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**SUPPORTING QUANTITATIVE VISUAL ANALYSIS
IN MEDICINE AND BIOLOGY
IN THE PRESENCE OF DATA UNCERTAINTY**

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in Medicine and Biology
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ABSTRACT

The advents of technologies have led to tremendous increases in the diversity and size of the available data. In the field of medicine, the advancements in medical imaging technologies have dramatically improved the quality of the acquired data, such as a higher resolution and higher signal-to-noise ratio. In addition, the dramatic reduction of the acquisition time has enabled the studies of organs under function. At the same pace, the progresses in the field of biology and bioinformatics have led to stable automatic algorithms for the generation of biological data. As the amount of the available data and the complexity increase, there have been great demands on efficient analysis and visualization techniques to support quantitative visual analysis of the huge amount of data that we are facing.

This thesis aims at supporting quantitative visual analysis in the presence of data uncertainty within the context of medicine and biology. In this thesis, we present several novel analysis techniques and visual representations to achieve these goals. The results presented in this thesis cover a wide range of applications, which reflects the interdisciplinary nature of scientific visualization, as visualization is not for the sake of visualization. The advances in visualization enable the advances in other fields.

In typical clinical applications or research scenarios, it is common to have data from different modalities. By combining the information from these data sources, we can achieve better quantitative analysis as well as visualization. Nevertheless, there are many challenges involved along the process such as the co-registration, differences in resolution, and signal-to-noise ratio. We propose a novel approach that uses light as an information transporter to address the challenges involved when dealing with multimodal data.

When dealing with dynamic data, it is essential to identify features of interest across the time steps to support quantitative analyses. However, this is a time-consuming process and is prone to inconsistencies and errors. To address this issue, we propose a novel technique that enables automatic tracking of identified features of interest across time steps in dynamic datasets.

Although technological advances improve the accuracy of the acquired data, there are other sources of uncertainty that need to be taken into account. In this thesis, we propose a novel approach to fuse the derived uncertainty from different sophisticated algorithms in order to achieve a new set of outputs with a lower level of uncertainty. In addition, we also propose a novel visual representation that not only supports comparative visualization, but also conveys the uncertainty in the parameters of a complex system.

Over past years, we have witnessed the rapid growth of available data in the field of biology. The sequence alignments of the top 20 protein domains and families have a large number of sequences, ranging from more than 70,000 to approximately 400,000 sequences. Consequently, it is difficult to convey features using the traditional representation. In this thesis, we propose a novel

representation that facilitates the identification of gross trend patterns and variations in large-scale sequence alignment data.

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CONTENTS

Abstract	i
Acknowledgments	iii
List of publications	iv
1 Introduction	1
1.1 Visualization in Medicine and Biology	2
1.1.1 Visualization in Medicine	2
1.1.2 Visualization in Biology	11
1.2 Research Challenges	13
1.2.1 Interdisciplinary Collaboration	13
1.2.2 Interactive Visual Analysis	14
1.2.3 Large and Dynamic Data	18
1.2.4 Uncertainty Visualization	21
1.3 Contributions	24
2 Large-Scale MSA Visualization through GVF	29
2.1 Introduction	29
2.2 Related Work	31
2.2.1 MSA Visualization	31
2.2.2 Gradient Vector Flow Analysis	33
2.3 Gradient Vector Flow Analysis	34
2.3.1 Mathematical Background	35
2.3.2 MSA Analysis	36
2.4 Visualization	39
2.4.1 Feature Emphasis	41
2.4.2 Conservation Exploration	42
2.5 Test Cases	42
2.6 Conclusions and Discussions	44
3 Analyzing and Reducing DTI Tracking Uncertainty	47
3.1 Introduction	47
3.2 Related Work	48

3.2.1	DTI Tractography	48
3.2.2	DTI Visualization	49
3.3	Uncertainty Derivation and Reduction	50
3.3.1	Wild Bootstrap Approach	51
3.3.2	Bayesian Approach	52
3.3.3	Probability Index of Connectivity (PICO) Approach	53
3.3.4	Uncertainty Reduction	54
3.4	Interactive System Setup	55
3.4.1	3D Fibers Visualization	55
3.4.2	Uncertainty Investigation Widget	56
3.5	Results and Discussions	57
3.5.1	Synthetic Data Set	57
3.5.2	Monkey Brain Data Set	58
3.5.3	Human Brain Data Set	59
3.6	Conclusions and Future Work	60
4	Deriving and Visualizing Uncertainty in Kinetic PET Modeling	61
4.1	Introduction	61
4.2	Related Work	62
4.2.1	Visualization Techniques	62
4.2.2	Kinetic Modeling Systems	63
4.3	Kinetic PET Modeling	64
4.4	Deriving Intra- and Inter-Model Uncertainty	66
4.5	Uncertainty-Aware Kinetic Parameter Visualization	68
4.5.1	Kinetic Parameters Uncertainty Visualization	68
4.5.2	Linking Kinetic Parameters with Spatial and Temporal Attributes	71
4.6	Evaluation	73
4.7	Conclusions and Future Work	74
5	Concurrent Volume Visualization of Real-Time fMRI	77
5.1	Introduction	77
5.2	Related Work	78
5.3	Application Setup	79
5.4	Signal Processing	80
5.5	Contextualized fMRI visualization using volumetric illumination	82
5.5.1	Local Ambient Occlusion	83
5.5.2	Using the fMRI Signal as Illumination Source	85
5.5.3	Visibility Enhancement	86

5.6	Evaluation of method	87
5.7	Results	88
5.8	Conclusion and Future Work	90
6	Quantitative Visual Analysis of Knee Movement Patterns	93
6.1	Introduction	93
6.2	Medical Background	96
6.3	Method	97
6.3.1	Enhanced GPU-based Feature Identification and Track- ing	98
6.3.2	Kinematic Parameters Measurement	101
6.4	Comparative Visualization	103
6.4.1	Radial Angle Plot	103
6.4.2	Time-angle Profile	105
6.5	Results and Discussion	107
6.6	Verification and Generalization	111
6.6.1	Verification	111
6.6.2	Generalization	113
6.7	Conclusions & Future Work	114
7	Conclusions	115
7.1	Summary of Contributions	115
7.2	Future Research	116
	Bibliography	117

CHAPTER 1

INTRODUCTION

In past years, there have been tremendous technological advances in medical imaging. These progresses enable an ever-increasing resolution and quality in acquired medical data of the human body. While the first CT scanner developed by Hounsfield required several hours to acquire a single scan and it took days to process the raw data, modern CT scanners enable high-resolution acquisition of objects of larger volumes in a matter of seconds. The current state-of-the-art CT scanner facilitates the scanning of volumes up to 1750 mm, in isotropic resolution, using a 1 mm slice, in just 38 seconds and delivering 1750 images ready for diagnostics in less than 3 minutes (R. Bull 2013). At the same pace, we have also seen a rapid growth in volume and diversity of biological data. Since the first sequenced genome, which is the single-stranded bacteriophage $\Phi X174$ containing approximately 5386 nucleotides (Sanger et al. 1977), the advents of next-generation sequencing technologies can now yield hundreds of millions of short-read sequences (Mardis 2008; Metzker 2010). Over past years, vast research efforts have been dedicated to the interpretation of the huge amount of obtained data. Due to the incredible ability of the human visual sensory system, we can quickly identify structures and relations through visual representations even in the case of fuzzy or incomplete data. As a result, visualization plays an important role in supporting visual analyses and gaining insights into the exponentially growing data that we are facing.

As the field of scientific visualization progresses, many visualization techniques have been developed and proven to be useful to reveal important structures in large and complex data. Nevertheless, to develop efficient visual representations to convey gross trend patterns, uncertainty as well as to support quantitative visual analysis of complex data are still open challenges. The results presented in this thesis aim at supporting quantitative visual analysis in the presence of data uncertainty within the domains of medicine and biology. We address the challenges to efficiently fuse and visualize different medical modalities in order to analyze them in a common context. We propose novel approaches to derive and highlight the underlying uncertainty in data and the involved data processing algorithms. We also present techniques to identify patterns for quantitative analysis in both static and dynamic data. Finally, to support quantitative visual analysis, we have developed specialized visual metaphors to efficiently convey the derived information.

In this chapter, we start with an overview of visualization in medicine and biology to provide the context of the work. We then identify the research challenges related to the work presented in this thesis in Section 1.2. In Section 1.3,

we outline the contributions of the thesis in addressing the identified research challenges.

1.1 VISUALIZATION IN MEDICINE AND BIOLOGY

The advents of technologies in medicine and biology have led to a huge amount of available data. Consequently, there have been great demands on efficient methods to support the analysis and reveal insights into the acquired data. In past years, many visualization techniques have been developed and applied to a wide variety of clinical applications as well as biological studies. A thorough coverage of the proposed visualization techniques would be beyond the scope of this thesis. As a result, in this section, we focus on basic visualization techniques for the medical imaging modalities as well as biological data that are related to the work presented in this thesis to establish the context of the work. In the following sections, we will describe the challenges, as the size and the complexity of data increase, and our contributions to address the problems.

1.1.1 *Visualization in Medicine*

As McCormick and colleagues stated, “The purpose of visualization is insight, not pictures”, in their field-defining report on scientific visualization, the goal of scientific visualization is to graphically illustrate scientific data to enable the understanding of the underlying information (McCormick et al. 1987). The definition of ‘insight’ may vary slightly from one field of research to another. Nevertheless, the aim of visualization is the identification of patterns and outliers, whereby leading to a better understanding of the phenomena under investigation.

Visualization in medicine, or for short, medical visualization, is a research area within the broader field of scientific visualization. While scientific visualization deals on scientific data arising from measurements, or simulations of real-world phenomena, medical visualization focuses mostly on data obtained through medical imaging techniques. Recently, the advancements in the acquisition and modeling of flow fields have provided an unprecedented quality of the output data. As a result, there have been several research efforts focusing on the visualization of data from simulation of blood flow patterns that helps to reveal the insights into the large amount of acquired data (Pelt, Oliván Bescós, et al. 2011; Pelt, Jacobs, et al. 2012).

Medical Imaging Modalities

As the initial focus of medical imaging has been the understanding of anatomical structures, vast research efforts have been dedicated to the acquisition and the interpretation of high-resolution static anatomical images. However, the later advances in medical imaging technologies led to a significant reduction of the acquisition times and, thus, made time-varying acquisition possible.

Table 1.1: Relative comparison between two properties: resolution and signal-to-noise ratio (SNR) of different medical imaging modalities.

	Resolution	SNR
CT	☆☆☆	☆☆☆
MRI	☆☆☆	☆☆☆
fMRI	☆☆☆	☆☆☆
DTI	☆☆☆	☆☆☆
PET	☆☆☆	☆☆☆

The resulting time-varying data can support a better understanding of organ functions and significantly improve the diagnostic workflow.

In this subsection, we focus on tomographic imaging modalities, particularly computed tomography (CT) and magnetic resonance imaging (MRI). We also describe positron emission tomography (PET), its clinical applications, and the drawbacks. Table 1.1 presents a *relative* comparison of two properties — resolution and signal-to-noise ratio (SNR) — of the previously mentioned medical imaging modalities based on the information in (Preim and Botha 2013). Although CT provides the highest resolution, and SNR data in comparison to other modalities, it is worth pointing out that there is no *absolute best* imaging technique for all applications, as each modality was designed with a particular set of constraints and, thus, supports a certain range of application scenarios.

Computed Tomography

Computed tomography (CT) is a commonly used modality in radiology for the evaluation of the anatomy. CT was first applied to get the cross-sectional images of the brain to support the investigation of a lesion (Hounsfield 1973). CT is based on X-ray imaging technology, whereby the X-ray source and detector are rotated around and moved along the object to measure the intensity of X-rays passing through the object as this spiral progresses. Consequently, CT data represent a series of individual X-ray images that are composed into one volume dataset. Each X-ray image represents an intensity profile measured by the detectors.

In a CT dataset, the densities of the scanned object are stored in the Hounsfield Unit (HU), which is a normalization that maps the intensity of water to zero and the intensity of air to -1000. Consequently, different tissues or bone structures are represented by ranges of values. Figure 1.1(a) illustrates the visualization of a slice from the CT of a human head. While the bone structures, which are mapped to white color, have the intensity range from +700 to +3000, gray and white matter, which are mapped to shades of gray, have the intensity range from +37 to +45, and +20 to +30 respectively. Due to the high resolution and high SNR in CT data, the boundaries between the bone structures and soft tissues

Figure 1.1: Visualization of acquired data from the same test subject using different imaging techniques. (a) is the visualization of a slice from a CT scan, (b) is the visualization of a slice from a MRI scan, and (c) is the visualization of a CT dataset. While the bone structures and the boundaries between bones and soft tissues are better defined in CT data, MRI imaging enables a better classification of different soft tissues.

are well defined.

In comparison to the conventional use of X-ray, CT offers several advantages. CT provides accurate localization of objects in depth as X-ray attenuations are recorded for small volume elements independently during the acquisition. CT also enables the classification of different soft tissues. Since the X-ray absorption is computed with high accuracy for each volume element, CT enables quantitative analysis based on the acquired data. For instance, the mean X-ray absorption in a selected region can serve as an indicator for the level of different diseases.

Driven by the demands of imaging organs in function, the scanning time of modern CT scanners has been dramatically reduced, which contributes to the reduction of motion and breathing artifacts from obtained data. As a result, dynamic CT scans become possible and show potential in clinical applications, such as the study of the flow of contrast from the arterial to venous phase for the assessment of the collateral status and defining the occlusion length in stroke (Frölich et al. 2013), and 4D CT image-based orthopedics (Alta et al. 2012).

One big drawback of CT is that the patients need to be exposed to a moderate or high radiation, which is a serious problem in special cases, for example, in children (Rice et al. 2007). By increasing the radiation dose, higher SNR CT data can be acquired. However, there is a trade-off between the image quality and the radiation with regard to the safety of the patients. In a recent survey, Sun and colleagues summarize a list of various dose-saving strategies and state that the focus of research in cardiac CT has shifted from improving the image

quality to dose reduction (Sun et al. 2012).

Although different tissues in a CT dataset can be classified, there are overlaps of intensity ranges between different tissues (Hounsfield 1980). In addition, the small contrast between different tissues in CT data makes it difficult to achieve a good classification of tissues, which can be improved by the following imaging technique.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) as a medical imaging modality was proposed by Lauterbur (Lauterbur 1973). MRI is based on the principle of nuclear magnetic resonance, particularly the dependency of the resonance frequency of protons on the magnetic field strength. In a typical MRI acquisition, a strong magnetic field is used to align the spin of hydrogen nuclei (protons) in the body. Then, radio frequency magnetic fields are applied to systematically alter the alignment of the magnetization. This causes the nuclei to produce a rotating magnetic field, which is detected by the scanner and used to reconstruct the final volumetric image of the scanned object. The measured values depend on the density and chemical surrounding of the hydrogen atoms, and the spatial localization of each value is controlled by small variations in the magnetic field.

Figure 1.1(b) shows a visualization of a slice from a scan of a human head using MRI. In comparison to the visualization in Figure 1.1(a), the classification of white and gray matter is better defined. Due to the requirement of the relaxation of the spins during the acquisition process, a typical MRI scan takes between 2 and 25 minutes. In general, the acquired MRI data have lower resolution and SNR in comparison to CT data. However, modern high-field MRI scanners enable the acquisition of higher spatial as well as temporal resolution image data.

One advantage of MRI is the flexibility of the parameter settings, which leads to several imaging protocols that enable the emphasis on different functional or physiological properties of the tissue. The complementary information from the results can be used together for quantitative analysis. As MRI offers the ability to discriminate different soft tissues, it is often used in neuroimaging to distinguish between white and gray matter. In addition, the magnetic fields used in MRI do not cause any known harmful effects on patients (Hartwig et al. 2009). Therefore, MRI is suitable for imaging the brain, soft tissues or joints, i. e., the shoulder and the knee.

In the following subsection, we describe two commonly used variants of the MRI technique: diffusion tensor imaging (DTI) and functional MRI (fMRI).

Diffusion Tensor Imaging (DTI). DTI is an magnetic resonance imaging technique that measures the water diffusion process in living tissues. Among the technologies currently available for the analysis of the white matter connections,

DTI is a promising modality. Based on the orientation captured at each point of the tissue, the connectivity between different regions of the brain can be established. This procedure is commonly called *fiber tracking*. A visualization of the reconstructed pathways offers unique insights into the 3D layout of white matter fiber bundles and, thus, provides great potential for both neuroscientific research and clinical applications such as neurology, neuroradiology, and neurosurgery.

Due to the fact that DTI is based on the application of strong gradient fields that cause an attenuation of the measured MR signal, and the acquisition requiring long echo times, DTI is an inherently signal-to-noise-sensitive imaging technique. This leads to the high amount of uncertainty in the acquired data that also causes uncertainty in other stages such as data processing and visualization. Although many techniques have been developed to address the uncertainty arising during acquisition, processing, and visualization, it is still an open challenge to analyze, reduce, and efficiently convey the uncertainty so that DTI can be widely used in clinical applications.

Functional Magnetic Resonance Imaging (fMRI). fMRI is another variant of the MRI technique, which enables the imaging of functional properties of tissues. fMRI detects changes, which are recorded in a time-intensity curve, in cerebral blood flow and oxygen metabolism as a result of neural activation (Friston 1994). The image acquisition is based on the blood oxygen level-dependent (BOLD) effect.

The ability to capture the functional properties of tissues makes fMRI a viable protocol for a wide-variety study of the brain. For instance, fMRI is used to support the access and resection planning in minimally invasive epilepsy and brain tumor surgery (Gumprecht et al. 2002), the detection of areas of the brain related to the language tasks (Binder et al. 1997; De Guibert et al. 2010).

Due to the long acquisition time and the complexity of the recorded phenomena, fMRI data suffer from low resolution and low SNR. In addition, sophisticated signal processing algorithms involved in the analysis of the activation patterns can also be a source of uncertainty. These pose challenges for both quantitative analysis and visualization of the acquired data.

Positron Emission Tomography

Positron Emission Tomography (PET) is a nuclear medicine imaging technique that generates 3D images of functional processes. Depending on the chosen tracer, which is a short-lived radiopharmaceutical substance, injected into a subject, PET can be used, for instance, to measure brain activity or to assess the impact of a cardiovascular event by enabling the analysis of the myocardium vitality.

Due to the requirement of a fast acquisition time and the characteristic

of the imaging technologies themselves, PET scans usually suffer from low resolution and low SNR. This leads to a high level of uncertainty in the acquired data. The motion artifacts caused by the movement of the scanned object are another source of uncertainty arisen in the acquired data. As a result, efficient signal processing methods and well-designed visualizations, which help to convey the underlying uncertainty, are needed to fully exploit the potential of this imaging modality.

Over past years, the advents of technologies have greatly improved the quality of the acquired data, i. e., higher resolution, higher SNR. Nevertheless, each modality still has its inherent drawbacks that need to be taken into account to achieve better quantitative analyses and visualizations.

Although CT offers higher resolution and SNR data than other modalities, it still suffers from the partial volume effect, which can be defined as the loss of the apparent information in small objects or regions. For instance, the limited resolution of a CT scanner causes an averaging effect when multiple tissues occur in a volume element. This leads to a different level of uncertainty in the analysis and visualization of small structures. As PET, MRI and its variant have lower resolution and SNR, the partial volume effect has a stronger influence on the acquired data. As a result, the artifacts caused by the partial volume effects need to be carefully taken into account for segmentation, classification, and quantitative image analysis.

It is worth pointing out that these imaging modalities are not exclusive to each other. For instance, CT and MRI are complementary. As MRI depends inherently on sufficient water content, the imaged skeletal structures do not have the same quality as when CT is used. On the other hand, due to the similarity of the X-ray attenuation in soft tissues, CT does not offer the ability to distinguish soft tissues as good as MRI. As a result, it is natural to fuse the acquired data from different modalities together to exploit the advantages of each modality and reduce the uncertainty to improve the quantitative analyses and visualizations (Beyer et al. 2007). However, there are several challenges that need to be addressed, such as the registration of data from different modalities, and the differences in resolutions and SNR.

Visualization Techniques

In the previous subsections, we have described several medical imaging modalities and their typical clinical applications as well as relevant research scenarios. In this subsection, we focus on basic visualization techniques to generate visual representations of the acquired medical volumetric data.

Medical image data acquired from the above-mentioned modalities are usually represented as a stack of aligned images or slices of the same resolution and adjacent position in the z direction. Volumetric data combines individual images into a 3D representation on a 3D grid to facilitate the visual representa-

tion of all images at the same time. In this grid, each data element is called a *voxel* (volumetric element).

As medical visualization, or scientific visualization in general, is based on computer graphics to store and render 3D geometric representations, most early medical visualization methods aimed at approximating a surface contained within volumetric data using geometric primitives. For instance, the methods, such as contour tracking (Keppel 1975), opaque cubes (Herman and H. K. Liu 1979), marching cubes (Lorensen et al. 1987), and marching tetrahedra (Shirley et al. 1990), fit geometric primitives, such as polygons or patches, to constant-value contour surfaces in volumetric datasets. Hence, these techniques are classified as *surface-based* methods, whereby the extracted surface representation can then be rendered using standard rendering techniques as described in the computer graphics literature.

While surface-based techniques have the advantage of reducing the huge amount of information contained in a volumetric dataset into 3D surface representations, they have several drawbacks. During the surface approximation process, it has to be decided whether a data sample belongs to the surface. This can lead to false positives (spurious surfaces) or false negatives (erroneous holes in the surfaces). In addition, this type of representation does not capture information about the interior or exterior of objects in volumetric data; thus, it does not fully exploit the potential of volumetric data representation.

To address the limitations of surface-based techniques, *direct volume rendering* (DVR) techniques were proposed. In comparison to surface-based techniques, DVR techniques do not simplify the huge amount of information stored in volumetric data through approximated surfaces. Consequently, the complexity of the algorithms and the rendering time increase. To improve interactivity, several optimization methods have been developed. Common DVR methods include ray casting (Levoy 1988), splatting (Westover 1990), and shear-warp (Lacroute and Levoy 1994). Instead of generating an intermediate representation, DVR techniques enable volumetric data to be displayed directly. For instance, the original samples are projected onto an image plane through a process that interprets data as an amorphous cloud of particles. As a result, information about surfaces and interior structures can be visualized without making assumptions about the underlying structures contained in the data. Thus, DVR techniques allow rendered images to contain more information than the surface-based techniques and play an important role in revealing insights into data. Smelyanskiy et al. have shown that ray casting is the most acceptable technique for high-fidelity requirements of medical imaging (Smelyanskiy et al. 2009). As a result, we focus on using a ray casting technique for the visualization of medical data in the rest of this thesis.

The basic idea of ray casting is to project data values from rays passing through the volumetric data onto the screen. As a result, the resulting color at each pixel is a blend of the colors represented by all materials along the corresponding ray. The mapping between materials and the corresponding colors is

facilitated by a mapping function called *Transfer Function* (TF). Different TF settings enable users to control the content to be shown in the dataset and how this content should be represented. As a result, TFs play an important role in DVR and a lot of research has been devoted to the design of optimal TF settings that help to reveal the inside structures in volumetric data and support visual exploration as well as quantitative analysis.

In general, TFs are mapping functions which basically map one property to another. TFs can be categorized into one-dimensional mapping functions and multi-dimensional ones. In one-dimensional TFs, the scalar values in the volumetric data are mapped to colors and opacities. In multi-dimensional TFs, more constraints can be introduced to improve the selection of content in the dataset that needs to be shown. For instance, in addition to the mapping between the scalar values and the colors, one can introduce the constraint about the boundaries, i. e., boundaries between soft tissues, and bones. Despite their advantages, multi-dimensional TFs are not intuitive to design; thus, they present a steep learning curve to users. Figure 1.1(c) presents a DVR visualization of a CT scan of a human head. In the TF settings, the bone structures are mapped to shades of yellow while the soft tissues are mapped to a gray color.

For further details on DVR techniques and related material, we refer to the following books and survey (Engel et al. 2006; Preim and Botha 2013; Rodríguez et al. 2013).

Volumetric Illumination Techniques

One of the major focuses of visualization in medicine is to enable the understanding of the anatomy in 3D. Consequently, the depth perception plays an important role in medical visualization to convey 3D positioning information in volumetric data. To achieve this, the perceptual capabilities of the human visual system need to be taken into account in the visual depiction of the underlying data. Langer et al. have shown that the choice of illumination model used in volume rendering has a major impact on the spatial comprehension (Langer et al. 2004). Sattler et al. showed that shadows serve as an important depth cue (Sattler et al. 2005).

Over past years, many illumination models for volumetric data have been proposed. Among the proposed illumination models, the local ambient occlusion (LAO) technique is closely related to the work presented in Chapter 5 of this thesis. LAO is an approximation of ambient occlusion that helps to improve the perception of shapes and tissues (Hernell et al. 2007; Hernell et al. 2010). In addition, the tissue luminous effects allow specific structures to be highlighted and provide better understanding of tissue density. In Chapter 5, we propose a novel approach to exploit light as a transport to efficiently fuse different volumetric datasets from different imaging modalities. In the proposed approach, we can overcome the challenges posed by the differences in resolutions and SNR of different imaging modalities. Moreover, as the proposed approach is based on the LAO illumination model, we also achieve high-quality rendered

Figure 1.2: Direct volume rendering of the fusion of an MRI scan of a human brain and an fMRI scan representing activity of the brain using the local ambient occlusion (LAO) technique. The high-resolution MRI data provide the context for the localization of the activities in the brain captured in the low-resolution fMRI scan, which is the focus. The employed illumination model helps to improve the depth perception and, thus, the localization of activities in the brain.

images with improved depth perception.

For further details on illumination techniques in DVR, we refer to the work of Hadwiger et al. and the survey conducted by Jönsson and colleagues (Hadwiger et al. 2009; Jönsson et al. 2013). In addition, we refer to the recent thorough user study in which the perceptual impact of seven volumetric illumination techniques was investigated (Lindemann and Ropinski 2011). The results of this study show that advanced volumetric illumination models make a difference when it is necessary to assess depth or size in images.

The medical imaging modalities presented in Section 1.1.1 have their own strengths and weaknesses. As mentioned in the previous subsection, it is natural to combine the information from the acquired data from different imaging modalities to exploit their advantages as well as suppress their weaknesses. Figure 1.2 presents the rendered image of the fusion between the MRI scan of a brain and the fMRI scan containing activities in the brain. As the MRI scan offers high resolution and high SNR, it can be used to serve as the context for the localization of the activities contained in the fMRI scan. In addition, the illumination model used in the generation of the rendered image helps

to improve the depth perception. However, it is a challenge to efficiently fuse different modalities together as they have different properties, i. e., resolution and SNR. In Section 1.2, we describe in more detail the challenges arisen as the complexity of data increases, and outline our contributions to address these challenges.

1.1.2 *Visualization in Biology*

In the previous section, we have presented different medical imaging modalities and basic visualization techniques to reveal insights from the acquired data. The aim of this section is to present different types of biological data and visualization techniques that are related to the results presented in this thesis.

Biological data visualization is a research branch of bioinformatics concerned with the application of computer graphics, scientific visualization, and information visualization to different areas of biological research. The emerging fields of computational biology and bioinformatics over the last two decades have led to significant progress in automated data generation and also acquisition in basic research labs. Accordingly, the fast expansion in volume and diversity of biological data has presented an increasing challenge for biologists. With large and complex datasets, i. e., ‘omics’ data, it is difficult to identify in advance the information that biologists are looking for. Thus, it is not possible to solve problems by solely using the automated data analysis techniques (Pavlopoulos et al. 2008; Gehlenborg et al. 2010). Through interactive visualization, which enables data explorations, and analysis, biologists can form new hypotheses and make use of automated analysis algorithms to verify the findings.

Biological data are diverse, ranging from genomes, alignments, phylogenies, and macromolecular structures to data from systems biology as well as image-based data. Many visualization techniques have been developed to provide visual representations for each type of data. A full coverage of visualization techniques for biological data would be beyond the scope of this thesis. We refer to the survey of biological data visualization techniques by O’Donoghue and colleagues for further details (O’Donoghue et al. 2010). In the rest of this section, we focus on the visualization of sequence alignments data, particularly large-scale sequence alignments data, as it is part of the results presented in this thesis.

A sequence alignment is a means to identify regions of similarity that lead to the functional, structural or evolutionary relationships between sequences of DNA, RNA or proteins. Consequently, sequence alignments are one of the basic ingredients for the generation of an evolutionary tree, which is becoming an integral part of various biological studies. Visualization of such a tree has been shown to facilitate the tasks of evolutionary analysis (Page 2012). On the other hand, visualization of sequence alignments enables the understanding of the molecular mechanisms that differentiate each species, down to the level of the individual nucleotide bases and amino acids. Figure 1.3 illustrates the visualization of a sequence alignment based on the commonly used table-based

<i>Hb_a</i>	L	S	P	A	D	K	T	N	V	U	A	A	W	G	K	V	G	A	-	-	-	-	H	A	G	E	Y	G	A	E
<i>Hb_b</i>	L	T	P	E	E	K	S	A	V	T	A	L	W	G	K	V	-	-	-	-	-	-	N	V	D	E	V	G	G	E
<i>Mb_SW</i>	L	S	E	G	E	W	Q	L	V	L	H	V	W	A	K	V	E	A	-	-	-	-	D	V	A	G	H	G	Q	D
<i>LebHB</i>	L	T	E	S	Q	A	A	L	V	K	S	S	W	E	E	F	N	A	-	-	-	-	N	I	P	K	H	T	H	R
<i>BacHB</i>	Q	T	I	N	I	I	K	A	T	V	P	V	L	K	E	H	G	-	-	-	-	-	V	-	T	I	T	T	T	T

(a)

<i>Hb_a</i>	L	S	P	A	D	K	T	N	V	U	A	A	W	G	K	V	G	A	-	-	-	-	H	A	G	E	Y	G	A	E
<i>Hb_b</i>	L	T	P	E	E	K	S	A	V	T	A	L	W	G	K	V	-	-	-	-	-	-	N	V	D	E	V	G	G	E
<i>Mb_SW</i>	L	S	E	G	E	W	Q	L	V	L	H	V	W	A	K	V	E	A	-	-	-	-	D	V	A	G	H	G	Q	D
<i>LebHB</i>	L	T	E	S	Q	A	A	L	V	K	S	S	W	E	E	F	N	A	-	-	-	-	N	I	P	K	H	T	H	R
<i>BacHB</i>	Q	T	I	N	I	I	K	A	T	V	P	V	L	K	E	H	G	-	-	-	-	-	V	-	T	I	T	T	T	T

(b)

Figure 1.3: Visualization of a sequence alignment using the traditional table-based representation. (a) is the standard visualization of a sequence alignment. (b) is the visualization of the same sequence alignment using the Clustal color-coding scheme to facilitate the identification of regions where specific properties predominate as well as to highlight the variations.

representation. In this representation, each row represents a sequence, and residues and bases are arranged accordingly in columns. While both visual depictions of the sample sequence alignment have the same layout of elements of sequences, the Clustal color-coding scheme used in the visual representation in Figure 1.3(b) facilitates the identification of regions where specific properties predominate and help to highlight the variations.

In the last 20 years, many tools for tree and sequence alignment visualization have been developed. Initial approaches, such as ESPript (Gouet et al. 1999), ALSCRIPT (Barton 1993), and Chroma (Goodstadt and Ponting 2001), focus on generating a static table-based representation of alignments, as illustrated in Figure 1.3(a). These approaches face some drawbacks, as the size of the rendered image is fixed, and they do not support interaction. Consequently, they became less useful as the number of sequences and the length of sequences increased. To improve alignment visualization, several color-coding schemes have been developed to facilitate the identification of regions where specific properties predominate and to highlight the variation, i. e., Taylor (Lin et al. 2002), Clustal (Larkin et al. 2007) color-coding scheme. In comparison to previous approaches, ClustalX (Larkin et al. 2007) and eBioX (Martínez Barrio et al. 2009) support interactive visualization of sequence alignments. In addition, ClustalX (Larkin et al. 2007) also allows symbols to be shaded on the basis of both their type and their predominance at each alignment position (see Figure 1.3(b)). This further improves the perception aspect of sequence alignment visualizations.

Recently, more advanced frameworks, such as JalView (Clamp et al. 2004; Waterhouse et al. 2009), PFAAT (Caffrey et al. 2007), and CINEMA (Li, Bhowmick, et al. 2013), have been developed. These frameworks not only pro-

vide visualization of sequence alignments, but also make alignments editing, annotation, and navigation possible to further support visual analysis. Among the advantages, the ability to incorporate domain knowledge into the visualization through annotations and collaboratively share them can significantly improve the workflow and facilitate gaining insights into the data.

It is worth noting that all the approaches mentioned above are based on the traditional table-based representation of sequence alignments. Consequently, they share the same drawbacks. As the amount of sequences rapidly increases, the visualization becomes less efficient in conveying gross trend patterns as well as variations. This leads to the challenge to the new visual representation that facilitates the identification of these patterns in large-scale sequence alignments.

1.2 RESEARCH CHALLENGES

In Section 1.1, we have described different data types and basic visualization techniques in medicine and biology. We presented different sources of uncertainty in medical volumetric data, such as uncertainty from the imaging modality, or from the processing algorithms, or from the fusion of different modalities. We also discussed the need for new visual representations of large-scale sequence alignment data. In this section, we focus on the research challenges related to the tackled problems presented in this thesis.

Since the introduction of the field-defining report (McCormick et al. 1987), scientific visualization has become a mature research area. Research results have been widely accepted and used in many fields to support a wide variety of purposes, such as scientific discovery, medical diagnosis, and education. In past years, several efforts have been made to look back on solved problems and identify future research challenges in scientific visualization (C. Johnson et al. 2006). In addition, critical evaluations of usability and utility of visualization software were also brought to attention as the field progressed (G. Johnson et al. 2004; House et al. 2005).

The results presented in this thesis aim at supporting quantitative visual analysis in medicine and biology in the presence of data uncertainty. In addition to the interdisciplinary nature, the presented work also deals with complex and large data stemmed from different sources. Another important aspect is the design of visual representations to support quantitative visual analysis.

1.2.1 *Interdisciplinary Collaboration*

Although visualization is itself a discipline, visualization research is not for the sake of visualization. The advances in visualization enable the advances in other fields, as visualization is the key to the understanding of complex phenomena. The interdisciplinary nature of scientific visualization makes it a fascinating and growing research area, but also makes it difficult because we need to know something, at least at a basic level, about all of the application domains involved.

1.2 Research Challenges

In order to achieve this, it is important for a visualization researcher to communicate with users and experts in other domains to understand the problems that need to be solved.

One of the difficulties in the collaboration between different domains is the difference in domain-specific terminology. In addition to the knowledge in scientific visualization, basic knowledge of other fields is required. This knowledge serves as a foundation for visualization researchers to understand the underlying data before generating meaningful depictions of the data. For instance, the basic understanding of the data acquisition process, signal processing stage, as well as the anatomy of the brain can help visualization researchers to understand the characteristics of the measured activities in the brain and, thus, to design a good visual representation of the data. As a result, meaningful information can be conveyed and insights can be gained through visualization. On the other hand, domain experts in other fields need to have basic knowledge about scientific visualization to understand the current limitations and possible approaches. This leads to meaningful discussions and avoids misunderstandings arising during the collaboration.

Another challenge is the reluctance of domain experts to try out new visual representations. In the case of medical visualization, although DVR techniques allow us to present all information in a volumetric data set at once and, thus, convey more information than the traditional 2D slice-by-slice representations, radiologists are more familiar with the later representation. Consequently, it is difficult to integrate new and advanced visualization techniques into the diagnostic workflow and get feedback from domain experts for fine-tuning the visualizations. To overcome this challenge, new visual representations must be well designed in such a way that they help to efficiently convey the information inside the data, and at the same time, do not require a steep learning curve. Clear benefits from visualization are an important factor to encourage domain experts to get involved and not only try out but also incorporate new visualizations into the workflow.

Conducting evaluations is another important challenge in the collaboration process. The definition of effectiveness and the targeting goals can be different from one field of research to another. A well-designed visualization has the power to reveal the insights of the underlying problem. However, visualization for the sake of visualization itself can provide misleading information and impair the scientific discovery process. Consequently, both the evaluation of the visualization and the evaluation of the findings supported by visualization are of necessity.

1.2.2 Interactive Visual Analysis

One important factor that differentiates scientific visualization from other fields of research is the emphasis on retaining a *human-in-the-loop*, which can be defined as a model that requires human interactions. While the goal of other fields, such as artificial intelligence and machine learning, is to remove the

human from the process by automated algorithms, the goal of visualization is to present meaningful information in such a way that the human can gain insights and make informed decisions. Moreover, based on the domain knowledge and experiences, users can provide feedback into the system to explore or further improve the output.

The crossing between disciplines has contributed to the complexity of the rapidly growing scientific data sources. Nowadays, data are often spatiotemporal and multivariate; they stem from different data sources, from multiple simulation runs, or from multiphysics simulations of interacting phenomena (Kehrer and Hauser 2013). As a result, we are facing not only the expansion in size, but also the complexity of the input data.

As data are getting larger and more complex, a single visual depiction of the data through visualization might not be enough to support the scientific discovery process. Interactive visual analysis (IVA), which is a relatively new field of research, plays an important role in exploring, analyzing, and presenting the findings from these types of complex data. The foundation of IVA is the combination of analytic procedures with interactive visual methods, such as linking and brushing, to enable a powerful drill-down mechanism into the presented information (Kehrer and Hauser 2013).

Visual Analysis and Interactive Methods for Spatiotemporal Data

Through the support of advanced computing, simulations of dynamic phenomena became possible. The output data are commonly high-resolution grids over large timescales and are called spatiotemporal data. When dealing with this type of data, a common goal is to identify the relation between time and space and, thus, discover the spatiotemporal patterns, such as special events or repeated behavior. One brute force approach to the visualization of such data is to generate a single rendered image of the whole phenomena. This is sometimes not possible due to the size of the input data, or as the amount of information condensed into a single visual representation is too much to be useful for analysis. Another approach is to deploy automated analysis methods to abstract the time-related characteristics of the data, i. e. to compute temporal data trends (Kehrer, Ladstadter, et al. 2008), or statistical aggregates such as mean values or standard deviations (N. Andrienko and G. Andrienko 2006). We refer to the survey on visual methods for analyzing time-oriented data conducted by Aigner and colleagues (Aigner et al. 2008) for more details.

Visual Analysis and Interactive Techniques for Multivariate Data

In many scenarios, each time-space location in spatiotemporal data can contain multiple attributes. This leads to not only the increase in size, but also the complexity of the data. Consequently, it is challenging to achieve an interactive visualization as well as visual exploration (C. Johnson 2004). Several approaches have been proposed to facilitate the analysis of this type of data. A common approach is to reduce the amount of data that needs to be visualized.

Again, this can be achieved by applying statistical, analytic, and dimensionality methods (Keim 2002; Bertini and Lalanne 2010).

One solution to simultaneously represent data containing multiple attributes at the same time is to make use of *preattentive visual stimuli* such as position, width, size, orientation, curvature, color (hue) or intensity (Cleveland and McGill 1984; Healey et al. 1996). As these features are rapidly processed by the human's low-level visual system, they can be used for visualizations of large data. It is worth noting that the combination of these stimuli might not be preattentive; thus, a new visual metaphor should be carefully designed.

Glyphs are a powerful visual representation to encode data attributes when dealing with this type of data. By using different visual stimuli, such as shape, size, and color, different attributes can be represented by glyphs. Consequently, relations between attributes can be directly perceived and compared (Fuchs and Hauser 2009). Focusing on medical visualization, Ropinski and Preim proposed a perception-based glyph taxonomy (Ropinski and Preim 2008). The authors classified glyphs into two categories: preattentive stimuli, such as shape and color, and attentive visual processing, which is mainly related to the interactive exploration process. In addition, the authors also propose guidelines for using glyphs in visualizations of multiple attributes medical data (Ropinski, Oeltze, et al. 2011). For instance, glyphs should be perceivable unambiguously from a different viewing direction, and the mapping of data attributes to glyphs should focus users' attention and emphasize important attributes.

Although glyphs are an effective visual representation, the rendered image might become cluttered as the number of data attributes increases. In addition, it is challenging to keep the visualization consistent between different view-points. One approach to solve these problems is to make use of multiple linked views, in which each view represents a subset of data attributes (Roberts 2004). Nevertheless, well-designed visualization is required to achieve mental linking between views to facilitate the data exploration and analysis process.

Visual Analysis and Interactive Techniques for Multimodality Data

The above-mentioned data type usually results from one data modality and represents different properties at the same time-space location, whereby multimodal data stems from different data sources. As each modality has its own advantages as well as disadvantages, the fusion of different modalities can help to suppress the drawbacks of each modality. However, the fusion of different modalities poses many challenges.

Data from different sources can have different properties, i. e., storage structure, resolution, and SNR. For instance, while the ultrasound data are usually stored in an irregular grid, MRI data of the same scanned object are stored in a regular grid. The resolution and SNR of the captured data using MRI and fMRI are different. Consequently, efficient techniques and visual representations are required for the analysis and visualization of such multimodal data. Another challenge is the data occlusion. This is not specific to multimodal data as it is

also a challenge to the visualization of other types of data. However, it is more challenging in the case of multimodal data due to the increased complexity and the amount of combined information.

In many visualization scenarios, multimodal data can be efficiently represented in a single rendered image. Cai and Sakas treat data properties as parameters to a multivolume illumination model in the visualization mapping stage (Cai and Sakas 1999). Alternatively, the authors proposed an approach that assumes that each volume has its own transfer function and each classification result is combined during the accumulation process. More recently, Lindholm et al. use a binary space partitioning technique and store depth information of the intersecting geometry in a view-dependent way to avoid the time-consuming depth sorting process (Lindholm et al. 2009). The proposed technique exploits the power of GPUs to provide high performance and high-quality rendering of multimodal datasets.

When dealing with large and complex data, a single visual representation is usually not enough. For instance, each data property may need to be associated with a visual representation. Thus, it becomes difficult to fuse them together into a condensed visualization while keeping the coherency between different view directions. Viola and colleagues proposed an approach to identify the most expressive viewpoint for features of interest (I. Viola, Kanitsar, et al. 2005). By smoothly changing the current viewpoint to the most expressive computed viewpoint for the features of interest, a clear view on the features can be achieved through focus+context visualization (I. Viola, Feixas, et al. 2006). Particularly, the current view serves as the context, while the transition to the most expressive computed viewpoint is the focus of the visualization.

Another approach to overcome the complexity and occlusion issues in the visualization of multimodal data is the deployment of a coordinated multiple-view setup. The concept of coordinated multiple views originates in the field of InfoVis (Roberts 2007). In a coordinated multiple-view setup, different data properties are shown, explored and analyzed in multiple linked views that are utilized side by side. Through a brushing mechanism (Becker and Cleveland 1987), data properties related to the selected data are highlighted in all linked views. Consequently, linking and brushing techniques enable the exploration of not only complex multi-field data, but also different related datasets. Instead of a binary selection, a fractional degree-of-interest factor, which is normalized to the interval $[0, 1]$, can be used to define the relation between data properties represented in multiple linked views (Furnas 1986). When combining with smooth brushing (Doleisch and Hauser 2002), a focus+context visualization can be achieved. In particular, a transition can be specified around the main region of interest, where the degree-of-interest information gradually changes and propagates through multiple linked views to visually discriminate features of interest (focus) from the rest of the data (context) (Doleisch, Gasser, et al. 2003; Burns et al. 2007; Muigg, Hadwiger, et al. 2007; Muigg, Kehrer, et al. 2008). A thorough review of the work in interactive visual analysis would be

beyond the scope of this thesis. We refer to the survey conducted by Kehrer and Hauser and the reports of Johnsons for further details (Kehrer and Hauser 2013; C. Johnson 2004; C. Johnson et al. 2006).

Although many research results have been proposed to address interactive visual analysis challenges, efficient fusions of multiple volumetric data sources, well-designed visual representations that minimize the occlusion, and an effective mental linking setup between spatial and abstract temporal data are still open questions and far from being solved. Among the results presented in this thesis, we successfully combine novel visual representations and coordinated multiple views to reveal the uncertainty in kinetic PET modeling and support the analysis and uncertainty reduction in DTI fiber tracking.

1.2.3 Large and Dynamic Data

In the previous subsection, we have described the challenges to the visualization and analysis of complex data. In this subsection, we focus on the challenges when visualizing large data in biology and dynamic data, which can be found in almost every major scientific discipline.

Large Biological Data

Advancements in the field of biology and bioinformatics have led to tremendous increases in the diversity and size of the available biological data and, thus, pose challenges to both the analysis and the visualization process. With regard to the contributions of this thesis, we focus on the challenge of visualizing large-scale sequence alignment data.

The sequence alignments of the top 20 protein domains and families have a large number of sequences, ranging from more than 70,000 to approximately 400,000 sequences (Punta et al. 2012). Consequently, it is a challenge to visualize these huge amounts of biological data in such a way that domain experts can gain insights into the problems under investigation.

One way to handle large sequence alignments data is to reduce the amount of data that needs to be rendered. This can be achieved by transforming the original sequence alignment data into an intermediate representation. A commonly used intermediate representation is the *summary plot* which filters out all of the spatial distributions of the data while keeping only the frequency of the dominant element in each column in the table-based representation. As the data reduction rate is extremely high in this approach, the summary plot is suitable for providing a brief overview of the data under investigation. However, this type of representation is not suitable for a detailed analysis due to the vast amount of data being removed.

To overcome this limitation, several *profile-based* techniques have been developed over the years. In profile-based techniques, the traditional table-based representation of sequence alignments is transformed into a simpler representation based on frequency analysis. In comparison to the summary

plot, profile-based representations take into account both the highest frequency and the smaller ones. Schneider and Stephens proposed a new visual representation of sequence alignments called *sequence logos* (T. D. Schneider and Stephens 1990). By applying frequency analysis techniques to the original sequence alignment data, the authors transform the commonly used table-based representation into frequency-based profile representation. As a result, the amount of data that needs to be visualized is significantly reduced. Schuster-Böcker et al. extended the previous work to incorporate emission and transition probabilities of the Profile hidden Markov model (pHMM) (Schuster-Böckler et al. 2004). Roca proposed another profile-based representation which depicts the frequency of residues at each position in combination with the traditional table-based approach (Roca, Almada, et al. 2008; Roca, Abajian, et al. 2013).

As a profile is an abstraction of the whole sequence alignment, the size of the data is reduced. This puts less stress on efficient visualization techniques to handle large data. Nevertheless, a profile does not capture important information such as the correlation between the positions of sequence elements in subfamilies and the visibility of specific subgroups in the original sequence alignments.

Another approach to handle large sequence alignments is to cluster sequences together. Darling et al. proposed a clustering approach to efficiently divide each sequence into blocks and achieve a less cluttered visualization (Darling et al. 2004). The authors also proposed matching criteria to assist the alignment process and highlight the relations between sequences in a sequence alignment. Clustering techniques can also be used to reduce the original data to a subset of representative sequences based on a sequence similarity metric (Kato and Toh 2008; Li and Homer 2010). Although clustering approaches enable data reduction, they have two major drawbacks. Firstly, as the number of sequences in a sequence alignment increases, the size of each cluster also increases. Thus, the challenge to efficiently visualize large sequence alignments is still not solved. Secondly, clustering algorithms are sensitive to the settings of the clustering metric. For instance, a strict clustering metric can lead to a large number of clusters; thus, a high data reduction rate cannot be achieved. On the other hand, a loose clustering metric can yield a high data reduction rate at the expense of hiding the subtle differences, which are important in many research scenarios.

Recently, Miller et al. proposed a system called *EVEVis* to support the visualizations of dense evolutionary data (Miller et al. 2011). Based on the multi-scale approach, the proposed system addresses the cluttering issue when visualizing large data by enabling users to interactively switch between different scales of the visualization to focus on the features of interest and filter out irrelevant information.

The research results mentioned above either apply data reduction techniques, which can remove meaningful information or introduce artifacts into the visualization, or combine interactive exploration techniques with traditional

visualization approaches to handle large data. The limitation of the traditional table-based representation when dealing with large data is still not addressed. Novel representations of large sequence alignment data that facilitate feature identification and extraction are still open challenges. In an effort to improve the visualization of large-scale data, we proposed a novel visual representation, which is a vector field representation, that enables the efficient analysis and visualization of large-scale sequence alignment. By combining with several visualization techniques, the proposed approach efficiently reveals gross trend patterns as well as variations in large-scale sequence alignment data.

Dynamic Data

The advent of technologies has made high-resolution simulations of real-world phenomena possible. The resulting data are becoming more complex, larger and contain thousands of time steps. Consequently, efficient visualization techniques are in great demand to support scientists getting insights into the phenomena under investigation.

One of the approaches for handling large time-varying data is to utilize spatial and temporal coherency, compression, and rendering (Shen et al. 1999; Westermann 1995). Shen et al. proposed an effective data structures called the time-space partitioning (TSP) tree to capture spatial and temporal coherence in time-varying data (Shen et al. 1999). The proposed data structure enables users to make a trade-off between image quality and rendering speed by providing different error tolerances. Younesy et al. proposed another data structure called the differential time-histogram table (DTHT) to encodes the temporal coherence and histogram distribution of dynamic data (Younesy et al. 2005). The DTHT data structure allows the reduction of the amount of data that needs to be loaded when changing between two adjacent time steps based on an error tolerance threshold. In addition, the spatial information can be utilized to accelerate the visualization. Later, Akiba et al. proposed the analysis of time-histograms to support simultaneous classification of time-varying data (Akiba et al. 2006). The authors showed that the proposed approach manages to capture important features in all of the time steps. Wang et al. proposed an approach to identify and present the most essential aspects of dynamic data by applying the analysis on the joint feature-temporal space (Wang et al. 2008). In addition, the authors proposed several effective visualization techniques to reveal the important aspects of dynamic data. More recently, Wang et al. proposed a compression scheme that enables the visualization of large-scale data (Wang et al. 2010). The proposed approach has the advantage of allowing domain experts to incorporate their domain knowledge into the compression stage of both spatial and temporal information.

Another approach is to exploit the power of graphics hardware, which has been developed rapidly over the last decades. Guthe and Straßer applied wavelet and MPEG compression to time-varying data and achieved real-time decompression and interactive playback with hardware acceleration (Guthe

and Straßer 2001). Lum et al. proposed a scalable technique to visualize time-varying data (Lum et al. 2002). The authors made use of DCT encoding in conjunction with a hardware-assisted palette-decoding scheme to support interactive exploration of time-varying data. Cao et al. proposed a compression approach, which makes use of the data extract (DXT) compression technique, that exploits the power of machine GPUs to support interactive visualization of large-scale datasets (Cao et al. 2010). Fogal and colleagues exploit the power of a clustered system and distributed memory multi-GPU to efficiently visualize datasets larger than 2 terabytes (Fogal et al. 2010). Recently, Fout and Ma proposed two prediction-based lossless compression methods targeting medical volumetric data (Fout and Ma 2012). Depending on the input data, different compression schemes can be chosen to achieve high compression rates. In addition, the authors also proposed a method for progressive transmission.

Focusing on medical data, CT scanners have developed tremendously over the last decade in terms of higher resolution and reduced acquisition time, which made the imaging of organs under function possible. Thus, they enable several potential clinical applications, such as 4D CT image-based orthopedics (Alta et al. 2012). This leads to the challenges to the quantitative visual analysis of dynamic data, which has not been addressed in previous work.

In clinical applications, quantitative analysis is an essential part of the analysis and decision-making process. To support quantitative analysis, it is crucial to enable domain experts to interactively identify and select features of interest across time steps in dynamic data. Since manual selection of features of interest across time steps is time-consuming and prone to errors, an efficient visualization system needs to provide a stable and accurate tracking of the selected features of interest over all time steps in an automatic manner. Another challenge in visualizing dynamic medical data is the need for visual metaphors that support comparative visual analysis. While inspecting an animation of the dynamic data might provide a first impression about the underlying conditions, combining the dynamics of the features of interest over the time domain into a single visual representation is necessary to support comparative and quantitative visual analysis. To address these challenges, we proposed a novel approach to facilitate a stable and consistent tracking of features of interest in dynamic CT datasets. In addition, we propose visual metaphors to convey quantitative measurements of kinematics parameters and support visual analysis.

1.2.4 *Uncertainty Visualization*

In the previous subsections, we have described the challenges to the visualization and analysis of complex and dynamic data. In this subsection, we focus on challenges related to the visualization of uncertainty in the data.

As the field of scientific visualization progresses and research results are widely used in other fields of research, identifying and representing errors and uncertainty has become one of the main topics for future visualization research (C. Johnson 2004; C. Johnson et al. 2006). It is worth pointing out

that both clinical and biological problems cannot be solved by solely employing visualization techniques. For instance, the image analysis and the resulting visualization might convey comprehensive understanding of the data, but the findings are strongly dependent on the quality of the original data. As a result, it is crucial not only to analyze and derive quantitative information from acquired data, but also to identify the underlying uncertainties. In addition, uncertainty information should be incorporated and highlighted into the visualization in such a way that users can gain deeper insights into the phenomena and make informed decisions.

Pang et al. presented a thorough survey of many aspects of uncertainty visualization (Pang et al. 1997). The authors propose a taxonomy of different uncertainty visualization methods. The sources of uncertainty are categorized into three groups: acquisition, transformation, and visualization. In the first category, measurement error and simplification of real-world models in simulations are typical examples. Although technological advances lead to high resolution and more accurate data, errors and uncertainty are still the natural property of measurement devices. The discrete nature of measured data defines boundary conditions for interpretation and analysis. In the second category, resampling and quantization of data values are two sources of uncertainty in the output. These uncertainties should be taken into account and highlighted in a visual representation. As discussed in Subsection 1.1.1, different volume rendering algorithms can lead to different results. Besides the ability to reveal interesting features contained within data, visualization techniques are sources of uncertainty themselves.

In many research and application scenarios, sophisticated algorithms can be overestimated (Preim and Botha 2013). In fact, the final rendered image is dependent on the quality of the input data, the processing algorithms involved, as well as the visualization technique used. The combination of DTI and fiber tracking to make inferences about the white matter pathways is a typical example in which a high level of uncertainty appears in all stages from data acquisition to the final rendering. As DTI is an inherently signal-to-noise-sensitive imaging technique, the level of uncertainty in the acquired data is high. Based on the acquired DTI data, fiber tracking algorithms are used to reconstruct the white matter pathways. This process introduces another source of uncertainty into the resulting constructed fibers, which originates from the underlying data as well as from the algorithms themselves. In the visualization stage, there are several operations involved, such as interpolation, simplification of the reconstructed fibers, and application of an illumination model. Consequently, another source of uncertainty can be introduced on top of the uncertainties arising in the previous stages. Therefore, it is necessary to address, or at least visualize, these sources of uncertainty in the final rendered images so that meaningful and correct inferences of the white matter pathways can be made (Brecheisen 2012).

While uncertainty is well acknowledged in DTI visualization, other areas suffer from a similar problem. Figure 1.4 illustrates a visualization of a CT

Figure 1.4: Visualization of a CT angiography data set. The rendered image in (a) indicates a stenosis, pointed out by the arrow. Based on this image, an unnecessary medical intervention was performed. (b) is the visualization of the same dataset, in which uncertainty analysis was performed, and shows that there is no stenosis. Images courtesy of Lundström et al. (Lundström et al. 2007).

angiography data set. In Figure 1.4(a), the visual depiction of the underlying data was wrong due to the sensitivity of TF settings and caused an unnecessary medical intervention. By taking into account the uncertainty arising during the visualization, the correct visual representation is achieved, as shown in Figure 1.4(b).

Grigoryan and Rheingans proposed a point-based approach for representing spatial uncertainty in segmented data based on the displacement of the surface (Grigoryan and Rheingans 2004). Hue and texture have been used to visualize isosurface confidence in multiresolution data (Rhodes et al. 2003). Kindlmann et al. proposed the visualization of shape uncertainty of an isosurface through flowline curvature (G. Kindlmann et al. 2003). Wittenbrink and colleagues presented techniques that enable the incorporation of glyphs to express uncertainty in multi-field data (Wittenbrink et al. 1996).

The above-mentioned approaches were designed to convey uncertainty information in surface-based visualizations. Due to the differences between surface-based and DVR techniques, it is difficult to extend these techniques to DVR. One of the approaches is to treat uncertainty information as any other attribute to be visualized and, thus, render it directly. Djurcilov et al. proposed the usage of multidimensional TFs to modulate the rendered result of the data volume with the rendered probability volume (Djurcilov et al. 2001). This approach suffers from a serious drawback as there is no correlation of obscured regions in the two renderings; thus, uncertain regions may have an impact on the final rendered result even if they are not visible in the regular rendering. Kniss et al. proposed a comprehensive volume visualization framework with predefined probabilistic classification (Kniss et al. 2005). The approach is based

on statistical risk and both DVR and surface rendering application were shown.

As motion perception is a prioritized preattentive process of human vision, another approach to convey uncertainty information is to use animation schemes. Gershon proposed an animation scheme based on an ordered set of segmentations to highlight fuzzy structures (Gershon 1992). Ehlschlaeger and Shortridge proposed an animation scheme to convey uncertainty information through a sequence of probabilistic realizations (Ehlschlaeger and Shortridge 1997). Lundström et al. proposed a novel approach to address uncertainty of tissue classification in medical volume data through animations (Lundström et al. 2007). Based on the fuzzy time-dependent transfer functions for direct volume rendering, the appearance of uncertain regions in a medical dataset can be varied through animations.

1.3 CONTRIBUTIONS

In the previous sections, we have presented an overview of visualization in medicine and biology as well as the research challenges that are related to the work presented in this thesis. In this section, we outline the contributions, which we describe in detail in the following chapters.

The research topics of this thesis focus on supporting quantitative visual analysis in the presence of data uncertainty in medicine and biology. The contributions of the thesis lie in the novel techniques to fuse data from different modalities, visual metaphors to convey the derived uncertainty as well as the dynamics of features of interest in the time domain.

We start with our contribution in handling and visualizing large-scale biological data, in particular large-scale multiple sequence alignment data. We then present our contributions supporting quantitative visual analysis of complex and dynamic medical data.

When dealing with large sequence alignment data, the traditional visual representation has shown its limitation as the number of sequences increases. Several approaches have been developed to incorporate interaction techniques into the visualization to facilitate visual exploration and analysis. Particularly, users can smoothly switch between different scales of the visualization, such as changing from the overview visualization to the detail view of the interesting portion of data. However, identifying the regions containing possible features of interest beforehand from a standard overview visualization is a challenging task. In addition, the drawbacks of the commonly used table-based representation are not fully addressed.

In Chapter 2, we propose a novel approach to identify and extract features of interest in large-scale sequence alignment data. To achieve this, we propose a new representation of the large-scale alignment data, which is a vector field. Consequently, various vector field analysis methods adapted to the analysis of sequence alignments can be used. We applied the gradient vector flow

(GVF) analysis technique to the problem of visualizing large-scale multiple sequence alignments. Besides the ability to handle large sequence alignment data, the proposed approach enables the extraction of features of interest. By using different visualization techniques, the extracted features can be visually emphasized. As a result, researchers can focus on the gross trend patterns inside the data. When combined with interaction techniques, the proposed approach allows researchers to drill down in the identified gross trend patterns for further analysis.

In Subsection 1.2.4, we have described different sources of uncertainty and visualization techniques proposed to convey this information. As science progresses, there is usually more than one approach to solve a specific problem. Each approach has its own advantages and disadvantages. Consequently, we propose a novel approach to derive uncertainties from different state-of-the-art algorithms, and present them in a unified manner. This enables us to exploit the advantages of each approach while suppressing the disadvantages at the same time. In Chapter 3, we apply the proposed approach to analyze and reduce the uncertainty arisen during the fiber tracking process. Particularly, we derive the uncertainty caused by three different fiber tracking algorithms. Based on the unified representation of the uncertainties, users can specify a threshold to achieve a new set of reconstructed fibers with a lower level of uncertainties. The proposed approach allows users to achieve a new set of reconstructed fibers, which is a combination of all of the lowest uncertainty portions of the results from different fiber tracking algorithms. The proposed approach can be extended, such that users can put emphasis on different aspects of the reconstructed fibers to achieve better results.

We have described different complex data sources and the associated visualization techniques in scientific visualization in Subsection 1.2.2. Although many visualization techniques have been proposed to support the visualization of multimodal data, it is still a challenge to produce an effective visualization which manages to convey the information from different modalities and avoid occlusion problems at the same time. Additionally, advanced techniques to fuse different modalities together in such a way that minimizes the uncertainty arisen due to the differences in resolution and signal-to-noise ratio properties are still open questions.

In Chapter 5, we propose a novel technique to efficiently fuse different modalities together by using light as an information transporter. This technique allows us to overcome not only the problems relating to the differences in resolution and SNR between modalities, but also the occlusion issues. We apply the technique to the visualization of brain activities in real time. In our approach, a high-resolution source, an MRI scan, serves as the context while the low-resolution source, fMRI signals, acts as light sources illuminating the corresponding active regions of the brain (see Figure 1.2). Through a user study, we demonstrate that the presented illumination model helps to improve the depth perception and, thus, improves the localization of fMRI signals in the

brain. It is worth pointing out that the illumination effects — mapping the intensity of the focused information to the strength of fMRI signals — are based on the information from the high-resolution contextual data. As a result, the lower-resolution source can be efficiently fused with the higher-resolution one without introducing artifacts or additional uncertainty, which is originated from the fusion of data from different resolutions and SNR. In addition to the advanced fusion technique, we also present an advanced framework for the visualization of activities in the brain. By exploiting the power of the GPU, the proposed framework enables visual depiction of fMRI signals in real time.

As multimodal data stems from different sources, data attributes can have varying characteristics. Consequently, it is crucial to support mental linking between different attributes in a visualization to support the quantitative analysis process. In Chapter 4, we present an approach to efficiently link spatial data to modeling data. We apply the proposed approach to the problem of kinetic PET modeling. Through a multiple-view setup, the mental linkings between the kinetic PET modeling results and the corresponding regions are facilitated. In addition, we propose a novel visual metaphors which is based on the ThemeRiver (Havre et al. 2000), to support comparative visualization of different components involved in a complex system. When applying to the problem of kinetic PET modeling, the proposed visual metaphor has been shown to be effective in both conveying uncertainty derived from the modeling process and supporting visual comparison.

In Subsection 1.2.3, we have described the need to support quantitative analysis of time-varying data through visualization. In clinical applications, while an overview of the functional data provides a first impression of the problem under investigation, it is essential to support quantitative analysis so that informed decisions can be made. During an analysis process, specific features of interest are usually identified. Manual identification and selection of features in the time domain are a time-consuming tasks and are prone to errors. In Chapter 6, we address this problem by proposing a stable and effective technique that facilitates semiautomatic tracking of rigid features across different time steps in a time-varying dataset. Through an interactive visualization setup, users can select features of interest in one time frame and the selected features are tracked automatically in the time domain, which enables an automatic features tracking technique. In addition, we propose different visual metaphors to convey angular relations as well as the patterns of the features of interest. These visual metaphors are designed in such a way that they enable quantitative visual comparison of 4D CT data. We apply the proposed techniques and visual metaphors to the problem of 4D CT image-based orthopedics. The results show that the proposed approach facilitates an accurate tracking of the knee-cap and, thus, provides consistent measurement of kinematic parameters. In addition, the visual metaphors enable comparative visual analysis of the pre- and post-operation data.

In this chapter, we have presented a brief overview of visualization in

medicine and biology. We have also identified four research challenges related to the work presented in this thesis as well as outlined our contributions. In the following chapters, we describe in detail the tackled problems and our contributions.

CHAPTER 2

LARGE-SCALE MULTIPLE SEQUENCE ALIGNMENT VISUALIZATION THROUGH GRADIENT VECTOR FLOW ANALYSIS

2.1 INTRODUCTION

Sequences of DNA, RNA, and proteins are the fundamental components of modern biological research. Multiple sequence alignment (MSA) is a way to organize these sequences, such that similar sequence features can be identified (Morrison 2010). With respect to protein sequence analysis, a feature can be for instance the protein's structure, its function, or its homology with an ancestor. In the context of genomic analysis, insertion places for engineered gene sequences are commonly investigated features of interest.

Recent advances in the development of sequence alignment algorithms have led to an improved performance for large data sets, which enables domain experts to generate large-scale MSA data. While MSA accuracy has also been improved, no single alignment algorithm is perfect for all data sets (Landan and Graur 2009), and MSAs from even the most accurate MSA algorithm can contain errors, often referred to as alignment artifacts (Landan and Graur 2009). Due to the increasing number of biological modeling methods depending on MSAs, it is essential that domain experts can bring in their knowledge to improve the data or to discover features of interest. For these purposes, a variety of tools and algorithms have been proposed for MSA visualization within the last two decades (Procter et al. 2010), of which many exploit the use of color-coding schemes designed for a better feature emphasis. Although color-coding schemes are known to provide an efficient visual metaphor for representing MSAs, they can also cause confusion in regions with complex patterns (Larkin et al. 2007). In addition, the sole use of color-coding schemes limits the effectiveness when dealing with large-scale MSAs. As modern MSAs can easily incorporate ten-thousands of sequences, it is clear that showing an overview as a color-coded table is not appropriate to enable the discovery of previously unknown features.

To support the analysis of large-scale MSA data sets, we propose a novel visualization approach that emphasizes features, which are of potential interest. We transform the traditional table-based representation of the MSA data into pixel-based representations, which we visually annotate to enable exploration and discovery. Our approach is motivated by three reoccurring analysis goals which we have identified in cooperation with domain experts who frequently

2.1 Introduction

Figure 2.1: Results of the proposed visualization technique applied to the L1R_F9L family. While the visualization using the Clustal color scheme provides an overview, features such as absolutely or highly conserved areas are hard to detect (a). By using GVF analysis, we can extract conserved areas (green), gaps inserted by the alignment algorithms (red), and areas containing residues of low conservations (yellow) (b). The detected features can be imposed onto the original MSA (here shown in gray scale) to support visualization (c).

analyze MSA data. First, the exploration of regions with different levels of conservation, which helps to identify residues that are important or even critical, depends on the degree of their conservation. Second, areas containing changes caused by the alignment process need to be detectable. Third, the detections of regions where there is no observable conservation are of interest in the context of sequence engineering. For instance, when applying rational protein design, these regions can help to identify locations for site-directed mutagenesis. While the remainder of this chapter focuses mainly on protein sequence analysis, the set of goals is often similar for genome sequence analysis, and our approach can therefore be extended to apply there.

In a traditional table-based representation of a MSA, there is a strong downward transition of the color patterns in highly conserved areas. On the other hand, the color patterns change disruptively or present sideways transitions in the areas containing gaps inserted by alignment algorithms. Consequently, to support the identification of absolutely or highly conserved areas as well as no observable conservation areas, which helps to target the mentioned goals, we employ gradient vector flow (GVF) analysis. GVF analysis enables us to detect relevant patterns, while at the same time supporting their shape aware highlighting for visualization purposes. The latter is of importance as feature extraction and annotation should not disturb the overall structure of the underlying MSA data. To be able to apply GVF analysis to MSA data, we transform a pixel-map of the MSA data into a vector field representation which we generate by taking into account the principal conservation axis, e. g., typically the y -axis as used in standard table-based MSA visualizations. Therefore, we can compute similarity and dissimilarity vectors to which we apply GVF analysis to extract relevant features on a larger scale and to further support their visual emphasis. The thus achieved visual representation has been designed by taking into account both, the capabilities of the human visual system and the goals identified together with domain experts. As a result, we are able to visually

annotate the existing table-based MSA visualizations in order to visually guide domain experts during the exploration process. Our two main contributions are:

- A novel approach to identify patterns within large-scale MSA data, based on gradient vector flow analysis.
- An intuitive visualization metaphor, which we have designed to enable the visual annotation of large-scale MSA visualization, and thus support visual guidance.

The remainder of this chapter is structured as follows. In the next section, we review work related to our approach. In Section 2.3 we describe our novel MSA feature extraction approach exploiting GVF analysis, while Section 2.4 introduces the proposed visualization approach developed to highlight the extracted features of interest within large-scale data. We present the results of the proposed visualization technique applied to different MSA datasets in Section 2.5, and conclude the chapter in Section 2.6.

2.2 RELATED WORK

2.2.1 MSA Visualization

Many tools for MSA visualization have been developed over the past 20 years (Procter et al. 2010). The output of an alignment algorithm can be interpreted as a matrix, in which each row is a sequence and each column defines equivalent positions across all sequences. Consequently, conventional MSA visualization techniques have adopted a table-based approach (Barton 1993; Goodstadt and Ponting 2001; Gouet et al. 1999). For instance, sequences are represented as rows and the corresponding residues and bases are depicted as letters arranged on a grid. Despite its simplicity, this type of visual representation provides a good control over the automatic generation of figures as well as the ability to work in both desktop and web-based environments. To further improve the visualization of MSAs, various color- coding schemes have been proposed (Martínez Barrio et al. 2009; Larkin et al. 2007; Waterhouse et al. 2009). The incorporated coloring effect helps to identify regions where specific properties predominate and at the same time highlight the variations. The existing schemes can be classified into two main categories: quantitative schemes which convey trends in specific empirical properties, and qualitative schemes which depict general physiochemical classes. Among various color- coding schemes provided in different visualization systems, the Clustal (Larkin et al. 2007) and the Taylor scheme (Lin et al. 2002) are widely supported, and used (Procter et al. 2010). Larkin et al. also proposed an alternative way of using coloring schemes called *shading* to avoid confusion in regions with complex patterns of variations (Larkin et al. 2007). Specifically, symbols are shaded on the basis of both their

2.2 Related Work

Figure 2.2: Amino acid color schemes. In addition to 20 nucleotides for representing protein sequences, B, X, and Z are three amino acid ambiguity codes. B is aspartate or asparagine, Z is glutamate or glutamine, and X is an unknown.

type and their predominance at each alignment position. Figure 2.2 presents several color-coding schemes commonly used in the visualization of MSAs. The first five schemes belong to the quantitative category and the last three schemes are qualitative ones.

When dealing with the visualization of large-scale MSAs, there are two major approaches: clustering of sequences and profile-based representation. The common goal of these two approaches is to reduce the amount of data to be visualized. By applying frequency analysis, Schneider et al. transform the traditional table-based representation of the MSA into a frequency-based profile representation (T. D. Schneider and Stephens 1990). The authors proposed a compact visual representation of the input MSA that reveals not only the consensus sequence but also the relative frequency of bases and the information content at every position in a site or sequence. Schuster-Böckler et al. proposed an extension to the Sequence Logos visual representation by incorporating both emission and transition of probabilities of the Profile Hidden Markov Models (pHMM) (Schuster-Böckler et al. 2004). As a result, the central aspects of the underlying pHMM can be revealed through the visualization. Roca proposed another profile-based approach to depict the frequency of residues at each position in combination with the traditional table approach (Roca, Almada, et al. 2008). While a profile is an abstraction of the underlying MSAs that helps to reduce the amount of data that needs to be rendered, it does not capture important information such as the correlations between amino acid positions in subfamilies, and the visibility of specific subgroups in the MSAs. Clustering techniques are commonly used in both large-scale MSAs and microarray analysis visualization (Saraiya et al. 2004; Hibbs et al. 2005), which shares many common challenges. Darling et al. proposed a clustering approach to efficiently divide each sequence into blocks and achieve a less cluttered visualization (Darling et al. 2004). The authors also proposed matching criteria to assist the alignment process and highlight the relationships between sequences in the MSA. Clustering techniques can also be used to reduce the original MSA to a subset of representative sequences based on a sequence similarity metric. However, as the size of the original MSA increases, number of sequences in the clustering result still poses challenges to the traditional visual representation of MSAs.

Recent sequence analysis systems, such as Jalview (Clamp et al. 2004; Waterhouse et al. 2009), and eBioX (Martínez Barrio et al. 2009) do not only visualize MSA data, but also incorporate analysis capabilities. Users can perform annotations and alignment editing, such that domain knowledge can be incorporated to achieve a better alignment result. Jäger et al. proposed a novel visual analytic approach to deal with time series alignment data (Jäger et al. 2011). Their system allows users to align multiple series experiments and visually explore the aligned expression profiles through the integration of different 2D and 3D views. Miller et al. have also proposed a multi-scale visualization approach that can handle dense evolutionary data (Miller et al. 2011). Moreover, other systems such as SEAVIEW and PHYLO_WIN allow users to easily modify parts of the alignment either manually or semi- automatically (Galtier et al. 1996). While current MSA visualization approaches and systems have shown to be useful in the analysis of MSA data, they all lack the ability of provide an overview of the whole set of sequences, from which gross trends can be identified. Recently, Herbig et al. have proposed the GenomeRing visualization metaphor (Herbig et al. 2012). By deriving a common coordinate system for all sequences in an MSA, visual annotations become possible. However, in contrast to our approach and the table-based layout adapted by most sequence renderers, GenomeRing exploits a circular layout. Although the circular layout nature of the technique helps to convey information efficiently for a small number of sequences, the visualization of large MSAs can be cluttered.

2.2.2 Gradient Vector Flow Analysis

Active contours, or snakes, are extensively used in the field of computer vision and image processing to identify the boundaries of objects. Gradient Vector Flow (GVF), which serves as an external force field for active contours, is a feature-preserving spatial diffusion of gradients (Xu and Prince 1998). It overcomes the limitation of traditional active contour models proposed for instance by Kass et al. (Kass et al. 1988). Particularly, GVF avoids the problem of getting stuck in boundary concavities and low capture range. Since its introduction, GVF has been successfully applied to different applications of image processing. Ray and Acton applied the GVF to track leukocytes from intravital video microscopy (Ray and Acton 2004). While Bauer et al. applied the GVF to extract skeletons from gray value images for virtual endoscopy (Bauer and Bischof 2008b), Hassouna et al. applied the GVF to compute continuous curve skeletons from generic volumetric objects (Hassouna and Farag 2007). Bauer et al. also proposed a novel approach to use the GVF as a replacement for the multi-scale gradient computation in the application of tubular object detection in medical images (Bauer and Bischof 2008a). In this chapter, we propose the use of GVF as a tool to convert pixel-based representations of large-scale MSAs into a flow of similarity and dissimilarity vectors, which enables us to detect global patterns, outliers, as well as data distributions within the MSAs. To our knowledge, this is the first approach exploiting GVF for MSA analysis and visualization.

2.3 Gradient Vector Flow Analysis

(a) first 10 sequences limited to the first 117 columns

(b) all 71 sequences for all columns

Figure 2.3: Table-based visualization of the MSA from the Abp2 family (PF09441) using the Clustal color-coding scheme. While the visualization of the first 10 sequences limited to the first 117 columns in the MSA provides both, focus and context (a), the visualization of the whole MSA makes the identification of features difficult (b).

2.3 GRADIENT VECTOR FLOW ANALYSIS

Figure 2.3 shows two table-based alignment representations of the Abp2 family (PF09441) containing 71 sequences using the Clustal color-coding scheme. Figure 2.3(a) manages to reveal both details down to the amino acid level and the feature patterns such as highly conserved areas, as well as non-conserved areas. However, the visualization of the whole 71 sequences in the MSA in Figure 2.3(b) shows already the limitation of this approach. As the number of sequences increases, the sole use of a color-coding scheme makes it more difficult to perceive gaps in columns. Consequently, it is more difficult to identify absolutely or highly conserved areas as well as areas containing no observable conservation.

In order to achieve a better overview visualization, we exploit the characteristics of patterns in large-scale MSAs. In highly conserved areas, there is

a strong downward transition of the color patterns. On the other hand, the color patterns change disruptively or present sideways transitions in the areas containing gaps inserted by the alignment algorithms. In order to convey these directional patterns more clearly, we employ a vector field representation of the MSA data. Therefore, we exploit GVF analysis that enables feature extraction and highlighting of all, continuous structures, conserved areas, and the disruptive changes resulting from gap insertion of amino acid replacements during the alignment process.

2.3.1 Mathematical Background

Active contours are curves that move in an image while trying to minimize their energy. The traditional active contour models, or the snake algorithm, proposed by Kass et al. uses an external force and an internal force to conform the contour to certain features in the image (Kass et al. 1988). While the external force is computed from the input image, the internal force is derived from the contour itself. The contour can be computed as follows. Let $s \in [0, 1]$ be a parametric curve, the curve that represents the snake, $X_t(s, t)$, at time t is defined as follows:

$$X_t(s, t) = \alpha X''(s, t) - \beta X'''(s, t) - \nabla E_{\text{ext}} \quad (2.1)$$

where $X(s) = [x(s), y(s)]$, X'' and X''' are the second and fourth order derivatives, α and β are constants that define the internal forces, and ∇E_{ext} is the external force.

The drawback of this approach is that the algorithm often gets stuck in boundary concavities and is sensitive to its initialization. The GVF proposed by Xu and Prince introduces a new external force to overcome the limitation of the traditional snake algorithm (Xu and Prince 1998). The external force, ∇E_{ext} , in Equation 2.1 is replaced by a vector field, $V(x, y) = [u(x, y), v(x, y)]$, that minimizes the energy function:

$$E(V) = \iint \mu(u_x^2 + u_y^2 + v_x^2 + v_y^2) + |\nabla f|^2 |V - \nabla f|^2 dx dy \quad (2.2)$$

where $f(x, y)$ is an edge map of the original image, ∇f is the corresponding gradient map, and μ is a constant that represents the noise level in the image. The solution of Equation 2.2 can be found by considering the vector field, $V(x, y)$, as a function over time:

$$\begin{aligned} u_t(x, y, t) &= \mu \nabla^2 u(x, y, t) - b(x, y)u(x, y, t) + c_1(x, y) \\ v_t(x, y, t) &= \mu \nabla^2 v(x, y, t) - b(x, y)v(x, y, t) + c_2(x, y) \end{aligned} \quad (2.3)$$

where $b(x, y) = f_x(x, y)^2 - f_y(x, y)^2$, $c_1(x, y) = b(x, y)f_x(x, y)$, $c_2(x, y) = b(x, y)f_y(x, y)$, and ∇^2 is the Laplacian operator. Here, the iterative numerical solution of Equation 2.2 can be obtained by substituting the following variables

2.3 Gradient Vector Flow Analysis

to Equation 2.3.

$$\begin{aligned}
 u_t &= \frac{1}{\Delta t} (u_{i,j}^{n+1} - u_{i,j}^n), & v_t &= \frac{1}{\Delta t} (v_{i,j}^{n+1} - v_{i,j}^n) \\
 \nabla^2 u &= \frac{1}{\Delta x \Delta y} (u_{i+1,j} + u_{i-1,j} + u_{i,j+1} + u_{i,j-1} - 4u_{i,j}) \\
 \nabla^2 v &= \frac{1}{\Delta x \Delta y} (v_{i+1,j} + v_{i-1,j} + v_{i,j+1} + v_{i,j-1} - 4v_{i,j})
 \end{aligned}$$

It is worth noting that the values for each position can be calculated independently of the other positions; thus, the GVF calculation for the whole MSA data can be parallelized. As a result, we can exploit the parallelism nature of the GPU to improve the performance of the algorithm.

2.3.2 MSA Analysis

The GVF algorithm discussed above contains two main stages: the computation of the initial GVF field and the propagation of the vector field based on the iterative solution of the underlying function. To enable the usage of GVF in the context of MSA analysis, we introduce constraints to both of these stages to directly incorporate the conserved structures as well as the disruptive changes into our algorithm.

Gradient Initialization

We first represent the MSA as a pixel map, in which each line is a sequence in the MSA and each pixel is a residue of the corresponding sequence. The corresponding pixel color is represented in the HSV color space to be able to separate residues based on their hue. However, depending on the used color-coding scheme, the distribution in the hue channel may not be uniform. Therefore, we perform histogram equalization on the hue channel to avoid bias in the vector calculation process. Based on this representation, we can now compute the initial gradient field, whereby we exploit different vector calculation methods. For the residues we calculate similarity vectors pointing into the direction of highest similarity, while for the gaps we exploit standard central differences gradient computation to obtain dissimilarity vectors. In the context of MSA analysis, the level of conservation is represented by the frequency of residues in the same column. This property can be represented as a flow pattern of highly conserved regions that is vertically directed. On the other hand, the disruptive change areas caused by the alignment process can be represented by a flow pattern that goes side ways. Therefore, the initial gradient field constructed from the input MSA image, I , is defined as follows:

$$grad(x, y) = \begin{cases} (0.0, \quad 1.0 - (I(x, y + 1) - I(x, y - 1))) & \text{for residues} \\ \left(\frac{I(x+1, y) - I(x-1, y)}{2.0}, \frac{I(x, y+1) - I(x, y-1)}{2.0} \right) & \text{otherwise} \end{cases}$$

Figure 2.4(a) shows the visualization the L1R_F9L family (PF02442) using

Figure 2.4: Vector field initialization based on the commonly used visual representation of MSAs. The visualization of the L1R_F9L family (PF02442) using the Clustal color scheme where black pixels denote gaps (a), can be transformed into the initial vector field used by the GVF algorithm (b). The x and y components of the vectors are encoded in the red and green channel; whereby high intensities are associated to positive values.

the Clustal coloring scheme where black pixels depict gaps in the alignment, and Figure 2.4(b) illustrates the initial vector field. To depict the vector field, we have color-coded the x and y components in the red and green channel, and high intensities depict large positive values. While the original structure of the MSA is preserved, the constructed vector field captures the transition in both conserved and non-conserved areas.

Gradient Propagation

In the second stage of the algorithm, the initial gradient field is propagated in such a way that original features of the input image are kept intact. In order to emphasize the features in the MSA, we introduce constraints into the propagation of the vector field. To achieve this, we make use of a weighting scheme applied to the Laplacian operator, ∇^2 , in Equation 2.3. A uniform weighting scheme is used to depict outliers, which are emphasized through isotropic vector propagation into all directions. In addition, we also introduce the constraint to avoid the connection of different residues in the same column

Figure 2.5: Result of the GVF analysis. Horizontal propagation enables the extraction of areas containing gaps as well as non-conserved residues (a), while vertical propagation allows us to identify highly or absolute conserved regions (b).

that leads to a false highly conserved area. In contrast, to emphasize the gaps introduced by the alignment algorithm in use, we constrain the propagation of the flow to a side-ways transition (see Figure 2.5(a)). Furthermore, constraining the propagation into the vertical direction allows us to extract the different levels of conservation in the MSA (see Figure 2.5(b)).

Figure 2.6 shows a comparison of isotropic and anisotropic propagation of the initial gradient field. In the standard isotropic propagation scheme, the initial gradient field is equally propagated in all directions as long as it minimizes the energy function in Equation 2.2. As can be seen in the top left of Figure 2.6(a), the isotropic property allows the gradients to propagate in all directions; thus, generate a circular shape (in shade of yellow) around the disruptive change (red). On the other hand, the initial gradient field is propagated unequally along different axes in the anisotropic propagation scheme (see Figure 2.6(b)). This enables us to extract highly conserved areas by emphasizing the propagation in the vertical direction. While the isotropic propagation scheme requires a smaller number of iterations to identify features of interest, it leads to the merging of regions that are close to each other, which is not always preferable for identifying conserved areas. However, the isotropic nature of the propagation

Figure 2.6: Visualization of isotropic (a) and anisotropic (b) gradient propagation in the GVF analysis. While isotropic propagation emphasizes residues of low conservation, anisotropic propagation emphasizes highly conserved regions and gaps.

process helps to identify the areas containing residues of low conservation. For instance, the isotropic propagation leads to the almost uniform distribution of gradient directions around the residues of low conservation. As a result, we can detect these features of interest through critical point detection.

As the gradient field propagation is an iterative process, the number of iteration can have impact on the result of the analysis. Figure 2.7 illustrates the results of anisotropic gradient field propagation in 0, 10, and 20 iterations. As the number of iterations increases, the gradient field propagation has the tendency to close the gaps between sequences in the MSA. Thus, we are able to extract regions, where no clean conservation is present, but a high frequency of the same residues with only local interruptions. The analysis on this result can help to provide a clean overview of the MSA as demonstrated in Section 2.4.

2.4 VISUALIZATION

The advantage of the commonly used color-coded table-based representation is the ability to reveal spatial correlations as well as local structures within MSA data sets. However, the visualization becomes less expressive as the number of sequences in the MSA increases. To deal with this downside when visualizing large-scale MSA data, often the spatial context is neglected and the sequences are depicted through statistics, as for instance residues histograms. While profile-based visualizations (Madera et al. 2004; T. D. Schneider and Stephens 1990; Schuster-Böckler et al. 2004) enable the abstraction of MSA by reducing the amount of information to be rendered, a profile does not capture any spatial information, such as the correlations between alignment positions, or the visibility of discernible sub-groups in the MSA. Consequently, such a visualization does not enable to obtain a detailed view of the whole MSA

2.4 Visualization

(a) 0 iterations (initial vector field)

(b) 10 iterations

(c) 20 iterations

Figure 2.7: Results of the anisotropic vertical gradient field propagation with a different number of iterations: 0 iterations (a), 10 iterations (b), and 20 iterations (c). A higher number of iterations leads to a gap closure between same residues, and thus allows to detect areas with a high frequency of residues but no clear conservation.

with all sub-structures. When on the other hand using sequence clusters to reduce the amount of data to be visualized, the spatial context can be preserved. However, large MSAs that contain tens of thousands of sequences still result in high a number of clustered sequences which is challenging for the table-based visualization approach. By exploiting the proposed GVF analysis, we are able to support the visual identification of patterns in large-scale MSA data. It is worth mentioned that the proposed GVF analysis is shape preserving. Particularly, the proposed technique does not introduce artifact into the original input data. As a result, the extracted features from the GVF analysis conform with the original structure in the MSA under investigation, and the proposed visualization technique does not introduce artifact into the original data.

Figure 2.8: Visualization of the MSA of the Sulfite exporter TauE/SafE (PF01925) consisting of 12,351 sequences with 1,220 residues using the Clustal color scheme (a), and the proposed visualization technique (b). Through GVF analysis, the disruptive changes and the level of conservation are captured and emphasized.

2.4.1 Feature Emphasis

Based on the GVF analysis, we can identify conservation areas, the patterns of the gaps inserted by the alignment algorithm, as well as the areas containing residues of low conservation. The colors of these features have been chosen to comply with the rules of pre-attentive perception (Theeuwes 1992). In the GVF, the flows that represent the conserved areas move vertically so they are colored green. On the other hand, the flows that moves horizontally, which reflect the gaps inserted by the alignment algorithm, cause disruptive changes so they are colored red. The residues with low conservations are colored in shades of yellow for highlighting. Figure 2.1(b) illustrates the visualization of features extracted from the GVF analysis applied to the L1R_F9L family (PF02442). While the green vertical lines depict the conserved areas, the red horizontal lines show the disruptive changes in the flow, which reflect the patterns of the gaps inserted by the alignment algorithm.

A common problem arising when visualizing large-scale MSA data is that the size of features can be small in comparison to the large amount of data that needs to be rendered. Therefore, in order to emphasize small features of interest in an overview visualization, special considerations are required. Particularly,

while the widely used morphology operators (Serra 1982) in image processing can help to highlight small features, they introduce artifacts along the way since they are not shape-preserving. The advantage of using the presented GVF analysis allows us to increase the propagation process of the gradient field to upscale the detected features and guarantee the coherence with the original structure of the MSA. In Figure 2.1(b), the residues with low conservation are shown as yellow-shaded circles and they adhere to the original structure as shown in Figure 2.1(a).

Now that we were able to depict features of interest, they need to be shown in the context of the original representation in order to link them to specific residues. While multiple linked view setups have been proven to be very useful when dealing with multiple visual representations (Tory 2003), its application to the visualization of large-scale MSAs can be limited due to the amount of rendered information as well as the complexity of underlying data distributions. As especially the latter makes the mental registration difficult, alternative concepts are needed. We make use of overlaying and use the extracted features as visual annotations. As illustrated in Figure 2.1(c), the detected features are color-coded and imposed onto the gray scale format of original MSA image, which serves as the background formation. This enables us to highlight features in the context of the original MSA and avoid a cumbersome mental spatial registration between the two visual representations. In addition, we allow for interactive changes of the degree of blending between the two representations.

2.4.2 Conservation Exploration

While the standard conservation histogram provides statistical information about the distribution of the residues in the individual columns, it does not capture their spatial distribution. By using GVF propagation with the vertical constraint introduced above, we can identify the length of the flow patterns to detect conserved regions. As the detected features adhere to the original structures, we can not only show the level of conservation but also visualize them in the original context. This enables us to facilitate the exploration of the conservation level in the MSA. Figure 2.9 illustrates the exploration of different levels of conservation in the MSA. From top to bottom is the visualization of the conserved areas that have the length greater than or equal to 20%, 50%, and 80% of the absolute conservation. As the level of conservation exploration can help researcher to quickly identify absolute conserved areas as well as highly conserved areas, it facilitates the detection of residues that are critical for function as well as residues that are probably important for function or structure stability.

2.5 TEST CASES

We applied the proposed visualization technique to two large-scale MSAs from the Pfam database (Wellcome Trust-Sanger Institute) (Punta et al. 2012). The

Figure 2.9: Level of conservation exploration. From top to bottom is the visualization of conserved areas that have the length greater than or equal to 20%, 50%, and 80% the length of the absolute conserved area.

Sulfatases are a highly conserved enzyme family, with similar overall folds, mechanisms of action, and bivalent metal ion-bindings (Ghosh 2007; The UniProt Consortium 2009). The MSA (PF00884) contains 18,763 sequences with the maximum length of 1,668 residues, whereby the MSA of the Sulfite exporter TauE/SafE (PF01925) contains 12,351 sequences with the maximum length of 1,220 residues. In both cases, as the number of sequences exceeds ten thousand, the ability to convey the gross trends of the whole family is a challenge.

Figure 2.10 shows the visualization of the Sulfatase enzymes family (PF00884) using our proposed visualization approach. In Figure 2.10(a), the whole family is visualized using the Clustal color scheme. Each line in the image represents a sequence and each residue is represented as a pixel at the corresponding position. Figure 2.10(b) illustrates the result of the extracted features based on the GVF analysis. Although the use of color helps to reveal the highly conserved position in the traditional representation, it is difficult to perceive the patterns of the gaps that disrupt the conservation. Our visualization in Figure 2.10(b) not only manages to reveal the highly conserved regions but also to emphasize the patterns resulting from gaps. The visualization depicts highly conserved

areas in a manually annotated data set, which has been previously visualized by Procter and colleagues (Procter et al. 2010). With our approach, the areas containing residues of low conservation are detected through the GVF analysis and highlighted through yellow-shaded circular shapes. The application to the Sulfite exporter TauE/SafE as shown in Figure 2.8 has similar qualities. Thus, our visualization enables a quick overview by depicting the gross trends which are of potential interest. By seamlessly blending between the standard Clustal representation and our extracted features, domain experts can explore large-scale MSA data sets by obtaining an overview and residue details simultaneously.

2.6 CONCLUSIONS AND DISCUSSIONS

In this chapter, we have proposed a novel approach for extracting and visually emphasizing patterns in MSA data. By transforming a pixel-based MSA representation into a vector field, we were able to apply GVF analysis in order to extract patterns, which are important during the MSA analysis process. Therefore, we combine isotropic and anisotropic vector propagation, which helps us to extract conserved as well as non-conserved areas. Due to the shape preserving nature of the GVF analysis, the extracted information can be used to visually emphasize the detected features, and ultimately annotate a standard table-based MSA representation. The proposed visual emphasis has been developed with respect to the perceptual properties of the human visual system and, thus, enables the user to spot patterns of interest even in overview visualizations of large-scale MSA data. We have demonstrated our approach by applying it to various MSA data sets used for protein analysis.

In the future, we would like to conduct a thorough evaluation to serve as a foundation for improving the presented approach. Thus, extending the technique to handle genome data, and making it available to a wider audience of domain experts are important steps. While we currently derive the initial vector field from a histogram-equalized pixel-based MSA representation, we plan to experiment with different value distributions. By distributing the intensities encoding residues in various ways, it would become possible to specifically emphasize transitions between certain amino acids or amino acid groups of interest. Furthermore, we would like to investigate how the presented approach can be used to compare the results of different alignment algorithms, and how we can exploit different sequence orderings, which we currently not address.

Figure 2.10: Visualization of the MSA of Sulfatase (PF00884) consisting of 18,763 sequences with the longest length of 1668 residues. The visualization of the whole MSA using the Clustal color scheme (a), in comparison to the features extracted and visualized using the proposed GVF analysis technique (b). While the vertical green lines depict the highly conserved areas, the horizontal red lines show the patterns of the gaps inserted by the alignment algorithms that cause disruption in the conservation areas. The residues of low conservation are shown in yellow-shaded circular shapes. The proposed technique enables highlighting of the absolutely or highly conserved areas as well as emphasizing the gaps that cause disruption.

CHAPTER 3

ANALYZING AND REDUCING DTI TRACKING UNCERTAINTY BY COMBINING DETERMINISTIC AND STOCHASTIC APPROACHES

3.1 INTRODUCTION

Diffusion Tensor Imaging (DTI) is a magnetic resonance imaging (MRI) technique that allows non-invasive imaging of the diffusion process of water molecules in biological tissues, such as muscles, or brain white matter. Experimental evidence has shown that the water diffusion in an organized tissue is *anisotropic* (Moseley et al. 1990), as the diffusion magnitude is dependent on the diffusion direction (Beaulieu 2002). These characteristics of water diffusion can be mathematically represented by a diffusion tensor field in which the main eigenvector of each tensor corresponds to the direction of the greatest diffusion (Basser, Mattiello, et al. 1994). By following the main diffusion within a tensor field, a DTI data set can be represented as a set of extracted fiber tracts, or three-dimensional pathways. Alternatively, more advanced techniques based on exploiting the use of probability models or bootstrapping can be used to reconstruct the corresponding three-dimensional pathways. As these tractography algorithms allow for extraction of information regarding connectivity in the brain, they are of great interest to a wide variety of medical and biomedical applications, such as the study of brain development, cerebral ischemia, neurodegenerative diseases (Ciccarelli et al. 2008), and neurosurgical scenarios, such as epilepsy surgery or other cranial surgical interventions. However, despite the potential of DTI, the reliability of the reconstructed fibers is often questioned. This is due to the fact that DTI data are usually of low resolution and suffering from a low signal to noise ratio. Additionally, many sources for uncertainty occur during the long acquisition process as well as the processing and visualization of DTI data. Consequently, the use of DTI fiber tracking in clinical practice is limited, and a more pervasive and reliable use of DTI tractography results can be enabled only by understanding and reducing the involved uncertainty.

In this chapter, we propose a novel approach for analyzing and reducing the uncertainty in the context of DTI tractography algorithms. To achieve this goal, we derive the uncertainty information from different sets of reconstruct fibers using different deterministic and stochastic fiber tracking algorithms. The derived uncertainty is then represented in a unified way and serves as the

foundation for the generation of a new set of fiber tracts with a lower level of uncertainty. This enables an effective approach to the fusion of different uncertainty sources, and the application to real-world and synthetic data shows that it yields improved fiber tracking result.

The remainder of the chapter is structured as follows. In the next section, we review work related to the proposed approach. In Section 3.3, we present the derivation and reduction of uncertainty from different fiber tracking algorithms. We then present our visual computing system used to reveal the information of the analysis process in Section 3.4. We apply the proposed technique to different data set and report the results in Section 3.5, and conclude the chapter in Section 3.6.

3.2 RELATED WORK

3.2.1 DTI Tractography

DTI fibers tracking represents a collection of different algorithms for reconstructing the brain nerve fibers from diffusion-weighted magnetic resonance (MR) data (Basser, Pajevic, et al. 2000; Mori and Zijl 2002). These algorithms can be roughly classified into two categories: deterministic and stochastic approaches. Deterministic algorithms do initially not associate uncertainty values with the reconstructed trajectory, and all reconstructed trajectories are inherently considered as equally probable. Moreover, deterministic algorithms, without extension, produce only one reconstructed trajectory per seed point, and therefore branching of fascicles will not be represented. However, bootstrapping makes it possible to obtain uncertainty information for the tracking results (Lazar and Alexander 2005; R. Liu 1988). While conventional bootstrapping requires several scans and introduces additional registration artifacts, it could be shown that the wild bootstrap technique, which works on a single diffusion-weighted data set (Whitcher et al. 2008), can achieve comparable reconstruction results (D. K. Jones 2008). In contrast to deterministic methods, stochastic algorithms incorporate multiple pathways emanating from the seed points and from each point along the reconstructed trajectories. These algorithms, however, are often criticized for making *a-priori* assumptions about the characteristics of uncertainty in the data (Friman, Farneback, et al. 2006; Parker et al. 2003). For instance, when using probability distribution functions (PDFs), it can lead to an ad hoc formulation of relationships between the anisotropy of the diffusion process and the uncertainty of the estimated principal eigenvector of the diffusion tensor (D. K. Jones 2008). Consequently, the sources of errors are not truly considered, and uncertainty is generally modeled based on a Gaussian formulation. However, when analyzing the uncertainty derived from both, wild bootstrap and probability-based techniques, new fiber tracts with a potentially lower degree of uncertainty can be obtained, and thus the dependency on the *a-priori* assumptions can be reduced.

Deterministic algorithms are based on line propagation algorithms that use local tensor information for each step of the propagation. The FACT (Fiber Assignment by Continuous Tracking) is one of the first streamline tracking techniques in this group (Basser, Pajevic, et al. 2000; Conturo et al. 1999; Mori, Crain, et al. 2001). Another commonly used fiber tracking algorithm is called tensorline (Weinstein et al. 1999), and makes use of the full diffusion tensor to deflect the estimated fiber trajectory. There have been two main drawbacks in deterministic tractography. As these algorithms cannot represent branching of fascicles, and provide no indication of the uncertainty, Whitcher et al. proposed the use of the wild bootstrap technique to derive uncertainty from the underlying diffusion-weighted data and then use these results as the foundation for tracking algorithms (Whitcher et al. 2008). While the traditional bootstrap technique provides good estimates of uncertainty in DTI datasets (Lazar and Alexander 2005; R. Liu 1988), it requires multiple scans, which is not an optimal solution in clinical practice. However, Jones has reported that the results from the wild bootstrap approach are comparable to the ones using the traditional bootstrap technique (D. K. Jones 2008). The main difference between the deterministic and the stochastic approaches is the use of a probability model, which allows to consider multiple pathways emanating from each seed point as well as from each point along the reconstructed trajectories. As a result, one obtains not only the fiber bundles but also the uncertainty associated with the fibers (Lazar and Alexander 2005; Whitcher et al. 2008; Friman, Farneback, et al. 2006).

3.2.2 DTI Visualization

The reconstructed fiber trajectories can be visualized in several different ways such as glyphs (G. Kindlmann 2004; Schultz and G. L. Kindlmann 2010; Wittebrink et al. 1996), streamlines, streamtubes (Merhof et al. 2006), and hyperstreamlines (Schultz and G. L. Kindlmann 2010; Vilanova, Zhang, et al. 2006). To reduce the complexity of the geometry of the fiber tracts, several techniques have been proposed, such as wrapped streamlines (Enders et al. 2005), hierarchical principal curves (Chen, Zhang, et al. 2008), color-mapping (Demiralp and Laidlaw 2009; Demiralp, Zhang, et al. 2006), texture patterning of fiber dissimilarity (D. Jianu et al. 2007), or topological simplification (Schultz, Theisel, et al. 2007). Furthermore, various clustering techniques can help to group similar fiber tracts to reduce visual clutter (Moberts et al. 2005). However, these techniques make it also more difficult to show the uncertainty associated with individual fibers. Lodha et al. proposed a visualization pipeline to reveal the uncertainty in fluid flow which can be applied to the visualization of DTI fibers (Lodha et al. 1996). Chen et al. proposed a novel interface for exploring densely sampled 3D DTI data (Chen, Ding, et al. 2009). Driven by known embedding methods, the proposed framework provides the ability to project characteristics of fiber tracts from 3D space to a 2D space in such a way that the distance between points are preserved as much as possible. A significant

Figure 3.1: Visualization of fiber bundles reconstructed by using the FACT algorithm with wild bootstrapping (a), the Bayesian approach (b), and the PICO approach (c).

drawback of this approach is the the lack of anatomical interpretation. Besides visualization, the ability for scientists to interactively explore and select DTI fibers for inspection is often desired. However, visual exploration and analysis of densely sampled DTI in 3D is challenging due to the visual clutter caused by the complexity of the geometry. Hence, a substantial amount of research has been focused on solving the difficulties in interacting with densely sampled DTI fibers by proposing new visual forms or novel interaction methods (Akers 2006). Sherbondy et al. proposed a set of interaction techniques for exploring the brain connectivity and interpreting pathways (Sherbondy et al. 2008). The main operations provided to neuroscientists are the placement and manipulation of box-shaped or ellipsoid-shaped regions in coordination with a simple and flexible query language. Blaas et al. proposed a similar approach for efficient selection of fiber tracts (Blaas et al. 2012). Jianu et al. proposed an interactive approach to navigate through complex fiber tracts in 3D (D. Jianu et al. 2007; R. Jianu et al. 2009). More recently, Brecheisen et al. proposed a novel framework to visually explore the effect of parameter variation to the reconstructed fiber tracts (Brecheisen et al. 2009). The basis for this visualization technique is the pre-computation of all fiber tracts from all possible combination of threshold values and thus provides the user with a better understanding of the tractography result.

3.3 UNCERTAINTY DERIVATION AND REDUCTION

In this section, we will introduce how to reduce fiber tracking uncertainty by incorporating three of the most widely used approaches: FACT with wild bootstrapping, the Bayesian approach, and the probability index of connectivity (PICO) approach. However, to be able to perform this desired uncertainty reduction, we need to first derive a common uncertainty measure for these incorporated tractography algorithms.

In a DTI experiment, the diffusion-weighted signal S is modeled by

$$S(g_j) = S_0 \exp(-b g_j^T D g_j) \quad \text{with } j = 1, 2, \dots, N \quad (3.1)$$

where S_0 is the signal intensity with no diffusion gradients applied, b is the diffusion weighting factor, D is an effective self-diffusion tensor in the form of a 3×3 positive definite matrix, g is a 3×1 unit vector of the diffusion-sensitive gradient direction, and N is the total number of experiments, including repeated measurements. By applying a log transform, Equation 3.1 can be structured into the well-known multiple linear regression form (Basser, Mattiello, et al. 1994):

$$y = X\beta + \varepsilon \quad (3.2)$$

where $y = [\ln(S(g_1)), \ln(S(g_2)), \dots, \ln(S(g_N))]^T$ are the logarithms of the measured signals, $\beta = [D_{xx}, D_{yy}, D_{zz}, D_{xy}, D_{xz}, D_{yz}, \ln(S_0)]^T$ are the unknown regression coefficients consisting of the six unique elements of the self-diffusion tensor, D , $\varepsilon = [\varepsilon_0, \varepsilon_1, \dots, \varepsilon_N]^T$ are the error terms, and X is a matrix of different diffusion gradient directions.

$$X = -b \begin{pmatrix} g_{1x}^2 & g_{1y}^2 & g_{1z}^2 & 2g_{1x}g_{1y} & 2g_{1x}g_{1z} & 2g_{1y}g_{1z} & 1 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ g_{Nx}^2 & g_{Ny}^2 & g_{Nz}^2 & 2g_{Nx}g_{Ny} & 2g_{Nx}g_{Nz} & 2g_{Ny}g_{Nz} & 1 \end{pmatrix}$$

Based on this mathematical representation, the diffusion tensor can be estimated through the use of weighted least squares (WLS) regression.

3.3.1 Wild Bootstrap Approach

This is a model-based resampling technique, designed to investigate the uncertainty in linear regression with heteroscedasticity, i. e., non-constant variance with different regressors of unknown form (R. Liu 1988). Wild bootstrap resampling is defined as:

$$y_i^* = x_i \hat{\beta} + e_i^* \quad (3.3)$$

where the resampling error e_i^* is:

$$e_i^* = \frac{y_i - \hat{\mu}_i}{(1 - h_i)^{1/2}} t_i \quad (3.4)$$

Here, t_i are independent and identically distributed (i.i.d) random variables with $E(t_i) = 0$, and $E(t_i^2) = 1$, the leverage value h_i is the i -th diagonal element of the hat matrix defined in the WLS process, and $\hat{\mu}_i$ is the i -th WLS fitted log measurement.

In this technique, a bootstrap sample set $y_i^* = [y_1^*, y_2^*, \dots, y_N^*]$ undergoes the WLS fitting procedure which leads to D^* , based on which a non-linear DTI parameter $\hat{\theta}^*$ such as fractional anisotropy (FA) is calculated. The repetition

of resampling e_i^* and calculating the non-linear parameter $\hat{\theta}^*$ through a fixed large number, N_B , of times (typically from hundreds to thousands of times) will yield the underlying uncertainty from the diffusion data. Particularly the N_B independent bootstrap samples $\hat{\theta}^{*b}$, $b = 1, 2, \dots, N_B$ represent the replication of $\hat{\theta}$, which is an estimation of the true unknown θ using the original sample y by WLS, with the associated uncertainty e_i^* .

In our approach, we apply an averaging scheme over the resampled e_j^* and use this as the uncertainty at each point along the reconstructed fiber

$$u_W = \frac{\sum_{j=1}^{N_B} e_j^*}{N_B}$$

In general, with all incorporated algorithms, we omit the usage of a direction-weighted error computation scheme, as the branching nature of the probability fiber tracts, enables us to obtain this uncertainty in a dense manner around each fiber.

3.3.2 Bayesian Approach

This technique makes use of the local PDF to capture the uncertainty at each voxel of the reconstructed fiber (Friman, Farneback, et al. 2006). In particular, it is assumed that there is only one fiber orientation in each voxel, and any deviations from the model will be captured as uncertainty in this orientation. In each voxel, given combination of data and model, the likelihood of the fiber orientation along an axis X is formulated as:

$$P(X|D) = \frac{P(D|X)P(X)}{P(D)} \quad (3.5)$$

Given the principal direction X , by applying WLS regression to solve the linear regression system described in Equation 3.2 for a fixed large number of times, N_B , the model yields the predicted measurement $\hat{\mu}_i$, $i = 1, \dots, N_B$. The observed data, y_i , is a noisy estimate of $\hat{\mu}_i$ which is modeled as:

$$\ln(y_i) = \ln(\hat{\mu}_i) + \varepsilon_i \quad (3.6)$$

where ε_i is Gaussian distributed as $N(0, \frac{\sigma^2}{\hat{\mu}_i^2})$, where σ^2 is the variance of the noise contained in the MRI data. As a result, the likelihood of the fiber along the axis X at a voxel is given as:

$$P(D|X) = P(y_1|\hat{\mu}_1)P(y_2|\hat{\mu}_2) \dots P(y_{N_B}|\hat{\mu}_{N_B}) \quad (3.7)$$

With the assumption that the prior distribution for all parameters except X is a dirac delta function, $P(D)$ is then the integral of $P(D|X)$ over the sphere. For diffusion tensor data, the priors of S_0 and the tensor eigenvalues are fixed around the maximum-likelihood estimate (MLE). Thus, the function $P(D|X)$

can be evaluated by setting the tensor principal direction to X and computing the likelihood of the observed data.

As shown in Equation 3.7, one can derive the underlying uncertainty information from the diffusion data and this information reveals the uncertainty associated with each reconstructed fiber. In this work, we apply an averaging scheme on the uncertainty derived from the Monte Carlo random walk process to derive the uncertainty of each point along the reconstructed trajectory

$$u_b = \frac{\sum_{i=1}^{N_B} P(y_i | \mu_i)}{N_B} \quad (3.8)$$

3.3.3 Probability Index of Connectivity (PICO) Approach

Parker et al. have proposed a novel approach to associate uncertainty with the reconstructed trajectories (Parker et al. 2003). This is achieved by relating the probability of a tract with the number of times it is reconstructed in a Monte Carlo random walk, where the characteristics of the random walk are governed by the properties of the diffusion tensor, i. e., fractional anisotropy (FA). The PICO approach incorporates the directional uncertainty into the fiber tracking process at every step along its length by defining a modified principal eigenvector $v_{1mod}(x, n) = v'_1(x) + \delta v'_1(x, n)$, where n indexes the iteration of a Monte Carlo process. Similarly, one can define $v'_{1mod}(x, n) = v'_1(x) + \delta v'_1(x, n)$ within a rotated frame of reference x', y', z' , where $v'_1(x)$ is simply $v_1(x)$ rotated into the new frame of reference with z' defined by $v_1(x)$. As a result, $\delta v'_1(x, n)$ is defined by the angles $\delta\theta'(x, n)$ and $\delta\phi'(x, n)$, which are obtained from the PDF of possible fiber bundle orientations at each point encountered during the tracing process.

Two methods have been proposed for calculating the uncertainty in the orientation of the principal diffusion direction v_1 : 0th order and 1st order cases. In the 0th order case, the uncertainty in the principal diffusion direction v_1 is defined by the tensor anisotropy, providing an isotropic normal distribution of orientation centered on the original estimate of v_1 . A sigmoid function is applied to the standard deviation (SD) of the distribution of possible values for $\delta\theta'(x)$ to link the uncertainty to FA. In the 1st order case, the uncertainty is dependent on the skewness of the tensor through the analysis of the minor eigenvectors, v_2 and v_3 , and their corresponding eigenvalues. As a result, this provides a more accurate distribution of orientation in the case of oblate tensor ellipsoids. Detail information about the choice of proper the PDF are discussed in (Parker et al. 2003) and (Seunarine et al. 2006).

To derive uncertainty, let $\chi(V, N)$ be the number of occasions a voxel V is crossed by the reconstructed trajectories over N repetitions during the fiber tracking process. The map of the probability, Ψ , of connection to the seeding point can be formulated as

$$\Psi(V) \approx \Psi(V, N) = \frac{\chi(V, N)}{N} \quad (3.9)$$

where Ψ reflects the definition of uncertainty of eigenvector orientation mentioned above. Therefore, in this work we use Ψ to depict the associated uncertainty for points along the reconstructed fibers and refer to it as u_p .

Although the uncertainty values as used in the different tractography algorithms can be traced back to the same data set, the outcome of the tracing stage can vary substantially. Figure 3.1 shows a comparison of the tractography results of the three discussed algorithms. The closeups on the right of each subfigure emphasize some characteristic differences. To be able to fuse uncertainties from different sources, it must be possible to relate them to each other. Therefore, it is important to note, that although the incorporated uncertainty values are calculated using different schemes, they are all based on the distribution of the FA parameter of the underlying diffusion tensor field. Although the idea of comparing the derived uncertainty from the wild bootstrapping and other Monte Carlos based techniques has been proposed in (Zhu et al. 2008; Chung et al. 2006), their approach focuses on the numerical analysis of the derived uncertainty and quantitatively assess the reconstructed fibers through visualization. In our approach, we provide the ability to not only compare the derived uncertainty but also allowing the reduction of these values through visual analysis. As a result, these uncertainty values can be used together as a foundation for the uncertainty reduction, as we show in Section 3.5. To allow a more meaningful relation, all derived uncertainty values are normalized to lie in the interval $[0, 1]$.

3.3.4 Uncertainty Reduction

Based on the analysis of the derived uncertainty discussed above, we propose a novel method to generate a new set of fiber tracts that has a lower uncertainty level. In order to achieve this, we first identify matching fiber tracts from different set of reconstructed fibers using different fiber tracking algorithms, e. g. FACT with wild bootstrap, Bayesian tractography, and PICO tractography. We then estimate the intersections between these fiber tracts. As the FACT with wild bootstrap, the Bayesian, and the PICO tractography are based on the line propagation algorithm to track the trajectories, the distance between two consecutive points along a reconstructed fiber depends on the step size used in the fiber tracking process. Moreover, in order to limit the effect of numerical error propagation, a lower bound and a upper bound threshold are pre-defined for the estimation of intersections. Let $d(p_i^k, p_j^l)$ denote the distance between the point p_i on the fiber k and the point p_j on the fiber l . Then, the condition for an intersection is formulated as

$$u \leq d(p_i^k, p_j^l) \leq v \quad (3.10)$$

where u is the lower bound and v is the upper bound threshold.

Once the intersections have been identified, the fibers are divided into segments. The average uncertainty of each segment is used as the foundation to generate a new fiber tract by combining corresponding segments with lower

uncertainty. As a result, this enables us to achieve a new set of fibers with low uncertainty. The advantage of using an averaging scheme is to reduce the *a-priori* assumption in the probabilistic tractography algorithms, e. g. Bayesian and PICO tractography. For instance, depending on the input *a-priori* information, the PDFs in the Bayesian tractography can lead to an ad hoc formulation of relationships between the anisotropy of the diffusion process and the uncertainty of the estimated principal eigenvector of the diffusion tensor (D. K. Jones 2008). On the other hand, the wild bootstrapping technique does not have this property. Therefore, an averaging scheme can help to reduce the *a-priori* assumption when fusing the uncertainty from these fiber tracking algorithms. It is worth noting that depending of the application cases or the involvement of domain knowledge the proposed technique can be easily extended to more advanced uncertainty fusion schemes.

3.4 INTERACTIVE SYSTEM SETUP

In order to verify our approach and to influence the proposed fiber reduction, we have developed an interactive visual computing system, which we briefly present in this section.

3.4.1 3D Fibers Visualization

There have been many visual representations proposed for visualizing fibers in the last years (G. Kindlmann 2004; Schultz and G. L. Kindlmann 2010; Merhof et al. 2006; Vilanova, Zhang, et al. 2006; Vilanova, Berenschot, et al. 2004; Mallo et al. 2005). Although the streamline representation has the advantage of being a fast method due to its low geometry complexity, lines with more than one pixel suffer from gaps in highly curved areas. In addition, depth perception is not supported when lines with a constant density are used (Merhof et al. 2006). On the other hand, streamtubes provide better depth cues as they allow a shaded surface visualization, which helps to improve the perception of the fibers' structure (Merhof et al. 2006). As a result, we make use of the streamtube representation in our system, to be able to represent the set of reconstructed fibers together with their uncertainty expressed through color saturation.

It is worth noting that the rendering of streamtubes are more demanding due to its complex geometry structure. In order to achieve high quality visualization, we exploit the use of vertex buffer objects (VBOs) to accelerate the visualization of densely sampled DTI fibers. For instance, we separate the geometry description of the fibers and their associated parameters, e. g. FA, MD, and uncertainty values. These values are stored in textures, which are associated with the fibers through texture coordinates. This enables us to map multiple values of interest into different visual representations to provide not only high quality visualization but also at an interactive frame rates, which is essential to explore the derived uncertainties. Figure 3.2 illustrates the visualization of the same reconstructed fibers with the color mapped to different properties. While

3.4 Interactive System Setup

Figure 3.2: Visualization of DTI fibers using the streamtube representation. (a) is the visualization of the reconstructed fibers using streamtubes with the color mapped to the normal vector at each point along the fibers. (b) is the visualization of the same fibers with the uncertainty mapped to the saturation of the color.

the color of the fiber is mapped to the normal at each point along the fiber in Figure 3.2(a), the derived uncertainty is mapped to the saturation of the color in Figure 3.2(b).

3.4.2 Uncertainty Investigation Widget

As mentioned in Section 3.3, the uncertainties from the wildbootstrap, the Bayesian tractography, and the PICO tractography are derived by resampling the diffusion tensor in each voxel of the input DTI data set. Therefore, there is an implicit relation between the distribution of the FA parameter obtained from the DTI, and the derived uncertainty on a per voxel basis. It turned out, that it is helpful to reveal this relation in the context of the reconstructed fibers to obtain an overview of the distribution of the derived uncertainty over the underlying FA. To this end we provide a 2D histogram view visualizing this relation. The image on the right in Figure 3.3 shows the 2D histogram representing the relation between FA and the derived uncertainty from the PICO approach. By placing colored primitives on this 2D histogram, the user can explore this relation. For instance, with the setup in Figure 3.3, the portions of the fibers that have a high FA and high uncertainty are highlighted in blue, while the portions with low FA values and low uncertainty or average FA and average uncertainty are highlighted in yellow and red respectively. Based on the result, the user can filter out for instance the fibers that have low FA and low certainty in the reconstructed fibers.

Figure 3.3: Visual depiction of the relations between the FA and the derived uncertainty in PICO tractography. While the portions of fibers that have high FA, high uncertainty is colored blue, the portions with low FA, low uncertainty or average FA and average uncertainty are highlighted in yellow and red respectively.

The proposed 2D histogram exploration widget can also be used to show the relation between different comparable derived uncertainties from the same DTI data set using different resampling techniques. This is helpful for the comparison of different resampling schemes as well as the comparison of a newly developed technique with the existing ones. The combination of visualization and interaction techniques realized in this system, has been applied to generate the results discussed in the next section.

3.5 RESULTS AND DISCUSSIONS

In this Section, we present and discuss the results of the proposed uncertainty analysis and reduction technique applied to both synthetic and real-world data sets. In order to have a controlled setup, we first apply the proposed technique to a synthetic data set. We then apply the proposed technique to two real-world data sets: the monkey brain, and the human brain. In all cases we have applied the visual computing system described above, whereby the interaction time used for the uncertainty reduction was below five minutes.

3.5.1 Synthetic Data Set

For a controlled setup, we use the linear synthetic data set (Deoni 2008), which contains scans for 30 directions, each scan has the size of $150 \times 150 \times 16$ voxels, and a signal-to-noise ratio (SNR) of 30:1.

The FACT with wild bootstrap, and the Bayesian fiber tracking algorithms were applied to the data set to generate the initial sets of reconstructed fibers. The resampling scheme were set for 50 iterations, and the seeding point was

Figure 3.4: For illustration purposes, we have applied the proposed uncertainty analysis and reduction technique to a simple linear synthetic fiber dataset (courtesy of S. Deoni (Deoni 2008)). (a) is the visualization of a straight forward combination of the reconstructed fibers using different algorithms. (b) is the visualization of the output of the proposed uncertainty analysis and reduction technique applied to the same data sets.

Table 3.1: Result from the uncertainty derivation and reduction applied to the linear synthetic data set.

	FACT (Wild Bootstrap)	Bayesian	Uncertainty reduction
Number of fibers	50	50	28
Average uncertainty	0.244	0.130	0.110
Min uncertainty	0.347	0.000	0.000
Max uncertainty	0.700	1.000	0.396

set on the original line. As a result, each fiber tracking algorithm produces a set of 50 reconstructed fibers. By applying the proposed uncertainty reduction method, we could achieve a new set of fibers, which contains whole fibers or the combination of portions of fibers with lower level uncertainty. The result is illustrated in Figure 3.4 and reflected quantitatively in Table 3.1. In addition to a lower average uncertainty level, the output of the uncertainty reduction technique also has a smaller range between the minimum and maximum uncertainty values. Moreover, the result is close to the original synthetic data.

3.5.2 Monkey Brain Data Set

In this test case, we use a DTI data set of the brain of a monkey, which contains scans of 30 directions, each scan has the size of $224 \times 224 \times 50$, and the voxel size is $2 \times 2 \times 2$ mm. The resampling scheme in the fiber tracking algorithms were set to 50 iterations, and 12 seeding points were set in the middle of the corpus callosum. Table 3.2 shows the result of the uncertainty before and after applying the proposed technique. The proposed uncertainty reduction technique not

Table 3.2: Results from the uncertainty derivation and reduction applied to the monkey brain data set.

	Bayesian tracking	PICo tracking	Uncertainty reduction
Number of fibers	600	600	198
Average uncertainty	0.558	0.609	0.490
Min uncertainty	0.238	0.000	0.000
Max uncertainty	0.708	1.000	0.824

only allows us to have a result with a lower average uncertainty level but also reduces the range between the minimum and maximum uncertainty.

3.5.3 Human Brain Data Set

For a more complex test case, we use the DTI data set from the VisContest 2010 which contains scans of 30 directions, each scan has the size of $128 \times 128 \times 72$, and the voxel size is $1.8 \times 1.8 \times 2.0$ mm. The resampling scheme in the fiber tracking algorithms were also set to 50 iterations, and 12 seeding points were set in the middle of the corpus callosum. As can be seen in Table 3.3, the proposed approach for analyzing and reducing uncertainty improve the output. This is indicated by the fact that the average uncertainty decreases. Figure 3.5(b) illustrates the result of the proposed uncertainty reduction technique in comparison to a brute-force combination approach. While the brute-force combination of the reconstructed fibers from the PICo and Bayesian tractography does not yield a better result (see Figure 3.5(a)), the proposed technique enables a new set of fiber tracts with low level of uncertainty (Figure 3.5(b)).

It should be pointed out that the reduction of the number of fibers does not result from discarding fibers, but from a combination of low uncertainty fibers. Having such a selection of lower uncertainty fibers can be beneficial for several applications. When for instance performing connectivity analysis, more reliable statements about the connectivity of regions can be made. As such connectivities influence the derivable functionality drastically, certainty is

Table 3.3: Results from the uncertainty derivation and reduction applied to the human brain data set.

	Bayesian tracking	PICo tracking	Uncertainty reduction
Number of fibers	300	300	87
Average uncertainty	0.506	0.701	0.39
Min uncertainty	0.036	0.000	0.000
Max uncertainty	0.69	1.000	0.65

Figure 3.5: Visualization of a brute force combination of the reconstructed fibers from PICO and Bayesian tracking algorithms (a), and the result of the proposed uncertainty reduction technique (b).

of high importance in this area.

3.6 CONCLUSIONS AND FUTURE WORK

In this chapter, we have proposed an novel approach for analyzing and reducing the uncertainty in reconstructed DTI fibers using different tracking algorithms. The uncertainty reduction is based on a unified uncertainty representation, which we derive from three deterministic and stochastic tractography algorithms: FACT with wild bootstrapping, Bayesian tractography, and PICO tractography. Through this combination, it becomes possible to incorporate fiber uncertainty from different sources in order to generate new tractography results with reduced overall uncertainty. Therefore, we hope that this is one important step towards a wider acceptance of DTI techniques.

Although, by using the proposed technique, fiber tracts with reduced uncertainty can be generated, it would be interesting to integrate additional tractography algorithms on top of the three discussed approaches. We would further like to investigate if a biased uncertainty fusion would be beneficial in some cases. At the moment, the uncertainties obtained from the different algorithms are taken into account with equal weighting. However, for specific application cases or domain experts, it may be beneficial to apply a non-uniform weighting.

CHAPTER 4

DERIVING AND VISUALIZING UNCERTAINTY IN KINETIC PET MODELING

4.1 INTRODUCTION

Positron emission tomography (PET) is one of the most widely used functional imaging modalities and it is applied in medical research as well as during everyday diagnosis. Depending on the chosen tracer injected into a subject, PET can be used, for instance, to visualize the brain activity or to assess the impact of a cardiovascular event by enabling the analysis of the myocardium vitality. In a typical PET study, PET data is obtained over a period of time and is composed of various signals that represent the tracer concentration for each time step. Kinetic PET modeling is based on mathematical models that enable isolating those components of the signal which are of interest. By applying this model analysis it becomes possible to understand the physiology and the pathophysiology of metabolism. Thus kinetic PET modeling paves the way for quantified PET analysis which enables comparative studies and researching the correlation between PET uptake and signals obtained from other modalities. Unfortunately the modeling process itself is tedious and time-consuming. Although the costs for developing a new tracer are in general lower than the costs for developing a new drug, the fact that 39% of new drug candidates fail due to inadequate pharmacokinetics (Walker 2004) suggests that effective modeling approaches are of great interest.

Like many other disciplines of medical research, kinetic PET modeling nowadays is performed with dedicated application packages (Carson, Huang, and Phelps 1981; Barrett et al. 1998; Burger and Buck 1997; Muzic and Cornelius 2001). The current practice is, however, to chose one modeling approach early on in the analysis process as the different kinetic modeling approaches are supported as separate features. In this chapter, we propose to assess the standard kinetic PET modeling approaches in an integrated manner in order to improve the modeling result. This allows us to derive inter-model uncertainty which is based on the different results of the standard modeling approaches. We further derive intra-model uncertainty, based on a single modeling approach, which is visualized in an integrated manner together with the inter-model uncertainty. To further facilitate the user in reducing the modeling uncertainties, we propose a visualization metaphor that is based on the *ThemeRiver* metaphor (Havre et al. 2000), and takes into account the spatial and temporal properties of the kinetic PET modeling process. By enabling to relate the kinetic modeling parameters

4.2 Related Work

with each other this metaphor bridges the gap between the different modeling approaches. Thus the main contributions of the work presented in chapter are:

- Intra- and inter-model uncertainty derivation based on standard kinetic PET modeling approaches.
- Integrated visualization of micro and macro parameter uncertainty to combine and compare the results of standard kinetic PET modeling approaches.

The chapter is structured as follows. In Section 4.2 we review the related work covering modeling systems and visualization techniques. In Section 4.3 we provide necessary background for readers, who are not familiar with kinetic PET modeling. The derivation of uncertainty is presented in Section 4.4. In Section 4.5, we describe in detail the proposed uncertainty-aware visualization technique as well as the design decisions for the integrated visualization of micro and macro parameter uncertainty. Section 4.6 presents the evaluation and the feedback of domain experts. The chapter concludes in Section 4.7.

4.2 RELATED WORK

4.2.1 Visualization Techniques

In the last years several general visualization techniques allowing representation of time-varying data sets have been proposed. A thorough review of the field would be beyond the scope of this chapter, we refer to the survey presented by Aigner and colleagues (Aigner et al. 2008) and focus on those techniques directly related to our approach. In addition, we also refer to (Pang et al. 1997; C. R. Johnson and Sanderson 2003) for more detail information on different uncertainty visualization techniques for volumetric data sets. The most basic techniques for time-varying data, i. e., line graphs or sequence charts, are in fact several hundred years old (Malik et al. 2011). While most of the views incorporated in our visualization can be considered as standard visual representations, we also propose a novel view linking abstract and spatial representations. This view is based on the *ThemeRiver* visualization metaphor which has been originally proposed to visualize variations over time in document collections (Havre et al. 2000). The metaphor is similar in spirit to line charts but allows a better correlation with external events. In contrast with the extension we propose in this chapter the original metaphor does not allow to be linked to spatial entities. The same is true for the widely used parallel coordinate display (Inselberg 1985). Huaiqing et al. showed that it is possible to include an uncertainty visualization into both parallel coordinates and star glyphs by introducing an additional dimension to the respective plot (Huaiqing et al. 2011). Recently, Malik et al. proposed a visual analytics system that allows exploration of time correlations by taking into account a spatial component (Malik et al. 2011). While this system puts more emphasis on abstract data, related work more

targeted towards scientific visualization also exists. Oeltze et al. presented an interactive visual analysis approach for the evaluation of perfusion data (Oeltze et al. 2007). The authors employed multiple views for high dimensional data visualization and combined statistics with brushing and linking for the analysis of diffusion data. A more general approach for integrating abstract and spatial data has been proposed by Balabanian and colleagues (J. P. Balabanian et al. 2008; J.-P. Balabanian et al. 2010). They integrate renderings of subvolumes of interest into a hierarchy visualization derived from the same data. Thus, they are able to show the components of a complex system in its hierarchical context. While this approach also targets towards the integration of abstract and spatial representations, it differs from our approach in a sense that the temporal component was not considered.

4.2.2 Kinetic Modeling Systems

There are several software packages supporting the kinetic PET modeling process, e. g., *KMZ* (Burger and Buck 1997), *BLD* (Carson, Huang, and Phelps 1981), *SAAM/SAAM II* (Barrett et al. 1998), and *PMOD* (PMOD Technologies Ltd., Zurich, Switzerland). The *KMZ* system separates the graphical user interface and the numerical calculation unit for extensibility. This system is, however, limited to the application of a rather low number of pre-defined kinetic model structures, and does not support model analysis and parameter modification as an integral part. *PMOD* is a flexible successor of *KMZ* and commercially available on various platforms. This software package allows different types of modeling, e. g., general kinetic modeling or pixel-wise modeling. It also supports image fusion and surface-based volumetric data visualization. Muzic et al. have proposed another flexible PET compartmental modeling framework named *COMKAT* (Muzic and Cornelius 2001). It provides the ability to implement arbitrary user-specified models through graphical and command-line interaction. *KIS* is an Internet-based kinetic imaging system for microPET (Huang et al. 2005). In comparison with other existing software systems, *KIS* incorporates an educational aspect aiding users in better understanding the modeling process. Even though this package was initially designed for microPET only its design allows handling general imaging studies in tracer kinetics and pharmacokinetics in other animal models as well as in humans. While all these systems are widely accepted and have thus often been used for tracer modeling, they differ from the approach presented in this work in mainly two ways. First, although the graphical modeling approaches are inherently visual, visualization does not play a major role in these systems. Second, the concurrent integration of multiple models and the ability to compare uncertainty of the output arisen during the process through visualization is not an integral part.

4.3 Kinetic PET Modeling

Figure 4.1: Three-tissue (or four-compartment) compartment model. This model consists of components of arterial plasma, $C_p(t)$, free ligand in tissue, $C_1(t)$, specific binding, $C_2(t)$, non-specific binding, $C_3(t)$, and six kinetic micro parameters, $K_1, k_2, \dots, k_6$, describing the rate constants.

4.3 KINETIC PET MODELING

Kinetic PET modeling helps to isolate the components of interest from the obtained PET data. As a result, the analysis of the underlying mathematical model provides insight into the kinetic behavior of the tracer under investigation.

Kinetic PET modeling techniques may be divided into two groups: model-driven and data-driven methods. The model-driven techniques require a model structure as a-priori information (see Figure 4.1). In contrast data-driven algorithms obtain this information directly from the kinetic data, e. g., a dynamic PET (dPET) scan. Figure 4.1 shows a three-tissue (or four-compartment) compartment model. The first compartment, C_p , is the arterial blood. This compartment is also known as the input function. From the arterial blood, the radioligand passes into the second compartment, C_2 , known as the free compartment. The third compartment, C_3 , is the region of nonspecific-binding which we are usually interested to observe. The fourth compartment, C_4 , is a nonspecific binding compartment that exchanges with the free compartment, C_1 . $K_1, k_2, \dots, k_6$ are the kinetic micro parameters describing the constant transfer rates between compartments. It is worth noting that K_1 is written in uppercase since it differs, with respect to several properties, from the other micro parameters, e. g., it is subject to a different measuring unit.

The following system of ordinary differential equations (ODEs) is the mathematical representation of the compartment model in Figure 4.1.

$$\begin{aligned}
 dC_1/dt &= K_1 C_p(t) + k_5 C_3(t) + k_4 C_2(t) - (k_2 + k_3 + k_6) C_1(t) \\
 dC_2/dt &= k_3 C_1(t) - k_4 C_2(t) \\
 dC_3/dt &= k_6 C_1(t) - k_5 C_3(t)
 \end{aligned} \tag{4.1}$$

where $C_p(t)$, $C_1(t)$, $C_2(t)$, and $C_3(t)$ are radioactivity concentrations at time t for each compartment. It should be noted that a compartment model is always analyzed with respect to a region of interest (ROI) which could, in the

Figure 4.2: Dependency of the computed kinetic parameters. In a given ROI, based on the input function and the measured TACs, the macro parameter can be obtained directly from the Logan or the Patlak plot. The compartment modeling allows us to obtain micro parameters from which again macro parameters can be derived.

most extreme cases, be the whole body or a single voxel inside an organ but is more often a single organ. When several organs are considered we refer to the model as a multi-level compartment model. Quantitative analysis of a compartment model is done through solving its mathematical representation. Depending on the given inputs different type of information can be obtained by solving the system of ODEs. For instance the mathematical prediction of the tissue activity (time-activity curve - TAC) can be obtained from a given input function, $C_p(t)$, and micro parameters. This is called the *forward* problem. On the other hand kinetic micro parameters can be estimated from a given input function, $C_p(t)$, and measured TACs. This is called the *backward* problem and can be solved by using different least squares fitting techniques such as linear least squares, non-linear least squares, weighted integration (Carson, Huang, and Green 1986), generalized linear least squares (Feng et al. 1996) or basis function techniques (Koeppel et al. 1985; Cunningham and T. Jones 1993; Gunn et al. 1997). In both cases the arterial radioactivity concentration, $C_p(t)$, known as the input function must be provided. There are two approaches to obtain the input function: invasive and non-invasive methods. Although the non-invasive methods provide less accurate measurements, they are usually preferred (Zanotti-Fregonara et al. 2011). Recent development of reference tissue models, e. g., (Watabe et al. 2000), however, help to avoid the blood sampling requirement.

Logan plots and Patlak plots are the two state-of-the-art data-driven modeling methods (Patlak and Blasberg 1985; Logan 2000). These techniques employ a transformation of the data such that a linear regression of the transformed data

4.4 Deriving Intra- and Inter-Model Uncertainty

yields the macro parameter of interest. Despite their inherent simplicity they can reliably provide good enough output. As a result, they are frequently used in practice. Nevertheless these techniques are biased due to statistical noise and requires special handling when the resulting plot becomes non-linear (Slifstein and Laruelle 2000). It should be noted that these macro parameters can also be derived from the micro parameters described above. For instance the net influx of the tracer obtained from the Patlak plot, K_i , can be derived from the micro parameters in the compartment model in Figure 4.1 as follows: $K_i = \frac{K_1 \times k_3}{k_2 + k_3}$. In comparison with the micro parameters, macro parameters represent the observed data rather than the individual parameter. Spectral analysis is another data-driven modeling approach which characterizes the system impulse response function (IRF) (Cunningham and T. Jones 1993). In this approach the non-negative least square fitting is used, and the macro parameters are calculated as functions of the IRF. Although these techniques do not provide information about the underlying model structure, spectral analysis provides the number of tissue compartments evident in the data.

4.4 DERIVING INTRA- AND INTER-MODEL UNCERTAINTY

In this section we explain the variety of kinetic parameters computed and analyzed by our system, as well as the derivation of the associated intra- and inter-model uncertainty.

The dependency of modeling parameters is shown in Figure 4.2. Micro parameters can be estimated from the compartment model. Macro parameters can be obtained either by using the Logan or Patlak method or through the derivation from the micro parameters. These different sources of macro parameters enable us to compute the inter-model uncertainty, while the covariance analysis can be used to derive intra-model uncertainty from the compartment model.

In the Patlak method the concentration of the tracer at time t after injection is described as follows

$$C(t) = \lambda \cdot C_p(t) + K_i \int_0^t C_p(\tau) d\tau \quad (4.2)$$

where $C(t)$ represents activity in the tissue as measured by the PET scanner, $C_p(t)$ is the plasma activity, K_i is the net rate of the tracer influx into the tissue, and λ is the distribution volume of the tracer. By dividing both sides of Equation 4.2 by $C_p(t)$, the macro parameter, K_i , can be estimated as the slope in the Patlak plot through the use of linear regression analysis. The Logan technique works in a similar fashion. For instance, the macro parameter which is the volume distribution of the tracer is obtained through a regression approach on the transformed data.

In compartmental modeling, micro parameters can be obtained by solving the system of ODEs. This is an optimization problem with the goal to minimize

the weighted residual sum of squares (WRSS) defined as

$$\begin{aligned}\text{WRSS}(\lambda) &= \sum_{j=1}^N w_i (C_{obs}(t_j) - C(t_j))^2 \\ &= \sum_{j=1}^N w_i (C_{obs}(t_j) - e^{-\beta t_j})^2\end{aligned}\quad (4.3)$$

where β represents the kinetic parameters to be estimated, w_i is the weighting scheme, N is the number of measurements, and $C_{obs}(t_j)$ and $C(t_j)$ represent the measured data and the model prediction of the tracer activity at time t_j respectively. It is worth noting that the concentration of the tracer is a nonlinear function of the parameter β over time: $C(t_j) = e^{-\beta t_j}$. In order to calculate the associated uncertainty of the estimates of the kinetic parameters the bootstrap technique is commonly used (Turkheimer et al. 1998). This technique is, however, computational expensive. In this work we propose the analysis of the covariance matrix of the estimates to calculate the certainty level of the estimated kinetic parameters. In general the covariance matrix of the estimates of the kinetic parameters is symmetric. Particularly the diagonal elements are the variances of the parameter estimates which are positive by definition and the off-diagonal elements are the covariances which may be either positive or negative. Finding the optimal result from the minimization of the Equation 4.3 is an iterative process. During this process the information matrix constructed by the weighting scheme w_i , and the derivative of the function used to fit the data represents the minimum achievable covariance matrix as in Equation 4.4

$$\text{Cov}(\hat{p}) \geq M^{-1}(\hat{p}) \quad (4.4)$$

where $\hat{p}$ is the estimates of the kinetic parameters, $\text{Cov}(\hat{p})$ is the covariance matrix of the estimates, and M is the information matrix. The information matrix approaches the covariance matrix of the estimates for a large sample size of tissue measurements and/or decreasing variance of the measurement error. Moreover the estimates also approach Gaussian distributions. It is worth noting that despite the fact that there are several sources of noise in PET imaging, the addition of these sources of errors tends to form a Gaussian distribution (Ikoma et al. 1998). Thus, for an optimal weighted nonlinear least squares fitting, the covariance matrix of the estimates needs to reach the lower bound fined by the information matrix. As a result, the analysis of the covariance matrix of the estimates reveals the precision of the estimates which represents the intra-model uncertainty.

Since the macro parameters, obtained from either the Patlak plot or the Logan plot, represent the observed data rather than the individual parameters, the relative comparison between these values and the corresponding derivation from the micro parameters can provide useful information. We refer to the differences of macro parameters based on these three sources as inter-model uncertainty. For a thorough understanding of intra- and inter-model uncertainty, an appropriate visualization techniques is essential, which also allows for relating the intra-model uncertainty based on the micro parameters to the inter-model uncertainty based on the macro parameters.

4.5 Uncertainty-Aware Kinetic Parameter Visualization

Figure 4.3: Workflow to derive the kinetic parameters and their associated uncertainties. Input data is fed into three different kinetic modeling techniques which are used to derive kinetic micro and macro parameters. These parameters are analyzed and the modeling uncertainty is derived based on the parameter variation. Thus the uncertain output data serves as a basis for changing model input parameters which can be interactively changed as depicted by the red arrows.

4.5 UNCERTAINTY-AWARE KINETIC PARAMETER VISUALIZATION

We motivate the proposed visualization techniques by giving an overview of the underlying modeling workflow as illustrated in Figure 4.3. The three state-of-the-art kinetic PET modeling approaches, Logan plotting, Patlak plotting, and compartment modeling as are employed to provide the estimates of the kinetic parameters. By visually depicting the resulting intra- and inter-model uncertainty ranges we enable the user to modify the modifiable model input parameters (red arrows in Figure 4.3) with the goal to minimize the uncertainty and thus allow more realistic modeling results. It is worth mentioning that depending on the underlying problem solving approach, the parameters being modifiable may vary.

4.5.1 Kinetic Parameters Uncertainty Visualization

To be able to obtain more realistic modeling results it is essential to depict the modeling parameters as well as the intra- and the inter-model uncertainties. Therefore we propose an uncertainty-aware visualization technique as illustrated in Figure 4.4. The proposed visualization technique is based on the *ThemeRiver* metaphor (Havre et al. 2000) which has been extended to visualize the parameter changes and the associated uncertainties dependent on spatial locations, i. e., micro and macro parameters together with the intra- and inter-model uncertainties computed for different ROIs. Each ROI is represented by a box that is subdivided based on the associated micro and macro parameters. Based on the connectivity in the underlying compartment model the boxes are

Figure 4.4: The uncertainty-aware visualization technique depicts differences in the micro and macro parameters. The color of the bands connecting the kinetic parameters between different ROIs is selected based on the pre-attentive process. Uncertainty is depicted by using blurring while certain values are emphasized through edge detections.

connected through bands which depict changes in kinetic parameters as well as the associated uncertainty. The colors of these bands have been chosen to comply with the rules of pre-attentive perception (Theeuwes 1992). Initially macro parameters are in focus so they are colored in red, while the micro parameters, which are of interest in a later processing stage, are colored in shades of blue. To allow a better comparison of the micro and the macro parameters the bands are drawn such that the width of the curves is not affected by its curvature.

Besides the parameter changes the bands are also used to depict the uncertainties of the currently selected ROIs. We have chosen to keep the uncertainty depiction simple in order to reduce visual clutter. As the silhouette perception is an essential part of the shape perception process, silhouettes are a powerful mechanism in visual communication. Therefore in our case, to depict the underlying uncertainty we have decided to use parameter uncertainty as a modulation factor for dissolving or emphasizing the segments' shapes by blurring or edge enhancement. It should be noted that depending on the connected ROI representations, the uncertainty along a segment may vary. To realize various degrees of dissolution and emphasize, we combine blurring and edge detection techniques realized as post processing of the connection segments. When the uncertainty to be depicted is below the uncertainty threshold u_{min} , the regions of the segment are emphasized by adding a silhouette edge indicating certain values. All regions subject to an uncertainty exceeding u_{min} are vertically blurred based on the degree of uncertainty. We have to consider two

Figure 4.5: A high degree of uncertainty is depicted by using vertical blurring: no uncertainty depiction applied (left), uncertainty depiction without edge detection (middle) and uncertainty depiction with edge detection (right).

things. First, the degree of blur needs to be based on the uncertainty, and second, the blurring should not affect the neighboring segment. To reach the first goal, we allow the user to define a maximum degree of blur specified through a maximal blur kernel size g_{max} as well as an upper uncertainty threshold u_{max} . Based on these values and the current uncertainty u , the kernel size g_{dim} for the Gaussian kernel used to achieve the desired effect can be derived by $g_{dim} = ((u - u_{min}) / (u_{max} - u_{min})) \times g_{max}$. To reach the second goal, and avoid bleeding effects between adjacent segments, the Gaussian filter is adapted in such a way that for samples lying outside the current segment a desaturated version of the color of the current segment is used. Thus we are able to achieve effects as shown in Figure 4.5. It is worth noting that since the uncertainty information was not taken into account in the image on the left in Figure 4.5, the color is more saturated.

To depict the spatial position of the associated ROIs, the events originally connected along the time axis are now located in the image plane in a way that enables an easy association with the ROIs shown in the 3D view. Thus the layout of the boxes is associated with different ROIs in an associated 3D view (see Figure 4.7 (top left)). This association is important, as it shows how a tracer behaves in different organs and allows the domain expert to gain further insight into the kinetic behavior of the tracer under investigation.

The proposed layout calculation algorithm contains two main steps and is executed whenever the ROI positions in the 3D view are changed, e. g., when the camera is rotated or zoomed. In the first step the ROI representations are positioned such that overlap is avoided and a direct mental linking with the original ROI positions in the 3D view can be established. In the second step we perform a relaxation of the position of the boxes in the horizontal and vertical direction, which maximizes the distances between these objects, and thus allows us to have sufficiently large connection between them. Thus, it improves the connectivity in the initial layout. The last step of the layout algorithm is performed in an animated manner and only when the user is not changing the positions of the ROIs in the 3D view. Thus we can ensure a coherent association with the ROI positions in the 3D view after the first step and a coherent transition to a layout optimized for the presented representation.

Figure 4.6: The compartment model (left) for three different organs can be considered as a state diagram, where the state changes over time. The TACs (right) are plotted over time after injection.

4.5.2 Linking Kinetic Parameters with Spatial and Temporal Attributes

While our uncertainty derivation and visualization methods provide further insights, they must be seen as an addition to previous visualization techniques and should be applied in a combined manner with these. As most of the data in the kinetic PET modeling process have both, spatial and temporal attributes, these properties need to be considered during the combination.

The TACs are, for instance, an abstract representation showing the tracer activity over time (see Figure 4.6 (right)). They are associated with a spatial position but are usually represented by a 2D plot, which has no spatial components. While the structure of the compartment model is usually presented in a 2D space, the compartment model itself inherently represents time through which the tracer transits between the compartments (see Figure 4.6 (left)). Moreover a compartment model is always associated with a spatial position given by the analyzed ROI. In contrast to the model structure the measured kinetic data given by the 4D PET is inherently spatial. Since PET is a rather low resolution modality, it suffers from partial volume effects. Thus PET is commonly fused with a co-registered CT scan to allow better spatial relations communication. As a result, the proposed integrated visualization combines these conventional 2D and 3D views to help users to relate the uncertainty, the TACs, and the model structure to their spatial anchor.

From the requirement analysis above we make use of the mental linking approach, which has shown to be a very useful when dealing with multiple visual representations in several application scenarios (Tory 2003; Gresh et al. 2000; Doleisch 2007; Busking et al. 2010; Krekel, Valstar, et al. 2010). It is worth noting that linking in our case is more difficult since the analyzed data, e. g., 4D PET scans, is inherently spatial while the analysis techniques are primarily based on abstract representations, e. g., model structures and

Figure 4.7: Our system employs multiple views supporting the kinetic modeling process. A multi-volume rendering view (*top left*) allows us to assess the spatial location of the input function sampling positions as well as of the ROIs. 2D slice views (*bottom left*) enable to assess tracer uptake in more detail and support repositioning of the image-derived input function sample locations. The plot (*bottom right*) shows the output of the Patlak graphical analysis. An uncertainty-aware widget (*top right*) reveals the modeling uncertainty.

regression analysis plots.

Figure 4.7 illustrates the organization of the different views in an integrated visualization. The top left view is a multi-volume rendering view which has been enriched by depicting the ROIs through silhouette enhancement techniques. The view operates on three volumetric data sets: the PET data, the co-registered CT data used to provide the spatial context, and a segmentation volume which encodes the ROIs. Generation of this segmentation volume is not part of our system. The 3D view is linked to standard 2D slice representations arranged in the bottom left view. When the user scrolls through the shown slices, the slice indicators (green and red rectangle) in the 3D view are updated and indicate the current slice position. This allows an in-detail inspection of the relevant structures, while the 3D view provides an overview of the spatial context. These 2D views allow a better interaction when performing selection tasks when changing the image-derived input function locations is necessary. The output of the Logan/Patlak plot is shown on the bottom right.

4.6 EVALUATION

To investigate the benefits of the proposed uncertainty-aware modeling concepts we have conducted an evaluation with three domain experts from the Turku PET Centre, which are working in nuclear medicine and conduct research related to kinetic PET modeling. The objective was to assess the users' ability to quickly perceive the uncertainty in the estimates of the kinetic parameters and derive meaningful information from the proposed visualizations.

In order to derive the uncertainty of the estimates we implemented a prototype software that supports compartmental modeling as shown in Figure 4.6. Spectral analysis is used to identify the initial number of compartments that are evident in the input data. The system also solves both the *forward* and the *backward* problems. In addition, the Patlak plotting and the Logan plotting techniques are also integrated.

We prepared four data sets containing different levels of synthetically introduced uncertainty into the ground-truth data, which lead to the different uncertainty in the estimates of the kinetic parameters. Figure 4.8 illustrates the uncertainty-aware visualization of two sets of kinetic parameters with different levels of uncertainty, whereby the uncertainty displayed in the ROI on the right is higher for all parameters. As it can be seen, color saturation and silhouette thickness vary dependent on the degree of uncertainty. We presented the visualizations of these four data sets to the three domain experts. While the ROIs on the left are subject to the same degree of uncertainty for each individual kinetic parameter, the ROIs on the right depict different sets of kinetic parameters with varying uncertainty. The participants were asked to perform the following tasks:

1. Organizing the visualizations in an increasing order of overall level of uncertainty in ROIs on the right.
2. Identifying the image in which the macro parameter K_i has the highest level of uncertainty.
3. Identifying the micro parameters that have the strongest influence on the uncertainty of the macro parameter K_i .

By using the proposed uncertainty-aware visualization technique all three participants could quickly perceive the underlying uncertainty of the kinetic parameters. In task 1, all the participants provided the correct increasing order of uncertainty level in ROIs on the right. We received one incorrect answer for the task 2. Particularly, the participant selected the image containing the second highest level of uncertainty. In task 3, the participants identified correctly the micro parameters that contribute most uncertainty to the derived macro parameter K_i . As we consider these results as very positive feedback, the proposed uncertainty-aware visualization technique seems to help to depict the uncertainty in the estimates of the kinetic parameters, while at the same time

Figure 4.8: The uncertainty-aware visualization supports the relative uncertainty comparison between two different sets of kinetic parameters.

providing insights into the uncertainty contribution of the micro parameters to the derived macro parameter.

Apart from the task results, we also received very positive comments from the domain experts. Among them the statement, that the proposed visualization technique enables to identify the uncertainty contribution of the micro parameters to the derived macro parameters, which is not possible with the standard bar plot used to depict the kinetic parameters. One domain expert also requested more information about the software and its availability.

When querying feedback regarding the uncertainty derivation approach the domain experts stated that the proposed uncertainty derivation approach is comparable to the commonly used bootstrap technique. As the bootstrap technique is a statistical approach, the analysis of the covariance matrix is a viable alternative. Since the analysis of the covariance matrix is done with an iterative weighted nonlinear least squares fitting, it requires less computation than the bootstrap approach.

4.7 CONCLUSIONS AND FUTURE WORK

In this chapter we have presented another approach to the derivation of uncertainty in the standard kinetic PET modeling. By combining the results of different state-of-the-art PET modeling techniques, e. g., Logan plots, Patlak plots and compartment modeling, together with sample-based and data-derived input functions, we are able to compute intra- and inter-model uncertainties for kinetic modeling parameters. To communicate the parameters and their associated uncertainty a novel uncertainty-aware visualization technique was proposed and incorporated into an integrated visualization. While the uncertainty-aware visualization allows the user to estimate the differences in the model output, the interactive visual feedback in the integrated visualization enables to adapt the input parameters in order to minimize the uncertainty. Furthermore the linked views in the integrated visualization also depict both the spatial and

temporal nature of the kinetic data to assist the kinetic PET modeling process.

There are several interesting research opportunities for the future. While the uncertainty-aware visualization technique enables users to compare the uncertainty in the estimates of the kinetic parameters, the combination with a machine learning techniques to assist the uncertainty reduction process is an interesting research direction. It could be possible to allow a semi-automatic uncertainty reduction based on the interplay between human and computer. Furthermore the integration of histological findings into the proposed integrated visualization approach would be an interesting next step towards more effective kinetic PET modeling.

CHAPTER 5

CONCURRENT VOLUME VISUALIZATION OF REAL-TIME fMRI

5.1 INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) makes it possible to map out intensity and spatial location of brain activity. The estimation of brain activity is based on the measurement of the blood oxygen level dependent (BOLD) signal. As the development of both equipment and methods for fMRI progresses very fast, the pulse sequences used for fMRI have increased spatial and temporal resolution and there has been a shift from studies of static activation maps towards studies of the neuro-dynamical activation of brain regions during task performance. In addition, advances in signal processing are allowing handling of fMRI signals in real-time. This enables studies of the dynamics in the time-series data while the test-subject is still located in the fMRI scanner. Among the potential uses of real-time fMRI we find cognitive training and planning of stroke rehabilitation, assessment of drug treatments, and pre-operative planning. The primary current use of real-time fMRI systems are, however, in research on fMRI technology and methodology and they serve as enabling tools for neuroscience research.

To fully exploit the potential of real-time fMRI there is a pressing need for more visualization tools that not only visualize static activation patterns, but also effectively deal with the increasing spatial and temporal resolution. We thus have the following requirements on the fMRI visualization:

- High resolution subject/patient specific anatomical context data
- Fusion of the fMRI signal into contextual data in real-time to support concurrency with streaming of live data of increasing temporal resolution
- fMRI signal presentation that does not obscure the anatomical features
- Highly interactive visualization with frame rates that allow for smooth visual exploration

To meet these requirements we have developed direct volume rendering (DVR) methods tailored for fMRI time-sequence data. The methods are deployed in a demonstrator set-up for real-time fMRI. First the anatomical brain context is obtained from an MRI T₁-weighted volume in a pre-processing stage. After being co-registered with the reference T₁ volume, the fMRI signal is treated as a light source in the DVR pipeline, making the anatomical context

data emissive depending on the signal location and strength. The result is that the brain *glows*, emitting light in active fMRI regions. The system supports several different shading models including the local ambient occlusion method described by Hernell and colleagues (Hernell et al. 2007). The main contributions of the the work presented in this chapter can be summarized as:

- Interactive DVR of the T1-weighted volume with the fMRI signal used to steer emission
- Inclusion of local ambient occlusion shading to improve the visual clarity of the anatomical context and the emission based on the fMRI activity
- A user study demonstrating the effectiveness of the proposed approach compared to standard 2D representations
- Demonstration of the use of the processing and visualization pipeline through a set of real-time fMRI experiments

The remainder of this chapter is organized as follows. First we give an overview of related works in the fMRI and rendering aspects of the system. We then give an overview of our system set-up. Then the real-time fMRI signal processing is described followed by an in-depth description of the DVR approach used and results of the user study are described. We then proceed to give the details of the experiments performed with the system and then give the details of results obtained. This chapter is concluded with some perspectives on possible future development.

5.2 RELATED WORK

Previous research on volume visualization of fMRI has, to a large extent, focused on the use of multi-volume rendering approaches. Stokking et al. describe a generic method, called normal fusion, to visualize the functional data within context of 3D surfaces extracted from the anatomical image data (Stokking et al. 2001). First, the functional information is projected onto the extracted 3D surfaces independently of the viewpoint. Then a color-encoding scheme based on the HSV model is used to fuse the anatomical and functional information. Weiskopf et al. used the software package ‘Turbo-BrainVoyager’, (Brain Innovation, Maastricht, The Netherlands) (Goebel 2001), for processing and visualization of fMRI data in real-time (Weiskopf et al. 2003). Activities are visualized by superimposing the analyzed functional data on anatomical slices. For 3D visualization, active regions corresponding to activities on the surfaces extracted from the anatomical volume are marked with different colors. Rößler et al. present a slice-based multi-volume rendering technique, which intermixes slices of volumes by depth sorting (Rößler et al. 2006). The authors also present advanced cropping techniques and render modes to highlight activities inside the brain. Schafhitzel et al. propose a combination of semi-transparent isosurfaces (SSD) with DVR to visualize the functional data (Schafhitzel et al. 2007).

Particularly, DVR is used to render activities inside the brain while SSD is used to render the surrounding brain structure. The use of line integral convolution to provide a sparse and informative representation of the anatomical cues, and hence improve the perception of the isosurface's shape, is also proposed. In these approaches, the structure of the surface is well conveyed with the use of diffuse shading. Jainek et al. use 'vicinity shading' to improve the depth and spatial perception in volume rendered images of functional data (Jainek et al. 2008). In addition to variety in rendering methods including non-photorealistic rendering and hybrid methods, a set of novel interactive tools for investigating the visualization is also presented. Beyer et al. introduce a multi-volume rendering workflow, in which high-quality visualization with interactive frame rates is achieved through a GPU-based implementation (Beyer et al. 2007). This workflow is extended by Reider et al. with a proposed solution for overlapping multiple volumes (Rieder et al. 2008). Joshi et al. introduced an integration of interactive cropping tools into a multi-volume rendering framework, for exploration of multimodal data in 3D (Joshi et al. 2008). In their work, irregular cropping techniques can be applied to both fMRI and anatomical data to produce useful visual representations. Recently, Firdaus et al. propose a method to visually analyze the time dimension of the functional data (Janoos et al. 2009). While an activation dissimilarity metric is proposed to capture the context of the neuro-functional phenomena being investigated, a hierarchical clustering procedure is developed to provide suggestions for interactive volume of interest selection from users.

Although standard fMRI examinations have been used for almost two decades now (Belliveau et al. 1991), the area of real-time fMRI is still relatively unexplored. Cox et al. were amongst the first to perform real-time fMRI analysis combined with on-line motion correction to compensate for head movements (Cox, Jesmanowicz, and Hyde 1995; Cox and Jesmanowicz 1999). Nakai et al. used the general linear model (GLM) on a sliding window as a real-time activity measure (Nakai et al. 2006). As an application, the use of real-time fMRI as an aid to cure chronic pain has brought a lot of attention to the topic (deCharms 2005). The interested reader can find an overview of possible future applications of real-time fMRI in (Christopher deCharms 2008). The recent developments of fMRI analysis have been focused on brain activity classification in real-time. Laconte et al. used a support vector machines (SVM) classifier to decide which of a number of stimuli could have caused a certain activity pattern (LaConte et al. 2007). Eklund et al. used a neural network for classification of brain activity to control a dynamical system (Eklund, Ohlsson, et al. 2009).

5.3 APPLICATION SETUP

At the core of the system is a 1.5T Philips Achieva MRI scanner, which is a commonly used scanner for clinical MRI. The fMRI volumes acquired from a

Figure 5.1: An example of the view of the operator. The operator can easily interact with the visualization in real-time by using the keyboard and the mouse.

test subject are sent to a separate computer for real-time signal processing. The processed fMRI volume is passed to a second computer which generates the visualization. The visualization can be viewed by the operator, see Figure 5.1 for an example, and/or fed back and displayed to the test subject in the scanner using a head mounted display developed to work inside of the MRI scanner. The operator can interact with the visualization and control what he/she sees and what the test subject sees in real-time. The signal processing and visualization computer receive a new fMRI volume every other second while the visualization is updated more than 10 times per second. All units communicate over a local area network.

5.4 SIGNAL PROCESSING

Estimation of brain activity from real-time fMRI measurements is a challenging task. High noise levels and a weak BOLD signal make it hard to separate active from inactive regions. We here chose to work with periodic paradigms. This simplifies analysis since we only need to look for periodic fMRI signals but restricts the subject to periodically alternate between doing a task and rest (20s + 20s used throughout our experiments).

We use canonical correlation analysis (CCA) to detect periodically varying signals. CCA finds the two linear combinations of signals (one linear combination from one set and a second from another set of signals) which are as correlated as possible. Let w_x and w_y be the searched coefficients in the first and second linear combination and let $x(t)$ and $y(t)$ be column vectors containing the signals in the first and second set. The canonical correlation

Figure 5.2: The 5 elements of $y(t)$ are constructed by weighing together fMRI measurements from nearby voxels as illustrated in the figure. In the 3-by-3 voxels arrangements, the voxel in the center is the one that the canonical correlation is computed for.

between $w_x^T x(t)$ and $w_y^T y(t)$ is then defined as

$$\frac{w_x^T C_{xy} w_y}{\sqrt{w_x^T C_{xx} w_x w_y^T C_{yy} w_y}} \quad (5.1)$$

where C_{xx} , C_{yy} and C_{xy} are the within and between sets covariance matrices, C_{xx} is e.g. defined by

$$C_{xx} = 1/N \sum_{t=1}^N x(t)x(t)^T. \quad (5.2)$$

The w_x and w_y that maximize the canonical correlation can be found by solving an eigenvalue problem, see (Friman, Borga, et al. 2003) for details.

In our case, the first set contains a number of basis functions

$$x(t) = [\sin \omega t \quad \sin 2\omega t \quad \cos \omega t \quad \cos 2\omega t]^T \quad (5.3)$$

where $\omega = 2\pi/T_p$, T_p being the period time of our paradigm (40s used here). By letting $y(t)$ be the fMRI measurement from a voxel, one could now obtain a measure of periodicity and hence activity in that voxel. The fMRI measurements are, however, contaminated by noise and $y(t)$ is therefore constructed by averaging together fMRI measurements from neighboring voxels. $y(t)$ will then consist of 5 elements and how their corresponding weights are defined is shown in Figure 5.2. The canonical correlation is computed voxel-by-voxel, as described above. In the computation of the within and between sets covariance matrices, C_{xx} , C_{yy} and C_{xy} , 80s of the most current fMRI measurements were used.

In order to compensate for head movement during the scanning, each fMRI volume is registered to the first collected fMRI volume. To do this we use a registration algorithm that is based on optical flow, but instead of the optical flow of the pixel intensity values that is normally used, we use optical flow of the local phase from quadrature filters. Phase-based volume registration is further described in (Eklund, Andersson, et al. 2010).

The registration between the low-resolution fMRI volume and the high resolution T1 volume is done by maximizing the mutual information between

Figure 5.3: The volume rendering pipeline has three major processing blocks, Ambient Lighting, Ambient Emission and Direct Volume Rendering. The DVR stage will be executed for every update and change of view, whereas the Ambient Emission will be updated only when the fMRI signal is updated. The Ambient Lighting stage will be updated infrequently as it only depends on TF changes.

the volumes, as proposed in (P. Viola and W. M. I. Wells 1995). This is the standard approach for registration of volumes between different medical modalities. This registration is done before the real-time phase is started and takes about 1.5 minutes.

5.5 CONTEXTUALIZED FMRI VISUALIZATION USING VOLUMETRIC ILLUMINATION

The choice of illumination model used in volume rendering has been shown to have a major impact on the spatial comprehension (Langer et al. 2004). In particular, shadows serve as an important depth cue (Sattler et al. 2005). The Local Ambient Occlusion technique, presented by Hernell and colleagues (Hernell et al. 2007; Hernell et al. 2010) is used in this work to achieve smooth shadowing effects, making the brain tissue structure easy to perceive. Furthermore, a novel approach is proposed where the fMRI signal is treated as a light source – mapping the intensity to the strength of the fMRI signal, and thus illuminating the anatomical T1 brain volume where brain activity is detected, examples of images showing the effect can be seen in Figure 5.4.

There are three major processing stages in the rendering pipeline used in this application, as illustrated in Figure 5.3. The pipeline is based on a Direct Volume Rendering (DVR) scheme, where the traditionally constant ambient term in the Blinn-Phong shading model is replaced with two components: an Ambient Light contribution, A^L , based on Local Ambient Occlusion (LAO) computed using the brain anatomy T1 volume, and an Ambient Emission contribution, A^E , also computed using LAO with the addition of the fMRI signal to drive the emission factor. Both A^L and A^E are computed and cached on the GPU in

Figure 5.4: *Left:* The anatomy is rendered using the local ambient occlusion shading model, the A^L reflective light, which enhances the perception of depth. A diffuse shading component is also applied. *Middle:* The fMRI signal rendered using the LAO emission, i.e. including A^E . The image represents the brain activation during repeated motion of the left foot. *Right:* The activation during mathematical problem solving. The instructions, as well as the visualization of the brain activity as shown in these images, are shown to the subject in a head mounted display, and thus there is significant activation of the visual cortex.

two separate volume textures. Since the anatomy is static, the Ambient Light volume only needs to be updated when the Transfer Function (TF) for the anatomy is changed. The Ambient Emission, however, will be updated when the fMRI signal changes, from the real-time capture, or when the Emission Transfer Function is changed.

5.5.1 Local Ambient Occlusion

LAO is a local approximation of ambient occlusion which considers only voxels in a neighborhood around each voxel. Thus shadows and light emissions are captured from local features computing the incident light from a limited spherical region around each voxel, while ignoring distant features which have less impact. The resulting illumination volume is then used in a rendering pass as the ambient light term in the volume rendering integral. For the sake of clarity this section will briefly revisit the LAO principles.

The basis for LAO is the commonly used volume rendering integral, expressed by Max (Max 1995) as

$$I(D) = I_0 \cdot e^{-\int_0^D \tau(t)dt} + \int_0^D g(s) \cdot e^{-\int_s^D \tau(t)dt} ds, \quad (5.4)$$

where the first term represents the light coming from the background, I_0 , attenuated with the optical depth, the integral of the extinction coefficient τ , and the second term represents the integration of attenuated light contributions, $g(s)$, for each location, s , along the ray. Traditionally, the light contribution function, $g(s)$, in Equation 5.4 has three components

$$g(s) = A(s) + k_d(L \cdot N)c(s) + k_s(N \cdot H)^p c(s) \quad (5.5)$$

where $A(s)$ is the ambient light contribution, frequently simply a constant factor, as in $k_a(s)c(s)$, and $c(s)$ is the color classification of each sample. The second and the third term represent the diffuse lighting and the specular highlight, respectively, based on the half-angle technique (Blinn 1977).

The substance of LAO in the volume rendering pass is primarily integrated into the ambient term, $A(s)$ in Equation 5.5. Since $A(s)$ is typically independent of viewing parameters it is beneficial to compute this term separately and cache the result in a 3D texture that is only updated when the transfer function or volume data change. As mentioned above, A is furthermore broken up into an Ambient Lighting component, A^L , and an Ambient Emission component, A^E . The rest of this section will focus on the definition of A^L . The rationale for computing A^L and A^E separately will be detailed in the next section.

LAO captures the effect of a local volumetric ambient light source surrounding each voxel in the volume, attenuated by classified voxels in the neighborhood, accounting for the continuous range between transparent and opaque voxels. This volumetric approach, with light contribution to each g , creates a soft shadow penumbra, in contrast to only considering light at the boundary, that is, all light contribution given by I_0 alone. In addition, the volumetric light also achieves smooth results with less rays cast around each voxel, and thus reducing computational requirements.

In LAO the raycasting integral, Equation 5.4, is deployed over a set of K uniformly distributed rays originating at a location, x , in the volume and sum the contributions into $A^L(x)$. Thus capturing the total incident light as

$$A^L(x) = \frac{1}{K} \sum_{k=1}^K A_k^L(x) \quad (5.6)$$

where the ambient light contribution, A_k^L , for each ray is defined by a reformulated version of the volume rendering integral, Equation 5.4. The integration direction is reversed, from center point to the boundary, as follows:

$$A_k^L(x) = \int_a^{R_\Omega} g_{A^L}(s) \cdot e^{-\int_a^s \tau(t) dt} ds \quad (5.7)$$

where R_Ω defines the radius of the local neighborhood and a is an initial offset to avoid self-occlusion, τ is the optical density, defined by a transfer function for the T1 anatomy volume. To differentiate the light contribution at each sample location along the ray in the LAO processing, g_{A^L} is used instead of g .

A basic definition of g_{A^L} , using a volumetric light source spreading the light contribution evenly along the ray, is expressed by

$$g_{A^L}(s) = \frac{1}{R_\Omega - a} \quad (5.8)$$

So far, the Ambient Lighting processing stage, producing A^L , in Figure 5.3

Figure 5.5: In the left image emission is only used in the raycasting pass. In the right image emission is applied both in the LAO and the raycasting passes, resulting in an increased glow effect around active regions. It is noticeable that the emission from within the brain “shines through” when LAO emission is used.

has been described. In the left image of Figure 5.4 an example of rendering of the T1 brain context using A^L together with a small diffuse addition is shown. We now proceed to describe the processing for Ambient Emission, A^E .

5.5.2 Using the fMRI Signal as Illumination Source

One of the major ideas in this work is to use the fMRI signal as a source for illumination. This is achieved by mapping the 3D fMRI intensity signal, indicating activity in the brain, through a separate transfer function defining a color emission, $c_E(s)$, for a location s along the ray. Adding color emission in the DVR stage requires a change to $A(s)$ used in Equation 5.5. In addition the Ambient Lighting from the LAO stage, described in previous section, will be included such that

$$A(s) = A^L(s)c(s) + c_E(s), \quad (5.9)$$

with the ambient light, $A^L(s)$, being reflected from the classified T1 sample, $c(s)$. As can be seen in the left image of Figure 5.5 this produces an emissive effect but the fMRI signal is not yet illuminating the surrounding brain tissue.

To achieve an illuminating effect of the surrounding tissue the LAO algorithm is required to compute a first order light scattering event, based on the emission $c_E(s)$ from the fMRI signal. This information is computed and cached in a separate volume to hold A^E . Again the LAO algorithm is applied, but with $g_{A^E}(s)$ as in

$$A_k^E(x) = \int_a^{R_\Omega} g_{A^E}(s) \cdot e^{-\int_a^s \tau(t)dt} ds, \quad (5.10)$$

Figure 5.6: In the right image voxels without fMRI activity have their opacity reduced by a factor of $\alpha_{\min}$. In this image, the factor is set to 0.07. The adjustment make interior signals more visible but still provides context in active areas.

where

$$g_{A^E}(s) = c_E(s). \quad (5.11)$$

The sum of the rays for Ambient Emission generate A^E in a similar way as for A^L in Equation 5.6. It is also evident that A^L and A^E can be computed separately. Since $g_A = g_{A^L} + g_{A^E}$, the sum of the ray integrals over g_A is equivalent to the total sum of the integrals over g_{A^L} and g_{A^E} , respectively.

The full expression for $A(s)$ used in the volume rendering integral to include ambient lighting, $A^L(s)$, and emission, $A^E(s)$, is thus given by

$$A(s) = (A^L(s) + A^E(s)) \cdot c(s) + c_E(s). \quad (5.12)$$

This ambient color contribution, invariant to light and view direction, is thus a combination of both volumetric light and emitted color from the fMRI signal, reflected against the classified T1 sample's color $c(s)$, the traditional post-classified associated color. The direct contribution of fMRI signal emission, $c_E(s)$, is also included in the DVR process. In Figure 5.4 middle and right the resulting images for two different activation patterns are shown.

5.5.3 Visibility Enhancement

An additional feature has been added in order to ensure that signals deeper inside the brain will become visible while the visual context cues are maintained. For the samples in the region containing the fMRI data, the opacity in the ray casting pass, embedded in $c(s)$, is lowered if there is no signal emission at the given voxel location. The adjusted opacity, α' , is computed as

$$\alpha' = \text{clamp}(\alpha \cdot \text{adjust_threshold}, \alpha_{\min}, 1.0)$$

Figure 5.7: The use of clip planes to study the interior extent of the fMRI signal. In this case the signal represents activation of the motor cortex from movements of the left hand.

The opacity reduction is limited by a lower threshold $\alpha_{\min}$, essentially the transparency factor applied to all non-emissive voxels. The function clamp is used to keep the value within the range $[\alpha_{\min}, 1.0]$. The result is shown in Figure 5.6.

Another mean to investigate the signals is by applying clip planes to the context and the signal. This makes it possible to better study the location and penetration of signal patterns. In Figure 5.7 the use of clip planes is illustrated.

5.6 EVALUATION OF METHOD

To investigate our proposed fMRI DVR approach and to compare it with traditional 2D slice visualization we conducted an evaluation with 4 participants. The objective was to assess the users' ability to perceive spatial information of active regions (position) and also the intensity of the activity.

We presented two vertically aligned images on a computer screen. Each image showed a brain activity pattern and the task was to compare the images and judge if they showed the same activity (same position) or not. In the slice visualization each image consisted of 30 slices arranged in a 6×5 matrix. Each slice had the active region marked in red, see Figure 5.8. In the DVR each image showed side-view and top-view of a brain volume with the active region marked in red.

We used two synthetic data sets, A and B, to generate the brain activities. In data set A two activity patterns differ by a translation of 4 pixels in the x and y direction and 1 pixel in the z direction. In data set B, a translation of 10, 10 and 1.5 pixels was used. Also, random noise in position and shape of activity was introduced to simulate brain activity changes. The experiment was divided into two parts and half of the participants started with the slice visualization and the other half with the DVR visualization. In each part the participant viewed a randomized sequence of 50 pairs of images, 25 pairs from dataset A and 25 from dataset B. The presentation time was 10 s and they then responded to the

Figure 5.8: The 2D slice representations used in the evaluation. The task is to tell if the set of slices on the left and the right represent that the same activity or not. The inset shows a close up of one of the slices indicating the actual screen resolution of the experiment.

question of whether the two images were: “same”, “different” or “I don’t know”.

Table 5.1 shows the evaluation results. Performance was better for DVR than for the slice visualization for both datasets. As the displacement between two different activities got smaller and more difficult to perceive (dataset A) performance improved by 31% using DVR compared to the slice visualization. This speaks in favor of our approach and future evaluations will expand on the results, providing a more comprehensive assessment of our approach.

5.7 RESULTS

Experiments – The real-time fMRI visualization pipeline was tested using a 48 year old healthy male subject. The subject in the scanner was given instructions and notified of the onset and end of the periodic stimuli through a head mounted display. A green box indicated activity and a red box indicated rest. The period of the stimuli was 40 seconds, i.e. 20 seconds of activity and 20 seconds of rest. During the experiment the subject performed a number of different activities such as left and right hand activity, mathematical calculations, left and right foot activity and language tasks. In the experiments, the visualization was fed back to the subject in the scanner, as well as being displayed outside the scanner on a monitor. All data used to generate the images shown in this work were obtained in this experiment.

Table 5.1: The response data for all participants (P) for both visualization and both data sets. The figures within brackets show accurate/error/don't know responses respectively.

	Test	P1	P2	P3	P4
Slice	A	(15/9/1)	(14/10/1)	(17/7/1)	(18/5/2)
	B	(24/0/1)	(23/1/1)	(22/3/0)	(23/2/0)
DVR	A	(20/5/0)	(19/2/4)	(21/4/0)	(24/1/0)
	B	(22/2/1)	(25/0/0)	(24/0/1)	(25/0/0)

Data acquisition and signal processing – Before the real-time phase could be started, a high resolution T1 weighted volume had to be captured. The resolution of the T1 volume was 140 slices, each with a resolution of 240 by 240 pixels. The T1 volume took about 5 minutes to acquire. The volume was then resampled using tricubic interpolation to a grid with $512 \times 512 \times 256$ voxels. The physical size of a voxel is then $0.479 \times 0.498 \times 0.547$ mm. Table 5.2 shows performance measurements of the described fMRI signal processing technique. The motion compensation and the calculation of activity is fast enough to collect a volume of data every other second. The resolution of the fMRI data is $64 \times 64 \times 22$ voxels, where each voxel has a resolution of $3.75 \times 3.75 \times 3.75$ mm. This means that we cover 8.3 cm of the brain in the sagittal direction. To obtain high BOLD contrast the echo time (TE) was set to 40 ms and the repetition time (TR) was set to 2000 ms.

Table 5.2: Signal Processing performance.

Signal processing step	Time (s)
fMRI Registration	0.8
Calculation of activity values	0.6
Total	1.4

Visualization – All of the volume rendered images have been generated using a standard PC equipped with an Nvidia GTX 285 graphics card with 1GB of graphics texture memory. The LAO map is computed with a , the initial offset to avoid self-occlusion, set to 0.8 voxel, the radius of spherical support, R_Ω , set to 2 blocks (1 block contains 16 voxels) and the number of steps per ray is 31 (see Equation 5.7).

Table 5.3 shows the performance for the calculation of the LAO map of the reference T1 volume and the fMRI signal. Initially, the LAO map of the reference T1 volume is calculated to provide a high resolution context with shadow effects. Since LAO requires processing of a neighborhood around each

5.8 Conclusion and Future Work

Table 5.3: Performance measurements for updating the LAO contribution of the T₁ brain and the fMRI signal.

LAO calculation		T1 (s)	fMRI signal (s)	
			full calculation	optimized calculation
Initialization	32 rays	5.38		
	64 rays	10.98		
	128 rays	22.02		
fMRI signal change	32 rays		0.82	0.21
	64 rays		1.54	0.38
	128 rays		3.02	0.68

voxel in the volume, it is computationally demanding, as shown in the first column of Table 5.3, to compute the LAO for the full T₁ brain volume. The fMRI signal is, however, only sampled in a subsection of the T₁ brain and as shown in section 5.5, the emissive LAO from the fMRI signal can be computed separately. This makes it possible to calculate the LAO emission from the fMRI signal almost an order of magnitude faster than the T₁ LAO computation. Furthermore, the signal is sparse and represents localized active regions. We can thus further improve the performance of the fMRI LAO calculation by skipping voxels that are not illuminated by the signal. This yields an additional 4× speed up, as shown in the third column of Table 5.3.

During the visualization, a change of transfer function can also be made. This requires both the recalculation of the LAO map of the reference T₁ brain volume and the recalculation of the emission from the fMRI signal. In between TF changes and fMRI signal updates the DVR framerate is 10.7 FPS. By ignoring the emission in the LAO stage the DVR framerate can be increased, at the cost of visual quality, to 12.7 FPS. In this setting there is also no overhead associated with fMRI signal updates.

5.8 CONCLUSION AND FUTURE WORK

In this chapter we have described a system for real-time fMRI and we have shown how the emission in direct volume rendering can be used to concurrently visualize fMRI signals in the anatomical context of an MRI volume of a patient/test subject specific brain. The local ambient occlusion method for volume rendering yields visually appealing images of the brain anatomy and a clear fMRI signal presentation while rendering takes place at interactive speeds. One of the main advantages of the method is that it effectively fuses the anatomy with the fMRI signal of lower resolution, thus guaranteeing that the activity is only shown where there is brain tissue, as defined by the current transfer function settings.

The real-time visualization aspect of the system also has wider importance

for normal fMRI use. The visualizations constitute a tool for many research situations as well as future clinical use. The in-vivo response of the system and high quality visualizations provide one of the important steps towards further utilization of the potential of fMRI. Among potential application areas of the real-time system we can mention cognitive training and planning of stroke rehabilitation, assessment of drug treatments and pre-operative planning. For instance, before performing brain tumor surgery, important areas of the brain are often mapped using a conventional fMRI experiment.

In future work we will further explore the possibility to feedback the visualizations to the test subject and see this as a part of a bio-feedback loop. We will also conduct more in-depth evaluations of the presented method. Of special interest is to compare how our method depicts signal strength as well as the spatial position in comparison to other 3D visualization methods. We will also apply our visualizations to existing clinical fMRI routines and perform a detailed evaluation of the visualizations in the context of these routines. Another important area is to develop ways to visualize the uncertainty of the fMRI signal.

CHAPTER 6

QUANTITATIVE ANALYSIS OF KNEE MOVEMENT PATTERNS THROUGH COMPARATIVE VISUALIZATION

6.1 INTRODUCTION

As the major focus of medical imaging has been the understanding of anatomical structures, vast research effort has been dedicated to the acquisition and interpretation of anatomical modalities. While these techniques enable the interpretation of high-resolution static anatomical images, time-varying data is now becoming more important. The better understanding of organ functions can provide more insight and significantly improve the diagnostic workflow. This has led to the emergence of many functional modalities, which allow multimodal imaging of physiological processes alongside the anatomical image data serving as a context. The latest exploitation of anatomical modalities in a functional context arose with the recent advances in CT (computed tomography) imaging. Driven by the demands of imaging the beating heart, the scanning time of modern CT scanners enables a dynamic acquisition under movement. As a result, dynamic image-based orthopedics becomes possible. Traditionally, orthopedics relies on anatomical data given by 2D X-ray or 3D CT and MRI imaging. However, previous research has shown that there is a disagreement in quantitative diagnosis results between the traditional and the 3D imaging techniques due to the failure to capture the dynamic nature of joints movement (Ward et al. 2002). Accordingly, the benefits of fast modern CT acquisitions have resulted in a novel trend in this area (McNally et al. 2000; Rasch et al. 2013), where dynamic scans are acquired in order to understand the complex kinematics, which influence proper joint movement.

There are three main challenges that arise from 4D CT imaging-based orthopedics. The first challenge is the quantification of complex joint movements based on dynamic CT data. While inspecting an animation of the dynamic data might help the medical doctor to get a first impression about underlying conditions, quantification is necessary to support a proper categorization. Since dynamic CT scans contain a vast amount of information, manual calculation of kinematic parameters is a time-consuming process and can lead to inconsistent results. The second challenge lies in the comparative analysis of joint movement patterns. When detected conditions require a surgery intervention, a follow up scan is often performed to measure the success of the operation. However, measuring surgical success requires a comparison of the status before and after

6.1 Introduction

Figure 6.1: 2D and 3D views of a knee joint. While the conventionally used Skyline view captured at 30 to 45 degrees of knee flexion looks normal based on X-ray (a) as well as 3D CT (b), only the joint movement pattern imaged through 4D CT ((c), (d)) reveals the patellar dislocation issue at the full extension.

the intervention, which makes a comparative analysis necessary. Finally, as medical reporting is required in all medical disciplines, sufficient techniques are required to be able to report on detected conditions.

In the analysis of patello-femoral instability issues, the Skyline or Merchant view captured at 30 to 45 degrees of the knee flexion or 3D CT is commonly used (see Figure 6.1(a), and 6.1(b)) (A. M. J. Bull et al. 2002; Elias and White 2004; McNally et al. 2000). However, these techniques have shown not to adequately reveal the anomaly due to the limitation of capturing the instability of the knee at full extension (Endo et al. 2011). With 4D CT, it becomes possible to obtain a 3D visualization of the patella's tracking in the femoral groove during a functional active flexion and extension movement with normal muscular force. As illustrated in Figure 6.1(c) and 6.1(d), the ability to obtain information at full extension with 4D CT helps to reveal the anomaly. Furthermore, dynamic CT scans make it also possible to demonstrate the effect of surgical intervention and optimize the surgical technique (A. M. J. Bull et al. 2002). The fact that there are more than a hundred of surgical techniques described indicates that no present method is perfect.

To meet the challenges in 4D CT image-based orthopedics, we propose novel visualization metaphors, which enable quantification, comparison, and reporting of joint movements as imaged through time-varying CT data. The proposed metaphors have been developed in close collaboration with medical experts who wish to investigate patello-femoral instabilities with time-varying CT acquisitions. In past years, research has been conducted on the visualization of angular relations. Gait analysis, which is a study of locomotion, can be considered as the origin of kinematic analysis (Whittle 2007). The central question in this area is the understanding of angle correlations. The angle-angle plot, in which each axis represents a kinematic or kinetic signal, is commonly used to convey angular information. By plotting one signal against the others, an angle-angle plot illustrates the coordinated motion of the two segments or joints. Manal et al. used an advanced color-coding scheme to incorporate additional

parameters into the standard angle-angle plot (Manal and Stanhope 2004). Later, the authors proposed the use of an additional dimension within the plot so that additional parameters can be visualized (Manal, Chang, et al. 2005). Côté et al. presented 2D projected stick figures to show the kinematic results of continuous hammering performed by different patient groups (Côté et al. 2005). While the proposed approach was sufficient when looking at joint height, it failed to reveal the kinematic relationships. Keefe et al. proposed a visualization system based on multiple views to show relationship within sequential kinematic data (Keefe et al. 2009). Krekel et al. focused on the visualization of the relationships between multiple connected joints by combining interactive filtering with visualization (Krekel, Valstar, et al. 2010). The approach probably most relevant to our research is that of Krekel et al., in which a technique for visualizing the range of motion of the shoulder joint is presented (Krekel, Botha, et al. 2006).

In addition, we propose a GPU-based enhanced FOI identification and tracking in the time domain based on the scale-invariant feature transform (SIFT) algorithm. For instance, the FOIs selected by users are tracked automatically over scans in dynamic CT data and thus, serve as a foundation for quantitative measurement of kinematic parameters. The SIFT algorithm (Lowe 1999; Lowe 2004) is a widely used technique in the field of computer vision to identify and match features between images. In the SIFT technique, stable features are detected through a scale-space analysis approach. Then, for each detected feature, descriptors are constructed in such a way that they are invariant to rotation, and translation. The constructed descriptors serve as the foundation for matching features between 2D images. While the technique was initially proposed to handle 2D images, the underlying mathematical foundation can be extended to handle n -dimensional data sets (Cheung and Hamarneh 2007; Scovanner et al. 2007). As a result, SIFT has been successfully applied into different application cases involving salient feature localization and matching such as motion tracking (Allaire et al. 2008; Paganelli et al. 2012; Scovanner et al. 2007), group- related studies (Toews and W. M. Wells I. 2012), volumetric ultrasound panoramas (Ni et al. 2008), and complex object recognition (Flitton, T. Breckon, et al. 2010; Flitton, T. P. Breckon, et al. 2013). Recently, SIFT has been compared to other feature detection algorithms and the result shows that SIFT achieves a balanced result between stability and performance (Yu et al. 2012). It is worth noting that while the investigation of patello-femoral instability has driven our research, the presented visualization techniques are in fact generalizable and thus can be transferred to other application cases, where complex joint movements are of interest (see Section 6.6.2).

While other research has been conducted on the visualization of complex joints (Krekel, Valstar, et al. 2010; Pronost et al. 2011), to our knowledge, the work in this chapter is the first to tackle time-varying CT data in order to support the analysis of joint movement patterns. Our visualization approach differs from previous work in the way we handle and derive kinematic information

from the input data. For instance, previous research focuses on using markers to track the kinematic behaviors of joints, we focus on extracting kinematic information directly from time-varying volumetric data sets. This enables a new and novel visual interpretation, as the analysis takes arbitrary feature points inside joints into account. Furthermore, patient instrumentation with markers is avoided. To support a better understanding of the acquired data sets and the contained joint movement patterns, we make three major contributions:

- Visualization metaphors for the quantitative assessment and comparison of joint movement patterns.
- Component separation and visualization to enable medical reporting of joint movement patterns.
- Interactive visual inspection of joint movement data based on an enhanced GPU-based feature identification and tracking technique based on the SIFT algorithm.

The remainder of this chapter is organized as follows. The medical background is covered in Section 6.2. Then, we present the in-depth description of the proposed approach and visual metaphors in Section 6.3 and Section 6.4. The results of the proposed approach applied to two real clinical data sets are presented in Section 6.5. Section 6.6 presents a verification of the technique and the possibilities to apply the propose approach to different type of joint. The chapter is concluded with some perspective on future developments in Section 6.7.

6.2 MEDICAL BACKGROUND

The patella (knee-cap) is a bone that is incorporated into the tendon of the quadriceps muscles of the thigh and moves within a groove at the lower end of the femur (thigh bone). When the knee bends, the patella engages the groove and is fixed to the center of the groove by muscle forces. On the other hand, the patella moves to the upper more shallow end of the groove when the knee is straightened. As a result, the patella will be more loose, and may move somewhat more lateral (to the outside) (Rhee et al. 2012). The medial patello-femoral ligament (MPFL) is the primary medial restraining structure against lateralization of the patella when the knee is straight or mildly flexed, and contributes up to 80% of the medial restraining forces to the patella (Desio et al. 1998).

A dislocation of the patella occurs when the patella comes completely out of its groove, gets fixed to the outside of the knee joint, and this causes significant pain. It commonly happens to young and physically active people, often during sporting activities. The annual incidence of primary patellar dislocations has been estimated to 43 per 100000 in children under the age of 15 (Nietosvaara et al. 1994). The first dislocation usually occurs as a significant injury with the

knee in near full extension, but the patella may dislocate much more easily thereafter. Recurrent patellar dislocations eventuate in 15-45% of primary dislocation cases (Hing et al. 2011) and can cause significant problems, not only prevent sport activity, but also be a hindrance in daily activity.

The primary treatment is bracing as well as physiotherapy to strengthen the stabilizing muscles (Beasley and Vidal 2004), especially the inner part of the quadriceps muscle (vastus medialis). By strengthening this muscle, it has been hypothesized that the patella will track more centrally in the groove, avoiding a more lateral position that may increase the likelihood of recurrent dislocation and instability symptoms.

In patients who have repeated dislocations, there are more than hundred surgical options described (A. M. J. Bull et al. 2002). It is possible to restore the normal anatomy by repairing the torn ligaments on the inner aspect of the knee, to deepen the groove, or to realign the patellar tendon to stabilize the patella in a more medial (inner) position (Rhee et al. 2012). In the last decade, it has been increasingly popular to reconstruct the MPFL, often as an isolated procedure (Christiansen et al. 2008).

The lack of accurate follow-up methods to assess the movement of the patellar in relation to the groove after rehabilitation or surgical intervention has led to the multitude of operations. Ordinary radiographic methods are inadequate for the assessment of patello-femoral malalignment. The most commonly used technique for visualization of the patello-femoral joint requires 30 to 45 degrees of knee flexion (A. M. J. Bull et al. 2002; Davis and Fithian 2002; Smith et al. 2010) (see Figure 6.1(a)). It is a static examination and the images are not obtained near full extension where the groove is most shallow and the patella is more unstable. Conventional CT-scans and MRI can get images with a straight knee, but they are static and will not display patellar tracking under functional movements (A. M. J. Bull et al. 2002). With the use of 4D CT, it becomes possible to get a 3D visualization of the patella's tracking in the femoral groove during a functional active flexion and extension movement with normal muscular forces. However, it is difficult to describe 3D motion in a distinct way. Fixed body axes in either the patella or femur can give confusing results (A. M. J. Bull et al. 2002). Thus, there is a great need for quantitative analysis of joint movements through apparent visualization methods to give a better understanding and also to get quantifiable results.

6.3 METHOD

Figure 6.2 presents the workflow of the proposed approach. In order to support the quantitative visual analysis of the knee movement patterns, the dynamic CT scan is pre-processed. Particularly, features are extracted and matched between scans to serve as the foundation for the interactive visual analysis stage. In the second stage, users can interactively select FOIs and the system automatically tracks these features between scans in the input dynamic CT data. Depending

6.3 Method

Figure 6.2: In the pre-processing stage, features in a dynamic CT data set are extracted and matched between scans. In the second stage, user can select FOIs and have these FOIs tracked in the time domain. Depending on the application in mind, different quantitative measurements can be performed and visualized for assessment.

on the application in mind, different quantitative measurements of kinematic parameters based on the selected features are performed. The results are then visualized through the proposed visual metaphors (see Section 6.4) to support quantitative and comparative analysis of the underlying kinematic information.

6.3.1 Enhanced GPU-based Feature Identification and Tracking

While our work is based on extensions of the SIFT algorithm to handle 3D volumetric data (Cheung and Hamarneh 2007; Scovanner et al. 2007), we exploit the parallel nature and computing power of the GPU to achieve interactivity. Moreover, we propose a novel descriptor construction technique that helps to improve the accuracy in the feature matching and tracking process. The algorithm is performed in three successive stages: *feature location detection*, *feature descriptor construction*, and *feature matching*.

Feature Location Detection

In the first stage, stable features in the input image are identified through a scale-based analysis approach. First, the volumetric input data, $I(x, y, z)$, is convoluted with variable-scale Gaussian functions, $G(x, y, z, k\sigma)$, to generate a scale space, $L(x, y, z, k\sigma)$, as follows:

$$L(x, y, z) = G(x, y, z, k\sigma) * I(x, y, z) \quad (6.1)$$

where k is a constant multiplicative factor for separating scales in the scale-space. The local extrema of the difference-of-Gaussian functions, $D(x, y, z, k^i\sigma)$, applied to this scale space are considered to be potential local features in the original volumetric data:

$$D(x, y, z, k^i\sigma) = L(x, y, z, k^{i+1}\sigma) - L(x, y, z, k^i\sigma) \quad (6.2)$$

Lindeberg and colleagues could show that these local extrema are a close approximation to the scale normalized Laplacian-of-Gaussian (Lindeberg 1994), $\sigma^2 \nabla^2 G$, which are the most stable features in the input image (Mikolajczyk et al. 2005). By applying a thresholding scheme based on the principle curvature analysis to filter out the blob-like and edge-like features, which are usually

of no interest, the stability of the detected feature locations can be further improved (Allaire et al. 2008).

The construction of the scale-space representation is a computation demanding process. Fortunately, the calculation at each voxel is independent of the calculation at others. Therefore, it is natural to make use of the parallel nature of the GPU to enhance the performance. For instance, the convolution of the input volumetric data using separable Gaussian kernels helps to dramatically improve the performance.

Feature Descriptor Construction

The aim of the second stage is to construct a unique descriptor to represent the detected feature location in such a way that is most invariant with respect to rotation, scaling, and translation. The construction of such a descriptor is based on the gradient orientations in the neighborhood of the detected feature locations and presented as a histogram of gradient orientations. In 3D, a gradient orientation comprises three components: azimuth, elevation, and tilt angle. While the elevation and azimuth components can be derived directly from the gradient itself, the tilt angle can only be derived through a more complex analysis of the neighborhood (Allaire et al. 2008). Consequently, a 2D histogram is required to capture the distribution of the azimuth and elevation angles when handling 3D images.

In the first step of constructing a descriptor, it is crucial to identify the dominant gradient orientation, which is the maximum peak in the histogram of gradient orientations, in the neighborhood of a detected feature. The rotation invariant property of the descriptor is achieved by re-orienting the other gradient orientations in the neighborhood to the identified dominant gradient orientation before generating the final descriptor (Lowe 2004). In addition, to avoid disruptive changes of gradient orientations in the neighborhood around a detected feature location and to further improve the uniqueness of the constructed descriptors, gradient orientations are divided into ranges of 45 degrees, and the neighborhood around each detected feature location is divided into sub-regions (Allaire et al. 2008; Lowe 2004). For example, the commonly used neighborhood size of 16x16x16 is divided into 64 sub-regions of 4x4x4. Thus, the final descriptor is a concatenation of histograms of gradient orientation corresponding to each sub-region. While the resulting descriptor is a unique representation of the detected feature, discarding the other gradient orientations of lower magnitude can have a negative impact on the feature identification stage. By creating additional descriptors based on smaller peaks, which are of 80% the maximum peak in the initial histogram of gradient orientations, the accuracy in the feature matching process can be vastly improved (Lowe 2004).

Previous research has shown that the size of the neighborhood can have a large impact on the uniqueness of the constructed descriptors, which affects the accuracy of the feature matching process between images (Allaire et al. 2008; Paganelli et al. 2012). This is due to the fact that the size of the neigh-

neighborhood is a global setting and is dependent on the input data. While a large size neighborhood (e.g., greater than $16 \times 16 \times 16$ voxels) might fail to capture the local characteristic of the detected feature, a small size neighborhood (e.g., less than or equal $8 \times 8 \times 8$ voxels) might put too much emphasis on the local property characteristic of the detected feature. To overcome this limitation, we propose a novel descriptor construction approach called *ring descriptor*. In our approach, the neighborhood is divided into non-overlapping sub-regions centered at the detected feature location. For each non-overlapping sub-region, the dominant gradient orientation is identified. This allows us to capture not only the local characteristic of the detected features but also reduce the impact of the neighborhood size setting on the uniqueness of the final descriptor. To achieve rotation invariant property, gradient orientations in the neighborhood are then re-oriented to the dominant gradient orientations of each sub-region before the construction of the histogram of gradient orientation. Our experimental findings have shown that not only the total number of descriptors is comparable to previous approaches, but also the uniqueness of the descriptors is increased. Consequently, the proposed descriptor construction technique helps to improve the accuracy of the feature matching process without scarifying the performance, which will be presented in detail in Subsection 6.6.1.

Another advantage of the proposed technique is the ability to introduce a weighting factor into the feature descriptor construction process. For instance, depending on the input data, the local property of the detected feature can be emphasized or de-emphasized through a weighting factor for the dominant gradient orientation of the non-overlapping rings. As a result, the size of the neighborhood has less influence on the result, which makes the proposed approach more flexible in handling different type of dynamic volumetric data.

One of the challenges for the realization of the proposed approach using the graphics hardware is the limitation of the memory architecture of the GPU. For instance, a large neighborhood setting can lead to a large histogram that cannot be fitted into the local/share memory on the GPU to exploit the highest performance as possible. To overcome this limitation, a multi-pass approach can be used (Shams and Kennedy 2007). In our approach, we have different OpenCL kernels that are optimized for different histogram size and a generic kernel for handling large size histogram. The system then automatically switches between optimized versions to achieve the highest performance.

It is worth mentioning that a smoothing operator applied to the constructed histogram of gradient orientations is required to reduce the impact of disruptive changes of gradient orientations (Lowe 2004) in standard implementation of SIFT. However, the type and the bounds of the smoothing operator are abstracted from the original input data. As a result, it is difficult to identify a good smoothing operator to improve the quality of the constructed descriptor. In the proposed technique, by moving the computing from CPU to GPU, we do not only exploit the parallel computing power of the GPU but also implicitly achieve the interpolation supported by the hardware. Particularly, the GPU

hardware enables us to achieve a bi-linear interpolation by default. Moreover, instead of re-orienting gradient orientations in the neighborhood around a detected feature location, the whole neighborhood is re-oriented to the dominant orientation and gradient orientations are updated accordingly. This allows us to minimize the effect of different interpolation scheme applied to a constructed histogram of gradient orientations as the interpolation in our approach is directly based on the underlying information from the input data.

Feature Matching

Once the features descriptors have been constructed for two data sets to be compared, they can be used to identify matching features using different techniques such as RANSAC (Fischler and Bolles 1981), Best-Bin-First (BBF) (Beis and Lowe 1997). Since a descriptor is basically a concatenation of histogram of gradient orientations, the Euclidean distance between descriptors is a good indicator for a high probability match:

$$d(p, q) = \sqrt{\sum_{i=1}^N (p_i - q_i)^2} \quad (6.3)$$

Here, p and q are two descriptors, p_i and q_i are the i -th elements of these descriptors, and N is the size of the descriptors. To find the matching features in the two data sets, I_1 and I_2 , the Euclidean distances from each descriptor in I_1 to all descriptors in I_2 are computed. The minimum distance value is an indicator of a high probability match. The finding of the minimum distance is a reduction problem. Due to the size of each descriptor, a GPU-based approach does not improve the performance. As a result, we present a hybrid approach to the problem of feature matching. The computation of the Euclidean distance between one descriptor in the first input image, I_1 , and all descriptors in the second image, I_2 , are performed in parallel using the GPU. The result is then passed to the CPU implementation to identify the minimum distance that serves as indication of a high probability match.

6.3.2 Kinematic Parameters Measurement

There have been various researches focusing on the methods used to describe patello-femoral joint motion in past years. The results can be classified into two groups: those that describe motion of the patella relative to the femoral groove and those that describe the motion of the patella relative to a fixed- body axis (A. M. J. Bull et al. 2002). The former are primarily imaging studies, in which CT and MRI have been used to investigate the patellar motion during dynamic knee joint movement (Brossmann et al. 1993; Powers et al. 1998; Shellock et al. 1993). One significant drawback of previous results is the inability to describe the patellar motion in three-dimensional space.

The congruence and tilt angles between the patellar and the femoral groove are two commonly used kinematic parameters in quantitative analysis of the

6.3 Method

Figure 6.3: Congruence and tilt angle measurement. (a) is the visualization of the knee overlay with a FOI (green), which marks the widest part of the on the left knee. (b) and (c) are the illustrations of the congruence and tilt angle measurement through a clip plane setup.

patello-femoral issue. As the congruence and tilt angles reflect the relation between the patellar and the femoral groove, we propose a geometry setup, in which the patellar and the clip plane cut through its widest part serve as the reference, for quantitative kinematic measurement (see Figure 6.3). The congruence angle is then defined by the angle between the bisected femoral trochlea (dashed line in Figure 6.3(b)) and the vector connecting the apex of sulcus angle, ABC, to the lowest point of the articular ridge of the patella (BD in Figure 6.3(b)). By using the same geometry setup, the tilt angle, θ , is defined as the angle subtended by a line joining the lateral edge and the lowest point of the articular ridge of the patella and the posterior condylar line as illustrated in Figure 6.3(c).

Besides the ability to describe the patellar motion in three-dimensional space, the combination of the proposed kinematic parameters measurement approach and the feature identification and tracking allows us to have a semi-automatic measurement of kinematic parameters. The manually selected FOIs (see Figure 4(a)) are automatically tracked across scans in a dynamic data set. As a result, the resulting clip plane setups can be achieved not only automatically but also consistently.

It is worth pointing out that when the patella moves out of the femoral groove, there is no intersection between the clip plane and the femoral groove, thus the congruence angle cannot be calculated. Consequently, the proposed approach reflects the fact that there is no congruence between the patella and the femoral groove, which the previous research results failed to capture and present.

In addition to the measurement of the congruence and tilt angle, we propose the measurement of the distance, d_G , from the lowest point of the articular ridge of the patella, R, to the femoral groove to convey the translation of the

patella in relation to the femoral groove as follows

$$d_G = \min_{1 \leq i \leq N} d(R, p_i) \quad (6.4)$$

where N is the number of point on the femoral groove, and d is the Euclidean distance function. In this approach, the femoral groove is approximated by a set of discrete point in order to reduce the computation demand. The presented feature tracking technique allows us to track the identified points, which approximate the femoral groove, in the time domain to facilitate the calculation and reduce the time-consuming process of manually select features through out all the scans in a dynamic data set. By applying the same approach, the distance between the drill holes on the patella and the drill hole on the femoral can also be calculated. The quantitative results enable doctors to assess the success of the surgical intervention in comparison to the pre-surgical intervention as well as the effect after the surgical intervention.

6.4 COMPARATIVE VISUALIZATION

6.4.1 Radial Angle Plot

The angle-angle plot is one of the most commonly used visual metaphor for depicting kinematic parameters (Manal and Stanhope 2004). In a traditional set up, each axis of the plot represents a kinematic parameter, whereby the plot reveals the relation of the individual parameters to each other. Figure 6.4(a) shows an example of the angle-angle plot depicting the relations between the abduction angle and the axial rotation of two subjects. Although the angle-angle plots help to reveal the relations between the two kinematic parameters, its representation does not reflect the visual mapping of the presented angular values within the context of the joint. As a consequence, the interpretation as well as the mental linking of the plot to the actual movement patterns requires a lot of experience and time. This becomes especially apparent when observing the comparative qualities of the angle-angle plot. When comparing the plotted data for Patient 1 (*orange*) and Patient 2 (*blue*), it becomes clear that the movement of Patient 1 includes a lower degree of axial rotation for abduction levels 40 to 130. However, as the spatial reference of the joint is missing, the rotation difference with respect to the joint is not immediately visible.

To address these shortcomings, we present *radial angle plots* as a joint-centered visualization metaphor to depict kinematic parameter relations. The radial angle plots have been designed in such a way that they can be easily applied to various joint types. Instead of using linear mappings for the x and the y -axis as illustrated in Figure 6.4(a), we combine linear and polar mappings of the angular values. While the x -axis is the linear representation of one kinematic parameter, the y -axis is converted into a polar representation as shown in Figure 6.4(b). This enables the visual mapping of the plotted values

6.4 Comparative Visualization

Figure 6.4: The relations between the abduction angle and the axial rotation of two subjects. The standard angle-angle plot allows quantification of the relation but makes mental registration with the spatial context difficult (a). The proposed radial angle plot represents the same data in a joint centered way, while at the same time exaggerating the differences for critical abduction angles (b).

to the actual angular changes, as given within the frame of reference of the joint under investigation. The concentric layout of the angular relations between kinematic parameters provides an implicit exaggeration of the most interesting kinematic parameter range, i. e., an angle representing full abduction or flexion. These extreme angles are the most problematic when dealing with joint issues, even small changes need to be considered and should thus be emphasized by the used visualization metaphor.

Figure 6.4 compares the traditional angle-angle plot to the proposed radial angle plot. In Figure 6.4(b), the x -axis represents the abduction angle while the axial rotations are placed on the corresponding shaded concentric half-circle (from -90 degrees to $+90$ degrees, from left to right). The gray scale gradient has been chosen to allow an intuitive quantification of the polar angle coordinates, as well as an emphasis of the joint center, which is located in the middle at 0 degrees. While the angle-angle plot also depicts the relations between the two kinematic parameters for both patients, the radial angle plot reflects the actual

Figure 6.5: A radial angle plot of the congruence angles from pre-operation (red) and post-operation (blue).

angular changes directly through its visual mapping.

When dealing with the patello-femoral analysis, which is addressed in Section 6.5, an additional benefit of radial angle plots is the fact, that they can be directly co-registered with the 2D Skyline view representation. As illustrated in Figure 6.5, the concentric layout and the polar representation of the congruence values not only enables us to emphasize the difference between pre- and post-operation result at extreme position (53 degrees flexion) but also implicitly co-registers the rotation to of the kneecap to the femoral groove (center of the radial angle plot). Moreover, the radial angle plot also reflects the medial and lateral patellar angles corresponding to the negative and positive halves of the rendering. It is worth pointing out that in the design of the radial angle plot, the range of the angular value can be normalized accordingly to emphasize the changes.

6.4.2 Time-angle Profile

Although the 3D visualization of a full scan in a time-varying data set can provide both the visual context and the detail information to support visual analysis, there is a large amount of data presented to the user, especially in the case of 4D CT. In addition, the occlusions in the 3D visualization of volumetric data can change drastically in the time domain, and affect the visual access to areas of interest. Consequently, this can cause distractions when a user changes from one time frame to another. As the kinematic analysis process usually focuses on a defined feature and derive its movement patterns over time, an abstract visualization focusing on the feature and its kinematic characteristic can help to improve the visual analysis process. We propose an abstract visualization of a defined feature in the time domain called *time-angle profiles*. The proposed visual metaphor is designed in such a way that it helps to filter out unnecessary information while maintaining the kinematic parameters of the feature under investigation. At the same time, it captures the whole movement within a single picture and thus supports medical reporting and pattern comparison.

To generate this representation, the feature must be identified in all time frames before all instances are combined into a single visualization. In a standard approach, the extraction of the feature under investigation in all scans of a dynamic data set is very time-consuming. Fortunately, the proposed feature identification and tracking technique allows us to derive affine transformations of the feature across all scans in the dynamic data. As a result, a single extraction of the feature is enough for the generation of the proposed visual representation. The combination of all instances of the feature in all time frames is then visualized through a 3D sweep structure. This sweep representation provides an overview of the whole kinematic changes in the time domain. However, it does not facilitate visual assessment of kinematic parameters due to the fact that a complex movement pattern is usually a combination of different components such as rotations, translations, and tilting. Inspired by the magic mirror metaphor introduced by König and colleagues (König et al. 1999), we

Figure 6.6: Visualization of the proposed time-angle profile metaphor. The extracted movement pattern of the patellar over time is rendered at the center of the image. Kinematic parameters are incorporated through projection technique onto the bottom, side, and back plane.

exploit the use of projection techniques to decompose the movement patterns for the extracted features. By projecting the whole movement pattern onto a multi-planar plane geometry, we can reveal the underlying components of the kinetic parameters. For instance, a projection from the top view can reflect the rotation, and a projection from the side view can show the translation over time. In addition, the semi-transparent sweep structure is color coded to depict the various degrees of kinematic parameter changes.

Figure 6.6 illustrates the proposed visual metaphor applied to the visualization of the movement pattern of the patellar. At the center of the image is the extracted movement pattern of the patellar over time. The transition from a lighter to a darker color depicts the degree of kinematic parameter changes. For instance, as the patellar rotates, tilts and translates more at the extreme position in comparison to the initial relaxed one, the color goes from a dark to a light shade of blue. By projecting the movement pattern using different viewing angles, the proposed visualization approach can achieve the decomposition of the complex kinematic characteristics. The orthographic projection of the trajectory onto the side plane reveals the shifting of the patellar out of its groove.

The projection onto the bottom plane reflects the changes in congruence angles, while the projection onto the back plane shows the degree of tilting. Although the proposed technique does not provide the contextual information by focusing only on the movement pattern, it can be used as an adjunct to the 3D visualization of the time-varying data in a multiple linked view setup. As a result, contextual information and an overview of the kinematic changes over time can be visualized in an integrated manner.

6.5 RESULTS AND DISCUSSION

We applied to proposed approach to two real clinical data sets to verify the ability to facilitate quantitative analysis of the patellar movements. Two subjects were examined for this study. The first subject is a 19 years old female, patient A, with bilateral pronounced instability problems since she was 13 years old without any significant injury. The left and right side of patient A were operated in 2011 and 2012 respectively. The left side has been stable since the operations and is now asymptomatic. However, patient A had an injury on the right side after the operation. The situation makes it hard to assess the reconstructed tendon with CT scan on the right side on which patient A still has some instability symptoms. As a result, a re-rupture or an elongation of the reconstruction are under suspicion. The second subject is a 23 years old male, patient B, with distinct problems after an injury on the left side. In addition, patient B also has minor instability problems on the right side. Patient B had an operation on the left side in 2013. The operation was successful and patient B has a stable knee three month after the operation.

Figure 6.7(a) illustrates an overview of the patello-femoral issue in both cases, in which the kneecaps are far out and tilted on the lateral side. In both cases, the operations were performed with a reconstruction of the MPFL with a gracilis tendon (see Figure 6.7(b)). First, two drill holes on the kneecap and another one on the femur were created. Then, the tendon is passed through the drill holes on the kneecap, both free ends are then passed into the drill hole on

Figure 6.7: Visualization of straight knees before the operation (a), and the reconstruction of MPFL with a gracilis tendon (b) (permitted by Storz).

6.5 Results and Discussion

Figure 6.8: Flexion (a) and extension (b) of the knees resting on the radiolucent knee support.

the femur, tightened with the use of sutures and then fixed with a resorbable screw in the femur.

About a month before the operation, a dynamic CT scan is performed. The patient is supine with both legs resting on a radiolucent knee-support as illustrated in Figure 6.8. The maximal knee angle is about 40-50 degrees when the heels are touching the bed as shown in Figure 6.8(a). The patient performs bilateral active knee extensions until full extension (see Figure 6.8(b)), referenced as 0 degree, and then flexions.

The acquired dynamic CT scans were pre-processed using the GPU-based enhanced FOI identification and tracking approach proposed in Subsection 6.3.1. In the quantitative visual analysis stage, the domain experts interactively select FOIs (see Figure 6.3(a)) in one time frame and have these FOIs tracked automatically through the whole dynamic CT scan. Consequently, kinematic parameters were calculated in an automatic manner. The results were then presented through the proposed visualization metaphors to convey the underlying kinematic parameters of interest.

Figure 6.9: Quantitative measurement of the distance from the lowest point on the articulate ridge to the femoral groove before operation (a), and post operation (b) from patient A.

Figure 6.10: Distance between the drill holes on the kneecap to the drill hole on the femur three months after the operation (a), and one year after the operation (b) for patient A. The measurements showed that the distances are stable between 3- and 12 month postoperatively.

Figure 6.9 presents the quantitative measurements of the distance from the lowest point of the articular ridge of the patella to the femoral groove. Patient A had subluxations of both kneecaps when straightening the knees before the operation. On the postoperatively asymptomatic left side, the distance to the groove has decreased from about 60 mm to 25 mm with straight knees. On the right side, patient A still has some instability symptoms; however, it is less than before the operation, the distance to the groove has decreased from about 53 mm to 28 mm. The result of the facilitated the measurement of the distance from the two drill holes on the kneecap to the one on the femur for patient A is presented in Figure 6.10. The measurement shows that the distances are stable between the 3 month post-operation and 12 month post-operation.

Figure 6.11 shows the result of tilt angle measurements using the technique proposed in Subsection 6.3.2. The proposed radial angle plot present not only the movement patterns of the kneecap but also present them with respect to the reference frame, which is the femoral groove. Figure 6.11(a) shows that the tilting pattern of the left and the right kneecap are similar. Due to the injury happened after the operation in 2012, patient A still has instability issue on

Figure 6.11: Quantitative measurement from the proposed approach for the tilt angles of the kneecaps three months after the operation (a), and one year after the operation (b) for patient A.

Figure 6.12: Visualization of the movement pattern of the left kneecap of patient B using the time-angle profile visual metaphor. (a) and (b) present the measurements of kinematic parameters from pre- and post-operation stage respectively.

the right side. Although the tilt angles are similar between the left and right side at full extension, the patterns are different when the functional movement comes to 45 degrees flexion, which is emphasized through the radial angle plot in Figure 6.11(b).

The movement patterns of the left kneecap of patient B are depicted in Figure 6.12. The decomposition of the complex kinematic properties are done through the projection technique. Particularly, the projection onto the side presents the shifting of the kneecap out of its groove. The projection onto the bottom plane reflect the congruence angle changes, and the projection onto the back plane conveys the tiltings of the kneecap with respect to the femoral groove. From Figure 6.12(a) and Figure 6.12(b), it can be seen that the kneecap shifts out of the femoral groove less after operation. In addition, the changes of tilt angles as well as the congruence angles are also less than before. In addition to the detail rendering of the transformation of the kneecap, the color-coding scheme also quickly provides the information about the kinematic changes. For instance, the color transition from dark to light between the 48 degrees and 35 degrees flexions in the rendering on the back plane indicates that the tilt angle reduces rapidly. On the other hand, the small color transition from 44 to 46 degrees flexion in the rendering on the bottom plane indicates that the congruence angle stays almost unchanged. This reflects the fact that the operation on the left side of patient B was successful.

According to the feedback from domain experts, the quantitative measurements facilitated by our proposed approach support the suspicion of the doctor about the instability of the right knee of patient A. For instance, patient A had

Figure 6.13: Visualization of the inhale lung. (a) is the visualization of the lung overlain with the detected feature locations (green) from the GPU-based enhanced FOI identification and tracking algorithm, (b) is the visualization of the inhale lung with the manually input landmarks (blue).

a more pronounced decrease of the groove distance for the asymptomatic left knee postoperatively compared to the right one, but both legs of the ligament reconstruction were unchanged according to the the distances between the drill holes between 3 months and 12 months postoperatively. This indicates that the injury happened after the operation could have elongated the reconstructed ligaments on the right side, but there were no further elongation the rest of the first postoperative year. Moreover, we also receive positive feedback from domain experts about the time-angle profiles. This visual metaphor is very useful in providing an overview of the movement pattern of the patellar under investigation. Besides the ability to decompose a complex movement pattern into several kinematic parameters through projection technique, the combination with the facilitated automatic kinematic parameters measurement enables the transition from an overview into a detail quantitative analysis.

6.6 VERIFICATION AND GENERALIZATION

6.6.1 Verification

To evaluate the proposed GPU-based enhanced FOIs identification and tracking, we compare our results to the recently published work (Paganelli et al. 2012). The test data set is a 4D CT thorax scan (E. Castillo et al. 2009; R. Castillo et al. 2009). The data is given by ten equally sampled phases of the respiratory cycle in which the maximum exhale phase and the maximum inhale phase are denoted as $L0$ and $L5$ respectively. The reconstructed volumes have the size of $512 \times 512 \times 128$ voxels. The reference landmarks in $L0$ and $L5$ were manually setup by domain experts. While the parameters used in our algorithm were

Table 6.1: Number of matches, median and variability of error distributions at maximum exhale, L0, and maximum inhale, L5, phases obtained by the proposed enhanced SIFT compared to results from the previous work (Paganelli et al. 2012) and the manual reference landmarks. Variability is the difference between the 25th and 75th percentiles.

	#Matches	Median (mm)	Variability (mm)
<i>L0–L5</i>	300	12.98	18.22
SIFT (<i>L0–L5</i>)	509	13.23	17.90
Proposed technique (<i>L0–L5</i>)	525	11.14	12.78

set to match the ones used in (Paganelli et al. 2012), our approach makes use of the proposed *ring descriptor* construction technique. In addition, due to the advantage of the GPU-based implementation, we do not apply smooth operator to the histogram to avoid disruptive changes of gradient orientations but instead rotate the neighborhood region to the dominant orientation, which implicitly takes advantage of the bi-linear interpolation on the GPU.

Feature Location Detection

We have evaluated the matches, whereby we have computed the error as 3D residual distance between identified and matched feature locations at the *L0* and the *L5* phase (SIFT *L0–L5*). Figure 6.13 illustrates the visualization of the inhale lung overlay with features of interest. While the detected features from the SIFT algorithm are colored in green (see Figure 6.13(a)), the manually input reference landmarks are colored in blue (see Figure 6.13(b)). The Mann-Whitney *U* test (Mann and Whitney 1947) was applied to the error distribution in the identified and tracked features as well as in the reference landmarks. Table 6.1 shows our results in comparison to the ones reported in (Paganelli et al. 2012). Besides the slightly higher number of matches between the maximum exhale and maximum inhale phase, the proposed approach has shown to improve the accuracy in the descriptor matching process, as we have achieved a lower median, 11.14 compared to 13.23, as well as a lower variability. In addition, the Mann-Whitney test confirms that the distributions of the residual distances in the reference landmarks and in the result of the enhanced SIFT operator are not significantly different (p -value = 0.736), which means that the proposed approach can be used to identify the feature locations.

Feature Matching

To measure the impact on the feature matching process, we detect the feature locations in the time-series data and track these features in two different variants. First, we always use the maximum exhale phase, *L0*, as a reference. Second, we move step-by-step along the breathing cycle such that the previous breathing phase is served as the reference for tracking the feature locations in the next

Table 6.2: Number of preserved feature locations along the breathing cycle from the maximum exhale, $L0$, to the maximum inhale, $L5$, phase.

	SIFT ($L0-L5$)	Proposed technique ($L0-L5$)
Reference (Phase o)	117	243
Along breathing cycle	9	264

breathing phase. For each approach, we computed the number of feature locations between all phases. Table 6.2 reports the number of detected feature locations which were preserved along the breathing cycle. While tracking along the breathing cycle allows us to achieve a higher number of preserved feature locations and excludes the trailing ones, tracking referred to a reference phase excludes the most stable feature locations over time. The results in Table 6.2 shows that our technique allows a more stable feature tracking in dynamic data set.

As reported in Table 6.1 and Table 6.2, the proposed enhanced descriptor construction helps to increase the uniqueness of the descriptors at feature locations. Thus, it helps to improve the accuracy of the feature matching process in time-series data. It is also worth noting that by exploiting the power of the GPU implementation, we also achieved a much better performance in time. For instance, the overall time required for descriptors generation for each volume and descriptors matching between volumes is approximately 5.0 minutes. This is ten times faster than the result in (Paganelli et al. 2012), which is 50 minutes. As for the interactive visual analysis, the feature descriptors can be pre-computed and thus, the interactivity can be achieved.

6.6.2 Generalization

Although the data analyzed and visualized in this work has been extracted from the patello-femoral analysis scans, the presented techniques can be extended and applied to different kind of joint movement analysis. As shown in Subsection 6.6.1, the proposed GPU-based feature identification and tracking can be applied to dynamic CT scans in general. Depending on the application in mind, different criteria for FOIs selection and kinematic parameters calculation can be implemented based on the tracking results.

The time-angle profile visual metaphor was designed in such a way that it can be easily extended through the use of different projecting criteria. By deploying different projection criteria, the time-angle profile visual metaphor can be used for visual analysis of different underlying kinematic parameters. Moreover, these projections can be co-related through a multiple linked-views setup to facilitate both the overview of the whole movement pattern as well as detail decomposition of the kinematic behavior under investigation.

Figure 6.4 shows the application of the radial angle plot to visualize the kinematics of a ball joint. The joint-centered nature of the radial angle plot is

clearly an advantage, as it allows a quantified interpretation of the rotational angle without hindering the embedding into the spatial context. To incorporate the additional degrees of freedom, either the plot can convey several kinematic properties, or multiple radial angle plots can be combined. As an alternative to these two variants, also parallel coordinate views could be integrated to show the correlation between different angles (Krekel, Valstar, et al. 2010). Finally, while the current radial angle plot supports an angle domain of $[-90; +90]$, increasing the arc length can be used to represent larger angle domains.

6.7 CONCLUSIONS & FUTURE WORK

In this chapter, we have presented new visual metaphors for the interpretation kinematic information derived from dynamic CT data sets. In addition, we proposed an enhanced GPU-based feature identification and tracking based on the SIFT algorithm. Besides the performance improvement, thus allows interactive feature identification and tracking, the proposed technique achieve a higher accuracy in the process of feature matching based on the novel descriptor construction approach. We have applied the introduced techniques to the analysis of the patello-femoral issue. Integrating the presented techniques into the analysis process of 4D CT scans has shown great potential as the quantitative measurement results from the system reflect the real clinical situation of the patients. Moreover, the presented visual metaphor enables medical doctors to have not only a quick overview of the movement pattern of feature under investigation in the dynamic CT scans but also the underlying kinematic information.

In the future, we would like to acquire 4D CT data of the shoulder joint and verify the application of the proposed visualizations. Furthermore, we plan to use our approach to derive a normal collective, which would allow us to automatically emphasize abnormal movement patterns. When dealing with a system of multiple joints for each patient, we would also like to combine multiple radial angle plots into a single view. Finally, we would like to investigate how time-angle profiles could be extended to support an embedding of several individuals.

CHAPTER 7

CONCLUSIONS

In the introduction, we present an overview of visualization in medicine and biology to provide the context for this work. We then identify the research challenges related to the work presented in this thesis and outline our contributions which are described in detail in Chapter 2 – 6. In this chapter, we summarize the contributions and discuss possible improvements. Finally, possible future research directions are discussed at the end of the chapter.

7.1 SUMMARY OF CONTRIBUTIONS

The contributions of the thesis which have been elaborated in the previous chapters can be summarized as:

- A novel representation that enables both the analysis and visualization of large-scale multiple sequence alignment data.
- A novel approach to achieve a lower level of uncertainty by fusing the uncertainty derived from different sophisticated algorithms.
- A novel visual metaphor that helps to convey the uncertainty of parameters in a complex system, that supports comparative visualization.
- A novel technique to fuse data from different sources with different properties, i. e., resolution and SNR, by using light as an information transporter.
- A novel approach that facilitates an automatic tracking of features of interest in dynamic data.
- Novel visual metaphors that enable comparative visualization of kinematic parameters and of the dynamics of features of interest in time-varying data.

It is worth pointing out that although the novel approach to fuse the derived uncertainty from different algorithms is proposed and applied in the context of improving DTI fiber tracking results, it can be extended and applied to other research areas.

7.2 FUTURE RESEARCH

This thesis has presented several contributions to support quantitative visual analysis in medicine and biology in the presence of data uncertainty. There are some research directions that can further improve the results. Although the novel representation of multiple sequence alignment data presented in Chapter 2 enables the analysis and visualization of gross trend patterns and variations in large-scale data, the incorporation of interaction techniques would further improve the exploration process, and support users gaining insights into complex and large data.

The averaging scheme for the fusion of derived uncertainties has shown to provide good results. An investigation of different fusion schemes, particularly, the ability to incorporate domain knowledge into the fusion of derived uncertainties is an interesting future research direction.

In our knowledge, the technique and results proposed in Chapter 6 are the first attempt to provide quantitative visual analysis of 4D image-based orthopedics. As the proposed approach offers stable quantitative measurements and performance, it would be of great interest to incorporate the proposed approach into clinical practice and build up a database of quantitative kinematics measurements. This can help to improve the diagnosis as well as treatment process.

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