi:https://doi.org/10.1016/j.jocn.2021.06.032. URL https://www.sciencedirect.com/science/article/pii/S0967586821003271.

[11] Volker Arnd Coenen, Timo Krings, Hubertus Axer, Jürgen Weidemann, Heidi Kränzlein, Franz-Josef Hans, Armin Thron, Joachim Michael Gilsbach, and Veit Rohde. Intraoperative three-dimensional visualization of the pyramidal tract in a neuronavigation system (ptv) reliably predicts true position of principal motor pathways. *Surgical Neurology*, 60(5):381–390, 2003. ISSN 0090-3019. doi:https://doi.org/10.1016/S0090-3019(03)00392-6. URL `https://www.sciencedirect.com/science/article/pii/S0090301903003926`.

[12] David C Preston. Magnetic resonance imaging (mri) of the brain and spine: Basics. `https://case.edu/med/neurology/NR/MRI%20Basics.htm`, 2016. Accessed: 2022-06-13.

[13] Doug DeCarlo, Adam Finkelstein, Szymon Rusinkiewicz, and Anthony Santella. Suggestive contours for conveying shape. *ACM Trans. Graph.*, 22(3):848–855, jul 2003. ISSN 0730-0301. doi:10.1145/882262.882354. URL `https://doi.org/10.1145/882262.882354`.

[14] Maxime Descoteaux. *High Angular Resolution Diffusion Imaging (HARDI)*, pages 1–25. John Wiley & Sons, Ltd, 2015. ISBN 9780471346081. doi:https://doi.org/10.1002/047134608X.W8258. URL `https://onlinelibrary.wiley.com/doi/abs/10.1002/047134608X.W8258`.

[15] F. Enders, S. Iserhardt-Bauer, P. Hastreiter, C. Nimsky, and T. Ertl. Hardware-accelerated glyph based visualization of major white matter tracts for analysis of brain tumors. In Robert L. Galloway Jr. and Kevin R. Cleary, editors, *Medical Imaging 2005: Visualization, Image-Guided Procedures, and Display*, volume 5744, pages 504 – 511. International Society for Optics and Photonics, SPIE, 2005. doi:10.1117/12.595511. URL `https://doi.org/10.1117/12.595511`.

[16] F. Enders, N. Sauber, D. Merhof, P. Hastreiter, C. Nimsky, and M. Stamminger. Visualization of white matter tracts with wrapped streamlines. In *VIS 05. IEEE Visualization, 2005.*, pages 51–58, Oct 2005. doi:10.1109/VISUAL.2005.1532777.

[17] Maarten H. Everts, Henk Bekker, Jos B.T.M. Roerdink, and Tobias Isenberg. Depth-dependent halos: Illustrative rendering of dense line data. *IEEE Transactions on Visualization and Computer Graphics*, 15(6):1299–1306, 2009. ISSN 1077-2626. Relation: http://www.rug.nl/informatica/onderzoek/bernoulli Rights: University of Groningen, Johann Bernoulli Institute for Mathematics and Computer Science; IEEE Information Visualization Conference/IEEE Visualization Conference ; Conference date: 11-10-2009.

[18] Florian Ferstl, Kai Bürger, and Rüdiger Westermann. Streamline variability plots for characterizing the uncertainty in vector field ensembles. *IEEE Transactions on Visualization and Computer Graphics*, 22(1):767–776, 2016. doi:10.1109/TVCG.2015.2467204.

[19] Mathias Goldau, Alexander Wiebel, Mario Hlawitschka, Gerik Scheuermann, and Marc Tittgemeyer. Visualizing dti parameters on boundary surfaces of white matter fiber bundles. In *Proceedings of the 12th IASTED International Conference on Computer Graphics and Imaging, CGIM 2011*, 02 2011. doi:10.2316/P.2011.722-012.

[20] G. Grigoryan and P. Rheingans. Point-based probabilistic surfaces to show surface uncertainty. *IEEE Transactions on Visualization and Computer Graphics*, 10(5):564–573, 2004. doi:10.1109/TVCG.2004.30.

[21] Pedro Hermosilla, Ralph Brecheisen, Pere-Pau Vázquez, and Anna Vilanova. Uncertainty Visualization of Brain Fibers. In Isabel Navazo and Gustavo Patow, editors, *Spanish Computer Graphics Conference*. The Eurographics Association, 2012. ISBN 978-3-905673-92-0. doi:10.2312/LocalChapterEvents/CEIG/CEIG12/031-040.

[22] Thomas Höllt, Ahmed Magdy, Guoning Chen, Ganesh Gopalakrishnan, Ibrahim Hoteit, Charles D. Hansen, and Markus Hadwiger. Visual analysis of uncertainties in ocean forecasts for planning and operation of off-shore structures. In *2013 IEEE Pacific Visualization Symposium (PacificVis)*, pages 185–192, Feb 2013. doi:10.1109/PacificVis.2013.6596144.

[23] Tobias Isenberg. A survey of illustrative visualization techniques for diffusion-weighted mri tractography. In Ingrid Hotz and Thomas Schultz, editors, *Visualization and Processing of Higher Order Descriptors for Multi-Valued Data*, pages 235–256, Cham, 2015. Springer International Publishing. ISBN 978-3-319-15090-1.

[24] W. M. Jainek, S. Born, D. Bartz, W. Straßer, and J. Fischer. Illustrative hybrid visualization and exploration of anatomical and functional brain data. *Computer Graphics Forum*, 27(3):855–862, 2008. doi:https://doi.org/10.1111/j.1467-8659.2008.01217.x. URL `https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-8659.2008.01217.x`.

[25] Neal F. Johnson. The role of chunking and organization in the process of recall. *Psychology of Learning and Motivation*, 4:171–247, 1970.

[26] Derek K. Jones. Determining and visualizing uncertainty in estimates of fiber orientation from diffusion tensor mri. *Magnetic resonance in medicine*, 49(1):7–12, Jan 2003. doi:10.1002/mrm.10331. URL `http://www.ncbi.nlm.nih.gov/pubmed/12509814`.

[27] Derek K. Jones. Tractography gone wild: probabilistic fibre tracking using the wild bootstrap with diffusion tensor mri. *IEEE transactions on medical imaging*, 27(9):1268–1274, Sep 2008. doi:10.1109/TMI.2008.922191. URL `http://www.ncbi.nlm.nih.gov/pubmed/18779066`.

[28] Marta Kersten-Oertel, Pierre Jannin, and D. Louis Collins. Dvv: A taxonomy for mixed reality visualization in image guided surgery. *IEEE Transactions on Visualization and Computer Graphics*, 18(2):332–352, 2012. doi:10.1109/TVCG.2011.50.

[29] Ron Kikinis, Steve D. Pieper, and Kirby G. Vosburgh. *3D Slicer: A Platform for Subject-Specific Image Analysis, Visualization, and Clinical Support*, pages 277–289. Springer New York, New York, NY, 2014. ISBN 978-1-4614-7657-3. doi:10.1007/978-1-4614-7657-3_19. URL `https://doi.org/10.1007/978-1-4614-7657-3_19`.

[30] G. Kindlmann and D. Weinstein. Hue-balls and lit-tensors for direct volume rendering of diffusion tensor fields. In *Proceedings Visualization '99 (Cat. No.99CB37067)*, pages 183–524, 1999. doi:10.1109/VISUAL.1999.809886.

[31] Gordon Kindlmann. Superquadric tensor glyphs. In *Proceedings of the Sixth Joint Eurographics - IEEE TCVG Conference on Visualization*, VISSYM'04, page 147–154, Goslar, DEU, 2004. Eurographics Association. ISBN 390567307X.

[32] Gordon Kindlmann, Xavier Tricoche, and Carl-Fredrik Westin. Delineating white matter structure in diffusion tensor mri with anisotropy creases. *Medical Image Analysis*, 11(5):492–502, 2007. ISSN 1361-8415. doi:https://doi.org/10.1016/j.media.2007.07.005. URL `https://www.sciencedirect.com/science/article/pii/S1361841507000746`. Special Issue on the Ninth International Conference on Medical Image Computing and Computer-Assisted Interventions - MICCAI 2006.

[33] Masashi Kinoshita, Katsuyoshi MIYASHITA, Taishi TSUTSUI, Takuya FURUTA, and Mitsutoshi Nakada. Critical neural networks in awake surgery for gliomas. *Neurologia medico-chirurgica*, 56, 06 2016. doi:10.2176/nmc.ra.2016-0069.

[34] Suresh Lodha, Alex Pang, R.E. Sheehan, and Craig Wittenbrink. Uflow: Visualizing uncertainty in fluid flow. In *Proceedings of Seventh Annual IEEE Visualization '96*, volume 1996, pages 249 – 254, 12 1996. doi:10.1109/VISUAL.1996.568116.

[35] D. Merhof, M. Meister, E. Bingöl, C. Nimsky, and G. Greiner. Isosurface-based generation of hulls encompassing neuronal pathways. *Stereotactic and Functional Neurosurgery*, 87(1):50–60, 2009. ISSN 1011-6125. doi:10.1159/000195720. URL `https://www.karger.com/DOI/10.1159/000195720`.

[36] Dorit Merhof, Martin Meister, Ezgi Bingöl, Peter Hastreiter, Christopher Nimsky, and Günther Greiner. Generation of hulls encompassing neuronal pathways based on tetrahedralization and 3d alpha shapes. In Alexander Horsch, Thomas M. Deserno, Heinz Handels, Hans-Peter Meinzer, and Thomas Tolxdorff, editors, *Bildverarbeitung für die Medizin 2007*, pages 308–312, Berlin, Heidelberg, 2007. Springer Berlin Heidelberg. ISBN 978-3-540-71091-2.

[37] Uli Mezger, Claudia Jendrewski, and Michael Bartels. Navigation in surgery. *Langenbeck's Archives of Surgery*, 398(4):501–514, Apr 2013. ISSN 1435-2451. doi:10.1007/s00423-013-1059-4. URL `https://doi.org/10.1007/s00423-013-1059-4`.

[38] Mahsa Mirzargar, Ross T. Whitaker, and Robert M. Kirby. Curve boxplot: Generalization of boxplot for ensembles of curves. *IEEE Transactions on Visualization and Computer Graphics*, 20(12): 2654–2663, 2014. doi:10.1109/TVCG.2014.2346455.

[39] Tamara Munzner. *Visualization Analysis & Design*, chapter 1, pages 1–18. CRC Press, 2015.

[40] Christopher Nimsky, Oliver Ganslandt, Frank Enders, Dorit Merhof, Thilo Hammen, and Michael Buchfelder. Visualization strategies for major white matter tracts for intraoperative use. *International Journal of Computer Assisted Radiology and Surgery*, 1(1):13–22, 2006. doi:10.1007/s11548-006-0003-2.

[41] Christopher Nimsky, Oliver Ganslandt, Dorit Merhof, A. Gregory Sorensen, and Rudolf Fahlbusch. Intraoperative visualization of the pyramidal tract by diffusion-tensor-imaging-based fiber tracking. *NeuroImage*, 30(4):1219–1229, 2006. ISSN 1053-8119. doi:https://doi.org/10.1016/j.neuroimage.2005.11.001. URL `https://www.sciencedirect.com/science/article/pii/S1053811905024468`.

[42] Christopher Nimsky, Oliver Ganslandt, Peter Hastreiter, Ruopeng Wang, Thomas Benner, A. Gregory Sorensen, and Rudolf Fahlbusch. Preoperative and intraoperative diffusion tensor imaging-based fiber tracking in glioma surgery. *Neurosurgery*, 61(1 Suppl):178–85; discussion 186, Jul 2007. doi:10.1227/01.neu.0000279214.00139.3b. URL `https://doi.org/10.1227/01.neu.0000279214.00139.3b`.

[43] Christopher "Nimsky, Miriam Bauer, and Barbara" Carl. *Merits and Limits of Tractography Techniques for the Uninitiated*, pages 37–60. Springer International Publishing, Cham, 2016. ISBN 978-3-319-21359-0. doi:10.1007/978-3-319-21359-0_2. URL `https://doi.org/10.1007/978-3-319-21359-0_2`.

[44] R.J.G. Otten, A. Vilanova, and H.M.M. Wetering, van de. Illustrative white matter fiber bundles. *Computer Graphics Forum*, 29(3):1013–1022, 2010. ISSN 0167-7055. doi:10.1111/j.1467-8659.2009.01688.x.

[45] Malte Ottenhausen, Sandro M. Krieg, Bernhard Meyer, and Florian Ringel. Functional preoperative and intraoperative mapping and monitoring: increasing safety and efficacy in glioma surgery. *Neurosurgical focus*, 38(1):E3, Jan 2015. doi:10.3171/2014.10.FOCUS14611. URL `http://www.ncbi.nlm.nih.gov/pubmed/25552283`.

[46] T.H.J.M. Peeters, V. Prckovska, M. van Almsick, A. Vilanova, and B.M. ter Haar Romeny. Fast and sleek glyph rendering for interactive hardi data exploration. In *2009 IEEE Pacific Visualization Symposium*, pages 153–160, 2009. doi:10.1109/PACIFICVIS.2009.4906851.

[47] Terry M Peters. Image-guidance for surgical procedures. *Physics in Medicine and Biology*, 51(14): R505–R540, jun 2006. doi:10.1088/0031-9155/51/14/r01. URL `https://doi.org/10.1088/0031-9155/51/14/r01`.

[48] Tobias Pfaffelmoser, Matthias Reitinger, and Rüdiger Westermann. Visualizing the positional and geometrical variability of isosurfaces in uncertain scalar fields. *Computer Graphics Forum*, 30(3):951–960, 2011. doi:https://doi.org/10.1111/j.1467-8659.2011.01944.x. URL `https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-8659.2011.01944.x`.

[49] Stefano Pisa, Paolo Bernardi, and Emanuele Piuzzi. Interaction between the rf field of mri apparatus and pacemakers. In Mithilesh Kumar Das, editor, *Modern Pacemakers*, chapter 11. IntechOpen, Rijeka, 2011. doi:10.5772/13857. URL `https://doi.org/10.5772/13857`.

[50] J. M. Portegies, R. H. J. Fick, G. R. Sanguinetti, S. P. L. Meesters, G. Girard, and R. Duits. Improving fiber alignment in hardi by combining contextual pde flow with constrained spherical deconvolution. *PloS one*, 10(10):e0138122–e0138122, Oct 2015. ISSN 1932-6203. doi:10.1371/journal.pone.0138122. URL `https://doi.org/10.1371/journal.pone.0138122`.

[51] Bernhard Preim and Charl Botha. Chapter 1 - introduction. In Bernhard Preim and Charl Botha, editors, *Visual Computing for Medicine (Second Edition)*, pages 1–11. Morgan Kaufmann, Boston, second edition edition, 2014. ISBN 978-0-12-415873-3. doi:https://doi.org/10.1016/B978-0-12-415873-3.00001-8. URL https://www.sciencedirect.com/science/article/pii/B9780124158733000018.

[52] Bernhard Preim, Alexandra Baer, Douglas Cunningham, Tobias Isenberg, and Timo Ropinski. A survey of perceptually motivated 3d visualization of medical image data. *Computer Graphics Forum*, 35(3):501–525, 2016. doi:https://doi.org/10.1111/cgf.12927. URL https://onlinelibrary.wiley.com/doi/abs/10.1111/cgf.12927.

[53] Christian Rieder, Felix Ritter, Matthias Raspe, and Heinz-Otto Peitgen. Interactive visualization of multimodal volume data for neurosurgical tumor treatment. *Computer Graphics Forum*, 27(3):1055–1062, 2008. doi:https://doi.org/10.1111/j.1467-8659.2008.01242.x. URL https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-8659.2008.01242.x.

[54] Rob van Boxtel, Jeanette Pijnenburg, William Pigmans, Maikel Brands. *ETZ - MRI OVERIG Handleiding Medtronic StealthStation S8*. ETZ, Tilburg, the Netherlands, 2022.

[55] Veit Rohde, Franz-Josef Hans, Lothar Mayfrank, Stephan Dammert, Joachim M. Gilsbach, and Volker A. Coenen. How useful is the 3-dimensional, surgeon's perspective-adjusted visualisation of the vessel anatomy during aneurysm surgery? a prospective clinical trial. *Neurosurgical Review*, 30(3):209–217, Jul 2007. ISSN 1437-2320. doi:10.1007/s10143-007-0076-6. URL https://doi.org/10.1007/s10143-007-0076-6.

[56] T. Schultz, N. Sauber, A. Anwander, H. Theisel, and H.-P. Seidel. Virtual klingler dissection: Putting fibers into context. *Computer Graphics Forum*, 27(3):1063–1070, 2008. doi:https://doi.org/10.1111/j.1467-8659.2008.01243.x. URL https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-8659.2008.01243.x.

[57] Thomas Schultz and Anna Vilanova. Diffusion mri visualization. *NMR in Biomedicine*, 32(4):e3902, 2019. doi:https://doi.org/10.1002/nbm.3902. URL https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/abs/10.1002/nbm.3902. e3902 NBM-16-0157.R2.

[58] Thomas Schultz, Holger Theisel, and Hans-Peter Seidel. Segmentation of DT-MRI Anisotropy Isosurfaces. In K. Museth, T. Moeller, and A. Ynnerman, editors, *Eurographics/ IEEE-VGTC Symposium on Visualization*. The Eurographics Association, 2007. ISBN 978-3-905673-45-6. doi:10.2312/VisSym/EuroVis07/187-194.

[59] Faizan Siddiqui, Thomas Höllt, and Anna Vilanova. A progressive approach for uncertainty visualization in diffusion tensor imaging. *Computer Graphics Forum (online)*, 40(3):411–422, 2021. ISSN 1467-8659. doi:10.1111/cgf.14317.

[60] Faizan Siddiqui, Thomas Höllt, and Anna Vilanova. Uncertainty in the dti visualization pipeline. In Evren Özarslan, Thomas Schultz, Eugene Zhang, and Andrea Fuster, editors, *Anisotropy Across Fields and Scales*, pages 125–148, Cham, 2021. Springer International Publishing. ISBN 978-3-030-56215-1.

[61] Pjotr Svetachov, Maarten H. Everts, and Tobias Isenberg. Dti in context: Illustrating brain fiber tracts in situ. *COMPUTER GRAPHICS FORUM*, 29(3):1023–1032, 2010. ISSN 0167-7055. doi:10.1111/j.1467-8659.2009.01692.x. Relation: http://www.rug.nl/informatica/onderzoek/bernoulli Rights: University of Groningen, Johann Bernoulli Institute for Mathematics and Computer Science.

[62] J.-Donald Tournier, Fernando Calamante, David G. Gadian, and Alan Connelly. Direct estimation of the fiber orientation density function from diffusion-weighted mri data using spherical deconvolution. *NeuroImage*, 23(3):1176–1185, 2004. ISSN 1053-8119. doi:https://doi.org/10.1016/j.neuroimage.2004.07.037. URL https://www.sciencedirect.com/science/article/pii/S1053811904004100.

[63] David S. Tuch. Q-ball imaging. *Magnetic Resonance in Medicine*, 52(6):1358–1372, 2004. doi:https://doi.org/10.1002/mrm.20279. URL https://onlinelibrary.wiley.com/doi/abs/10.1002/mrm.20279.

[64] A. Vilanova, S. Zhang, G. Kindlmann, and D. Laidlaw. *An Introduction to Visualization of Diffusion Tensor Imaging and Its Applications*, pages 121–153. Springer Berlin Heidelberg, Berlin, Heidelberg, 2006. ISBN 978-3-540-31272-7. doi:10.1007/3-540-31272-2_7. URL https://doi.org/10.1007/3-540-31272-2_7.

[65] Robin Walia, Ankit Aggarwal, and Yogita Wadhwa. Investigating eeg characteristics of a pregnant woman. *International Journal of Emerging Research in Management & Technology*, 2:14–19, 12 2013.

[66] Eiju Watanabe, Takashi Watanabe, Shinya Manaka, Yoshiaki Mayanagi, and Kintomo Takakura. Three-dimensional digitizer (neuronavigator): New equipment for computed tomography-guided stereotaxic surgery. *Surgical Neurology*, 27(6):543–547, 1987. ISSN 0090-3019. doi:https://doi.org/10.1016/0090-3019(87)90152-2. URL https://www.sciencedirect.com/science/article/pii/0090301987901522.

[67] F Weiler, HK Hahn, A Köhn, O Friman, J Klein, and H Peitgen. Dealing with inaccuracies in multimodal neurosurgical planning – a preliminary concept. In *Proceedings of the 22nd International Congress and Exhibition of Computer Assisted Radiology and Surgery*, pages 77–78, 2008.

[68] A. Wenger, D.F. Keefe, S. Zhang, and D.H. Laidlaw. Interactive volume rendering of thin thread structures within multivalued scientific data sets. *IEEE Transactions on Visualization and Computer Graphics*, 10(6):664–672, 2004. doi:10.1109/TVCG.2004.46.

[69] Carl-Fredrik Westin, Stephan E. Maier, B. Khidhir, Peter Everett, Ferenc A. Jolesz, and Ron Kikinis. Image processing for diffusion tensor magnetic resonance imaging. In Christopher J. Taylor and Alan C. F. Colchester, editors, *Medical Image Computing and Computer-Assisted Intervention - MICCAI'99, Second International Conference, Cambridge, UK, September 19-22, 1999, Proceedings*, volume 1679 of *Lecture Notes in Computer Science*, pages 441–452. Springer, 1999. doi:10.1007/10704282_48. URL https://doi.org/10.1007/10704282_48.

[70] Ross T. Whitaker, Mahsa Mirzargar, and Robert M. Kirby. Contour boxplots: A method for characterizing uncertainty in feature sets from simulation ensembles. *IEEE Transactions on Visualization and Computer Graphics*, 19(12):2713–2722, 2013. doi:10.1109/TVCG.2013.143.

[71] Brandon Whitcher, David S. Tuch, Jonathan J. Wisco, A. Gregory Sorensen, and Liqun Wang. Using the wild bootstrap to quantify uncertainty in diffusion tensor imaging. *Human brain mapping*, 29(3):346–362, Mar 2008. doi:10.1002/hbm.20395. URL https://doi.org/10.1002/hbm.20395.

[72] Song Zhang, C. Demiralp, and D.H. Laidlaw. Visualizing diffusion tensor mr images using streamtubes and streamsurfaces. *IEEE Transactions on Visualization and Computer Graphics*, 9(4):454–462, 2003. doi:10.1109/TVCG.2003.1260740.

[73] Tilen Žele, Boštjan Matos, Jernej Knific, Fajko F. Bajrović, and Borut Prestor. Use of 3d visualisation of medical images for planning and intraoperative localisation of superficial brain tumours: our experience. *British Journal of Neurosurgery*, 24(5):555–560, 2010. doi:10.3109/02688697.2010.496876. URL https://doi.org/10.3109/02688697.2010.496876.