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Visualization methods for analysis of 3D multi-scale medical data

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ABSTRACT

This thesis was developed within the framework of the EU MultiScaleHuman Project [15], whose central aim lies on improving the current understanding of physiological human articulation with the application of supporting the diagnosis and treatment of musculoskeletal diseases. Towards this goal, this work contributes several novel methods in order to improve the visualization and processing of biomedical data. It especially addresses scientists whose workflow involves potentially massive amount of biomedical information.

A complete study of the characteristics of the human body involves multiple spatial scales and correspondingly data sets from different acquisition modalities. The analysis of a specific feature is typically performed within one scale, with a particular data set being subjected to the expertise of a narrowly focused specialist. An interplay across spatial scales is beneficial for a complete analysis of biological phenomena as it connects the aforementioned information distributed over the multiple scales. However, this interplay is difficult since different spatial dimensions, levels of abstraction and other data properties require different visualizations. Thus, biomedical data sets are still commonly analyzed using isolated visualization systems that are established to address only a specific scale and domain of expertise. Current multimodal frameworks, which attempt to explore the complete range of acquisition modalities, are typically insufficient to aid scientists, as for instance small scale features are not distinguishable in large scale views, and semantic means are not provided to visually understand internal relations between data sets. Consequently, the presentation and exploration of this plethora of information is currently not feasible.

In order to overcome the aforementioned limitations in the current state of the art, this work contributes concepts for multi-scale visualization, particularly providing:

- A 3D multilayered environment and a combination of scientific and information visualization (SciVis and InfoVis), in which global and detailed information from multi-scale biomedical data can be presented and explored, overcoming the limitation of using one group of visualization methods to represent multi-scale biomedical information [150, 192].

- An incorporation of semantics into the visualization applied in a multi-scale scenario, which allows the obtaining of visual parameters and other semantic information from the biomedical data for the creation and enrichment of the multi-scale visualization [35].

- Enhanced intra-scale visualizations, improving the presentation and analysis of data within the considered scale in order to support the clinical workflow. In this context, this thesis presents concepts for

the analysis of kinematical data of human joint articulation at the behavioral scale [151, 153].

The above concepts have been incorporated in a multi-scale visualization environment which allows for the presentation of a complete set of multi-scale data with different visualization properties in a single view. It particularly provides an integrated detailed and overall view of the relevant data sets as well as tools for visually navigating through them.

The proposed multi-scale visualization environment has the potential to amplify the understanding of biomedical processes in the human body. This has been exemplarily confirmed in an application scenario focusing on the investigation of knee joint kinematics based on experimental data collected in collaboration with LBB-MHH, the latter being a project partner within the MultiScaleHuman Project [151, 153]. It was demonstrated, that the developed processing methods relying on Lie group theory and the corresponding visualization techniques allow for an intuitive interpretation of helical axes and their geometrical relation with respect to the knee joint anatomy, an efficient differentiation among several cases and states of knee joint, and a flexible exploration of the discussed data sets and of related data, thereby supporting the clinical workflow during the analysis of the knee joint articulation.

While several key aspects of above contributions have been firstly published by the author in the indicated works and have shown promising results in applications to biomedical data sets provided by the MultiScaleHuman consortium, this thesis expands upon those results and presents an in-depth discussion and a unified framework for the exploration of multi-scale biomedical data, satisfying the requests for efforts found in recent literature.

Diese Arbeit wurde im Rahmen des EU-MultiScaleHuman Projekts entwickelt [15], dessen zentrales Ziel die Verbesserung des aktuellen Verständnisses der physiologischen menschlichen Gelenke ist, um bei der Diagnose und Behandlung von Muskel-Skelett-Krankheiten zu unterstützen. Zu diesem Thema werden mehrere neuartige Methoden aufgezeigt, um die Visualisierung und Verarbeitung von biomedizinischen Daten zu verbessern. Diese Arbeit richtet sich vor allem Wissenschaftler, deren Workflow potenziell enorme Menge von biomedizinischen Informationen umfasst.

Eine vollständige Untersuchung der Eigenschaften des menschlichen Körpers beinhaltet multiple räumliche Skalen und entsprechende Datensätze aus verschiedenen Akquisitionsmodalitäten. Die Analyse einer bestimmten Funktion wird in der Regel innerhalb einer Skala durchgeführt, wobei ein bestimmter Datensatz der Expertise eines Fachmanns ausgesetzt ist. Das Zusammenspiel verschiedener Bereiche der Wissenschaft auf räumlichen Skalen wäre von Vorteil für eine vollständige Analyse biologischer Phänomene. Dies ist jedoch schwierig, da die Datensätze unterschiedliche räumliche Dimensionen, Abstraktionsebenen und andere Dateneigenschaften aufweisen und somit unterschiedliche Visualisierungen erfordern. Folglich werden biomedizinische Datensätze häufig in isolierten Visualisierungen durch unterschiedliche Fachgebiete analysiert, denen nur ein bestimmtes Maß an Expertise zur Verfügung steht. Gegenwärtige multimodale Visualisierungsrahmen sind demzufolge unzureichend, um Wissenschaftler zu unterstützen, da beispielweise Merkmale aus kleinen Skalen in Übersichten mit großem Maßstab nicht zur Verfügung stehen und außerdem keine semantischen Zeichen angeboten werden, um die internen Beziehungen zwischen Datensätzen visuell zu verstehen. Somit ist die Präsentation und Erforschung dieser Fülle an Informationen in einer einzigen Ansicht derzeit nicht realisierbar.

Um die oben genannten Einschränkungen, die aus dem aktuellen Forschungsstand hervorgehen, zu überwinden, präsentiert diese Arbeit verschiedene Konzepte für multiskale Visualisierungen:

- Eine 3D-Mehrschichtumgebung und die Kombination von wissenschaftlicher Visualisierung (Scientific Visualization, SciVis) und Informationsvisualisierung (Information Visualization, InfoVis), mit denen detaillierte und globale Informationen von den biomedizinischen Daten dargestellt und untersucht werden können. So wird die Beschränkung auf eine dieser Visualisierungsmethoden überwunden, um biomedizinische Informationen in unterschiedlichen Abstraktionsebenen darzustellen [150, 192].

- Eine in einem multiskalen Szenario angewandte semantisch unterstützte Visualisierung, die den Erhalt der visuellen Parameter und anderer semantischer Informationen der biomedizinischen Daten ermöglicht, um eine bereicherte Multiskalen-Navigation zu kreieren [35].

- Erweiterte intra-skala Visualisierungen, die die Darstellung und Analyse von biomedizinischen Daten auf einzelnen Skalen verbessern, um den Arbeitsablauf von Fachgebietsspezialisten zu unterstützen. In diesem Zusammenhang präsentiert die vorliegende Arbeit Konzepte für die Verhaltensskala, die sich auf die Analyse von kinematischen Daten der menschlichen Gelenke konzentrieren [151, 153].

Die oben genannten Konzepte wurden in eine multiskale Visualisierungsumgebung eingebaut, die die Präsentation eines kompletten Satzes von Multiskalendaten mit unterschiedlichen Visualisierungseigenschaften in einer einzigen Ansicht ermöglicht. Insbesondere bietet die Visualisierungsumgebung den Fachgebietsspezialisten sowohl eine detaillierte als auch eine Gesamtübersicht über alle relevanten Datensätze zu bekommen und zudem die Mittel, um visuell durch sie zu navigieren.

Die vorgeschlagene multiskale Visualisierungsumgebung hat das Potenzial, das Verständnis für biomedizinische Vorgänge im menschlichen Körper zu vertiefen. Dies wurde in einem Anwendungsszenario exemplarisch bestätigt, das sich auf die Untersuchung der Kniegelenkkinematik konzentriert. Das Szenario basiert auf der Grundlage experimentell gesammelter Daten, die in Zusammenarbeit mit der LBB-MHH, einem Projektpartner innerhalb des MultiScaleHuman Projekts, erfasst wurden [151, 153]. Es wurde gezeigt, dass die entwickelten Verarbeitungsverfahren, die auf die Lie Gruppentheorie und die entsprechenden Visualisierungstechniken aufbauen, eine intuitive Interpretation von Drehachsen und ihren geometrischen Beziehungen in Bezug auf die Anatomie des Kniegelenks, eine effiziente Differenzierung zwischen verschiedenen Zuständen des Kniegelenks und eine flexible Erforschung der diskutierten Datensätze und der zugehörigen Daten ermöglichen, wodurch die klinischen Arbeitsabläufe bei der Analyse des Kniegelenks unterstützt werden können.

Während mehrere Schwerpunkte der oben genannten Beiträge bereits vom Autor in den angegebenen Werken publiziert wurden und vielversprechende Ergebnisse in Anwendungen mit biomedizinischen Daten, die von dem MultiScaleHuman Konsortium zur Verfügung gestellt wurden, gezeigt haben, erweitert die vorliegende Dissertation diese Ergebnisse und präsentiert eine eingehende Diskussion und einen Rahmen für die Erforschung von multiskalen biomedizinischen Daten, um die in der aktuellen Literatur genannten Aufforderungen zufriedenzustellen.

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The aim of the MultiScaleHuman Project is the creation of a multi-scale biological data visualization and knowledge management system for improved understanding, diagnosis and treatment of musculoskeletal diseases in the physiological human articulation.

The MultiScaleHuman Project is based upon a strong network of expertise in which each partner brings its knowledge, know-how and data from different research environments. This network comprises the following institutions:

- MIRALab, University of Geneva (Switzerland).
- University Hospital of Geneva (Switzerland).
- University of Minho (Portugal).
- Hannover Medical School (Germany).
- IMATI, National Council of Research (Italy).
- Softeco Sismat Srl (Italy).
- Welfenlab, Leibniz University of Hannover (Germany).

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"Caminante, son tus huellas el camino y nada más.
Caminante no hay camino, se hace camino al andar.
Al andar, se hace camino, y al volver la vista atrás
se ve la senda que nunca se ha de volver a pisar.
Caminante no hay camino, sino estelas en la mar."

"Wanderer, der Weg sind die Spuren deiner Füße und sonst nichts.
Wanderer, es gibt keinen Weg, der Weg entsteht beim Gehen.
Beim Gehen entsteht der Weg und wendest du den Blick zurück,
so siehst du den Pfad, den man nie wieder betreten wird.
Wanderer, es gibt keinen Weg, nur Kielwasser im Meer."

Proverbios y cantares, Antonio Machado, Spanish poet.

KEYWORDS

KEYWORDS:

- Multi-scale biomedical visualization
- Scientific and information visualization
- Knee joint and bones

SCHLAGWORTE:

- Biomedizinische multiskale Visualisierung
- Wissenschaftliche Visualisierung und Informationsvisualisierung
- Kniegelenk und Knochen

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INTRODUCTION

> “Rendering beautiful images is nice but usually not the first-hand task.”[155]

> “Visualization research will have to become more interested in neighboring, related fields of research, [. . .] for focus+context visualization and the visualization of multi-dimensional data [. . .], and for user-centered visualization.”[101]

Musculoskeletal diseases are common disorders that affect the human body’s motion. The study of them becomes very important, as they are frequent causes of physical disability and different pathologies that currently affect around 100 million people in Europe, and yet are undiagnosed in over 40% of the population [30].

Generally, the study of biological processes in the human body involves interactions of information relating diverse spatial scales. Musculoskeletal pathologies, such as osteoarthritis [88], are an example where changes at the molecular scale lead to variations in larger scales (e.g. cellular, organ), which finally cause alterations to biomechanical function at behavioral scale. Therefore, a complete study for such kind of phenomena requires the merging of data from measurements throughout several domains of science. However, these domains, such as tissue engineering, radiology and biomechanics, investigate independently very different spatial scales, at cellular, organic and behavioral scales, respectively.

Current visualizations lack on facilitating scientists tasks for the integration of the aforementioned plethora of biomedical information, its presentation and exploration. Current scientists’ workflows make use of isolated visualization systems, which allow only the exploration of features involving a concrete data type, but not the integration of biological data from all the scales in a single picture. Visualization methods that generate images from the measurements should constitute a means to help scientists to understand the relations across evidences existing in the biomedical data: "how can visualization help in extracting information from several scales that otherwise is not easily reachable nor understood?" [152]. The main problem is based on the fact that these data have not only different spatial dimensions, but also different levels of abstraction, and consequently, diverse visualization properties, requiring innovative strategies for supporting the extraction of valuable knowledge.

This work presents processing methods and visualization techniques for the improvement of the visualization of multi-scale biomedical data, making use of knee joint articulation data as application scenario. This approach proposes a scientist-centered integrated visualization for the analysis of multidisciplinary biomedical data, based on the following contributions:

- **Novel multi-scale visualization**: Musculoskeletal diseases are constituted by hierarchical processes which occur simultaneously at different spatial scales of the body. Events measured on cellular scales propagate upwards to the tissue and organic scales creating interdependency between evidences at different scales. Multi-scale visualization aims at the coupling data coming from different spatial scales for a simultaneous presentation [145]. However, current multi-scale biomedical visualizations are insufficient for a complete understanding of phenomena, as small scale data do not have visibility in large scale views and visual means to indicate interdependencies between data are not provided. In this work, a novel multi-scale visualization by means of a 3D multilayered environment is proposed, in which detailed and global data of different scales as well as their relationships can be presented and explored.
- **Combination of scientific visualization and information visualization techniques**: The presentation of relevant biomedical data sets for the exploration of musculoskeletal diseases remains limited if choosing methods belonging to only one of the two main subfields of visualization research: either scientific (SciVis [56]) or information (InfoVis [59]) visualization. In this work, this traditional division in the field is overcome in the visualization environment in order to facilitate a complete analysis of all the biomedical data. The multi-scale medical data is presented by making use of both subfields for a complete analysis: InfoVis methods as cognitive amplification (e.g. representations of graphs for gait patterns, properties of meniscus), and SciVis methods for realistic representations coming from physical data (e.g. computed tomography, magnetic resonance imaging).
- **Incorporation of semantics into the visualization applied in a multi-scale scenario**: The presentation of multi-scale biomedical data in one single view would overwhelm the specialist without if exploring without visual semantic means to understand the context and the relations of the data. Knowledge formalization can organize biomedical data sets into semantically connected pieces of information. In this work, semantic visualization is applied in a multi-scale scenario to support a meaningful presentation and navigation across the data sets of multi-scale nature. This approach provides semantic means to identify relevant items for its presentation to the specialist user of the visualization environment. This includes the use of profiles to adapt the visualization content to the scientist's needs and the enrichment of the visualization with semantic relations among the data sets.
- **Enhanced intra-scale visualizations**: New processing methods and visualization techniques are required in order to accurately characterize and interpret data on concrete spatial scales. Those methods allow to improve the workflow of the specialists who are experts in those data, as well as to contribute to the overall study of processes of multi-scale nature. In this work, efforts have been made at the

behavioral scale for the visualization and analysis of the knee joint functional articulation based on helical axis method. Previous tools based on this method [218] were insufficient for clinical practice since they were lacking in terms of robust analysis capabilities and intuitive visualizations. This work describes how the use of sophisticated and advanced mathematical concepts of Lie group, Lie algebra and the respective exponential map in the context of rigid body motions leads to intra-scale visualizations which improve the clinical workflow in biomedical engineering for the analysis of kinematical data of the knee joint articulation. In this context, the overall multi-scale visualization environment constitutes a framework in which intra-scale developments improve the understanding of the encompassed data, facilitating the study of processes of multi-scale nature.

The growth of new medical appliances and diagnostic techniques requires new ways of working within an interdisciplinary team which encompasses clinical knowledge and technical know-how [29]. In this context, visualization that renders images from all those measurements must aim to help scientists understanding complex relations between data at diverse spatial scales. A multi-scale framework, resulting from a multidisciplinary conception among scientists from the involved disciplines and visualization researchers tends to gain a deeper understanding of multi-scale diseases [32].

This work has been performed under the framework of the EU Marie Curie ITN MultiScaleHuman Project [15]. The aim of the project has been the creation of a multi-scale biological data visualization and knowledge management system for improved understanding, diagnosis and treatment of musculoskeletal diseases in the physiological human articulation.

STRUCTURE

First, Chapter 2 describes the **basic principles and the related work** regarding the exploration of multi-scale medical data, as well and their shortcomings. Subsequently, Chapter 3 presents the **proposed methodology** and its contribution with respect to the described state of art. Chapter 4 specifies the design and the development of the **multi-scale visualization environment** for multi-scale biomedical data. Chapter 5 describes an **application scenario**, focusing on the development of enhanced intra-scale visualizations and the use of the multi-scale visualization environment for the analysis of the knee joint functional articulation. Along these chapters, the approaches of this work listed above are described in detail including diagrams and examples. Finally, Chapter 6 summarizes the **conclusions and directions for future work**.

2

BASIC PRINCIPLES AND RELATED WORK

Vision is the human sense that provides the quickest and widest channel for interpreting information. In the biomedical fields visualization is indeed the primary channel through which biomedical data is communicated. Visualization enables biomedical researchers to observe computations from physical measurements of their experiments and simulations. As the ultimate goal, visualization can facilitate researchers the exploration of biological processes, supporting the foundation of new theories or fundamental truths.

Nowadays, the need for handling huge amounts of information from several sources of data is becoming increasingly important for biomedical scientists. Traditionally, imaging techniques had various modalities which measured different physical effects from the same object and shared dimensions and resolution. A complete analysis required the combination of such sources of data coming from different modalities, e.g. computed tomography (CT) and magnetic resonance imaging (MRI). Currently, there exist an increasing number of complex use cases in biomedical science and clinical diagnostics that require not only the combination of sources from different modalities, but also data from various domains of expertise that are related with a different spatiotemporal scale. In this context, multi-scale visualization can help physicians and scientists to explore and understand all this plethora of data.

Section 2.1 summarizes the foundation of **visualization**, describing its purpose and the classification of the extensive number of methods. **Multi-scale visualization** is presented in Sec. 2.2, illustrated with techniques to perform such kind of visualization and applications. Section 2.3 discusses the **visualization of biomedical data**, its complexity, the need for a multi-scale environment and describes several works in this direction. Section 2.4 reviews current lines of work proposed in the literature for the **design of visualization for scientists**. **User interaction** plays an important role in the visualization tools, as visualization combined with and controlled by user interaction constitute the two inherent components in any tool for biomedical data exploration. Therefore, in Sec. 2.5 a short summary of the foundation of the Human Computer Interaction (HCI) and an overview of related work on user interaction are given. Another important aspect is the organization of all the multi-scale biological information, which requires methods for managing all this knowledge. Notions of **knowledge formalization and ontology** are given in Sec. 2.6. Finally, the **shortcomings** of the state of art to take into consideration for this work are described in Sec. 2.7.

2.1 VISUALIZATION

Visualization is the visual representation of a domain using graphics in order to obtain understanding from a process. What initially started only in the human mind, nowadays takes advantage of computers for supporting this cognitive process. Visualization allows not only to get answers from concrete questions, but most important: to explore the unknown. Visualization tools allow their users (in the present work: scientists) to get "insight" from these processes.

In this section, primary concepts about visualization are described. First, **definitions of visualization** highlight the process of understanding as the essential aim of the user employing a visualization tool. Second, the **visualization pipeline** describes the process required to move from a real measurement or simulation to reach the human cognition in order to get that understanding. Finally, the field visualization consists of a huge family of methods and algorithms, which are categorized in two major subfields: **information and scientific visualization**.

2.1.1 *Definition*

Visualization can generally be defined as a graphical representation of data or concepts, whose aim is to provide insight into aspects related to a phenomenon we are interested in [210]. As a very primary definition, visualization constitutes a cognitive process performed by humans in forming a mental image of a domain space. In the last decades, due to the birth of information science and the growth in computational technologies being combined, this meaning was widened. The definition was extended from only an internal construct of the mind to also an external artifact which supports this cognitive process happening in the human mind [238]. Nowadays, it is widely accepted that visualization is "the use of a computer for comprehending data or to extract knowledge from the results of simulations, computations or measurements" [142].

The process of understanding a phenomenon does not happen entirely in the brain of individuals, requiring also the interaction with other entities, such as cognitive tools [235]. In this context, visualization constitutes a very important cognitive tool which facilitates the attainment of insight from a phenomenon, as it translates a phenomenon into the language of human vision and cognition [180]. Vision is indeed the human sense which provides the quickest and widest channel to interpret information, as the eye and the visual cortex of the brain provide the highest bandwith channel into human cognitive centers [235]. An individual working with a visual tool is depicted in Fig. 2.1. The interface between them is provided by visualization as the primary channel to acquire information. Visualization and understanding are closely related: this coupling depends on the quality of this interface. And the result of this coupling constitutes a new and more powerful cognitive system.

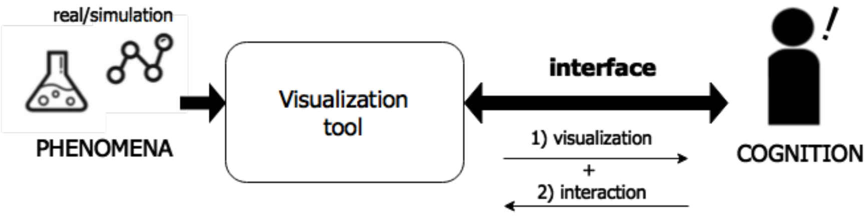


Figure 2.1: Coupling between a visualization tool and an individual.

Note that interaction constitutes a fundamental auxiliary channel for visualization, as it is the way to control its flow. The exploration of a phenomenon is indeed facilitated by using interfaces in which the perceiver can not only observe some graphical representation of the phenomenon but also interact with it. Interaction is effective when the feedback channel decides in real-time the contents that are going to be presented, and therefore supporting the perceiver to satisfy his concrete enquiries during the exploration. Therefore, the decisional input of the perceiver-user supported by interactive visualization is crucial.

Visualization helps to provide answers to quantitative or qualitative questions regarding phenomena [210]. In case of quantitative questions (e.g. "given a gait analysis of a patient, what are the values of knee joint angles during stance phase?") visual representations help to understand the data, facilitating the exploration of small-scale features of data. Fine-tuned visualizations pursues to answer those questions, in which the process to get understanding follows a bottom-up pattern, i.e. after satisfying precise questions it is possible to generalize and understand or establish theories.

In other situations, the questions are qualitative (e.g. "given a CT scan of a patient knee, are there any diseases?") or simply there exist no prior questions to the observation. In those cases, visual representations have the important role to support a user interested in examining a process in order to explore novel facts and establish relationships. Open-ended visualizations or exploratory visualizations contribute to this aim, which the process to get insight follows a top-down pattern.

This last role of visualization matches the perspective of a scientist interested in examining a process in order to obtain new scientific insight and support new scientific discoveries, such as the exploration of relations of biological processes by a medical practicioner. Visualization helps scientists to go beyond precise questions, allowing them to comprehend huge amounts of data, understand features at large-scale, and even perceive emergent patterns and properties not previously anticipated, which facilitates hyphotesis formulation (Fig. 2.2).

2.1.2 *Visualization process*

The visualization process (or visualization pipeline) consists of a group of operations which manipulate the acquired data from a phenomenon,

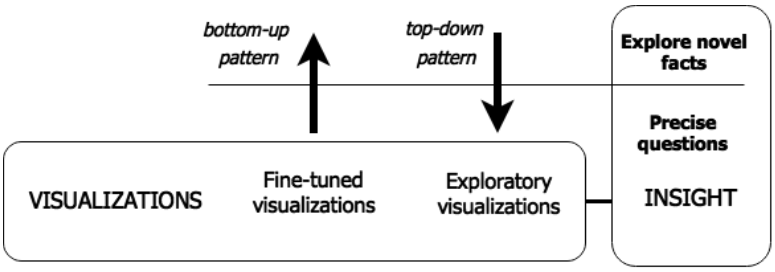


Figure 2.2: Classification of visualization tools according to the insight they provide.

obtained by measurements of a real process or by computational simulations. The human mind (of the user of the visualization tool) is the receiver in this chain, which gets insight into the original phenomenon [210, 235]. The operations involved are (Fig. 2.3):

- *Data acquisition* encompasses the collection of the input data from the measuring device or simulations, the conversion of the raw data to a chosen specific data set format, and its storage, e.g. in a CT scan of the body, physical measurements of CT scan devices are processed and finally stored in the file format DICOM [28].

- *Data filtering* involves the methods applied to the acquired data in order to extract relevant information to target research questions, e.g. a subset of interest for radiologists from a CT scan, such as the knee joint bones. This operation is crucial for the visualization, as it is necessary to preserve only information of interest.

- *Mapping* specifies the visual attributes which encode the filtered data, converting the (until now invisible) data into a (visible) data set in a visual domain. This visual domain has dimensions which are visual features, such as color or position. For instance, the mapping of a CT scan to a visual representation is usually made by a volumetric visualization (see Sec. 2.1.3.1). Mapping constitutes the core operation in the visualization process and its effectiveness determines the quality of the visualization.

- *Rendering* creates the final image from the mapped data with visual attributes and several viewing parameters tuned by the user. In the pipeline, its aim is to specify remaining visual attributes that users can tune to examine the scene. Rendering simulates the physical process of lighting a visible 3D scene according to the viewpoint as well as settings of the user, ultimately being visible in the generated image [173].

- *Human perceptual and cognitive processing* are exploited by the user of the visualization tool, who uses the rendered image and the advantages of the human visual and cognitive systems to get understanding

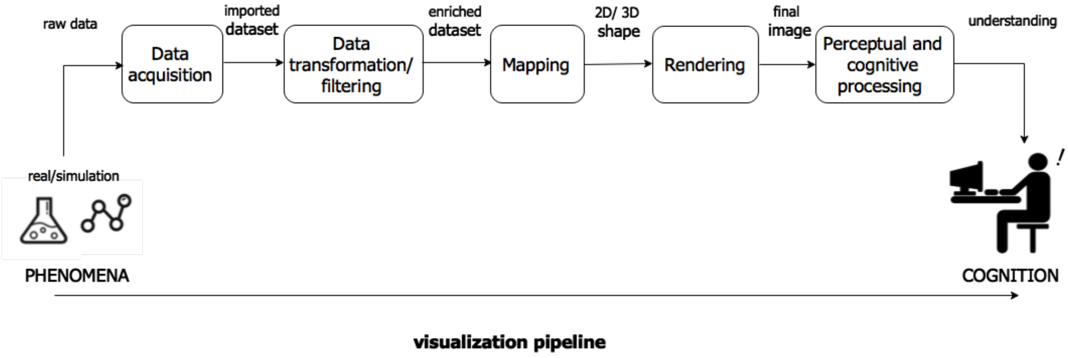


Figure 2.3: Visualization process.

of the phenomenon. Note that the introduction of the user in the visualization process makes possible that both viewer and visualization tool can be considered a single information-processing system [180].

Regarding the last operation, some authors [215, 235] have highlighted the importance of considering perception factors in visualization research. In order to maximize the overall coupling among the phenomenon and its understanding (Fig. 2.1), the study of the human visual system reveals that there exists a best way to transform the data into something that people understand for optimal decision making. A wide number of guidelines for the design of visualization regarding perception factors have been proposed [235].

2.1.3 *Classification of visualization methods*

There is an extensive number of visualization methods and algorithms used in visualization applications. Many algorithms, techniques, and interactions have been explored and improved since the growth in visualization of scientific data in the late 1980's. Visualization methods have since been traditionally categorized into two major areas which became the main subfields of visualization: scientific and information visualization.

2.1.3.1 *Scientific visualization*

Scientific visualization [56] (SciVis) aims to present data that are inherently spatial in a visual form. It typically aims to represent data based on physical measurements. For instance, CT-imaging evaluates the respective physical measurements of electromagnetic waves (using sophisticated mathematical computations) in order to finally present an appropriate visualization of the respective spatial data, e.g. volumetric visualization of knee joint segments.

The main fields of application of scientific visualization are biomedicine, engineering, mathematics and Earth sciences.

One widely extended classification of the visualization algorithms is based on the type of attribute of the data they operate on [98]:

- *Scalar visualization* operates on scalar data, taking basically as an input one or two-dimensional scalar data sets. For instance, *color mapping* designates a color as a function of the scalar value, e.g. medical visualization with luminance (Fig. 2.4a). *Contouring* presents all points that have a given scalar value, e.g. a isobar map. Two concrete types of scalar data have an own group of methods:
    - *Image visualization* operates on image data, i.e. scalars sampled on uniform 2-dimensional grids. Image processing constitutes a huge field (per se an own field) and is present in scientific visualization systems [199], contributing in several operations of the visualization pipeline for complex representations.
    - *Volume visualization* targets three-dimensional scalar fields sampled on uniform grids. In biomedicine, huge amount of data can be acquired by modalities that generate volumetric data sets, e.g. CT, MRI, PET (Positron Emission Tomography). The main idea of volume rendering is the creation of an image in which the value of each pixel depends on a transfer function. This transfer function indicates (according to some criteria) the scalar value corresponding to a 3D data set along a ray parallel to the viewing direction [210]. Different transfer functions categorize different techniques [81], such as volume ray casting (Fig. 2.4c) or texture-based volume rendering.

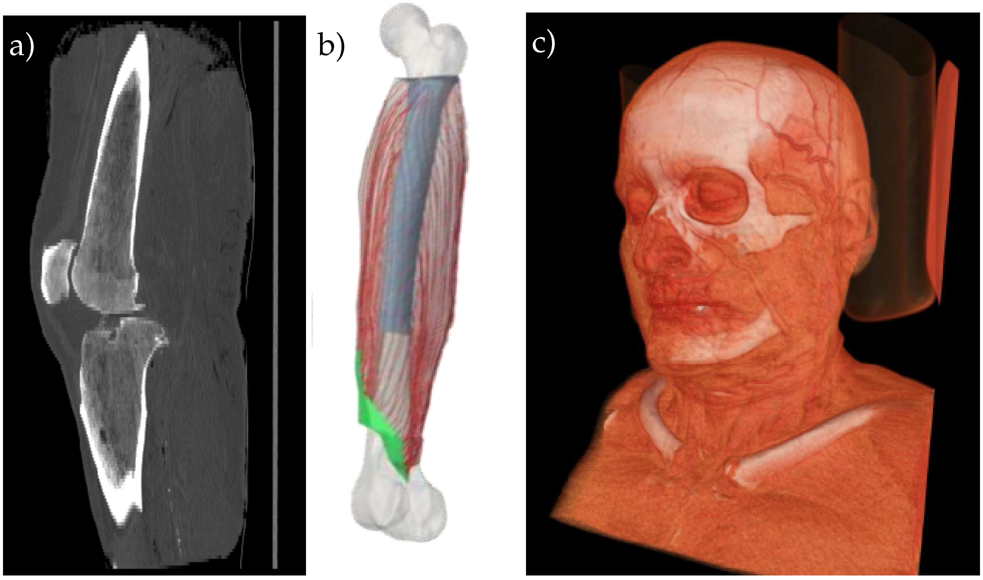


Figure 2.4: Examples of SciVis techniques: (a) scalar visualization of the sagittal view of CT of knee joint, (b) vector field representation of fiber arrangements (source [67]) and (c) volume ray casting of head MRI (source [81]).

- *Vector visualization* operates on vector data. A first group encompasses the visualization of the short-term motion of the points in the vector field. *Vector glyph mapping* relates the properties of a vector icon (such as direction and size) with each sample vector of the data set. Note that the visual properties used for encoding the motion have different impact in its perception [51]. *Vector color coding* maps different colors to different directions of each sample vector of the data set. *Displacement plot* allows to visualize a vector field by deforming a surface along its normal. A second group is constituted by *stream objects* (streamlines, streamtubes), which describe the trajectory of some input object in a vector field over a larger interval (Fig. 2.4b). Finally, *texture-based vector visualization* employs a texture signal that encodes the direction and magnitude of the vector field.

- *Tensor visualization* operates on tensor data. This data are usually visualized with one of the aforementioned techniques, after the reduction of such information to one scalar or vector field by employing Principal Component Analysis (PCA) procedures [68]. This visualization is an active area in medical visualization, as Diffussion Tensor Imaging (DTI) techniques are employed to quantify the diffussion of water in living tissues [177].

A major part of SciVis is actually involved with visualizing data obtained from computational simulations of physical processes. This applies with different degrees of abstraction in many fields of engineering including computational fluid dynamics, gas dynamics and electrical engineering where scientists visualize dynamical systems modeling relevant aspects of the respective physical processes. The latter computational simulations are applied as well for modeling important aspects of biomedical processes such as heartbeat and nerve impulse [94, 239]. It is expected that in the future those computational simulations will strongly go in their importance. This holds because physical experiments are often cumbersome and difficult. Therefore with the aim to reduce the latter effort needed for studies in engineering or for analyzing biomedical processes scientists are trying to replace physical experiments by simulating computations and their resulting visualizations (e.g. Fig. 2.10). It should be noted that in the overall context of the aforementioned topic morphology and biomedical processes are intimately related because biomedical structures depend on physical shapes and their changes. This issue has been studied in the area of science called mathematical morphology [195], which analyzes mathematical laws that control changes of shapes and have biological impacts.

Realistic representations provided by the subfield of SciVis improve the visual experience [152]. Enhancing the quality of rendering is an ongoing research subject in SciVis [233, 244]. Medical images are visualized together with the representation of different structures by using simultaneously several techniques. For instance, texture based volume rendering can be used to give the user an overall impression of the measured data, while surface rendering can be a method of providing extra-information for structures of interest (Fig. 2.5).

SciVis also presents challenges in representing biological data gathered on a nanoscale level. The data often have a large size and do not have a

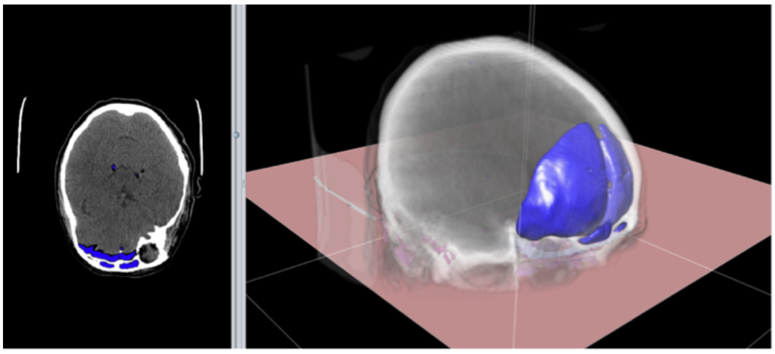


Figure 2.5: Segment visualization in the open software for visualization, segmentation and analysis of volume data YaDiV [82], showing intracranial air after brain surgery (source [152]).

naturally understandable representation as in the previous case. Therefore, visualization of these nanostructures has to create interpretations of the measurements. A set of different techniques, such as volume rendering, isocontouring and dynamic mesh reduction are used for visualizing and navigating these data-intensive structures [42].

2.1.3.2 *Information visualization*

Information visualization [133] (InfoVis) constitutes the subfield of visualization applied to abstract quantities and relations in order to get insight in the data [65]. Examples of Infovis data are found everywhere in the information society, such as computer file systems, databases or stock exchange courses. Such data are frequently called abstract data, as this information has not an innate visual form [210]. InfoVis helps users to create a mental image about data which have not a given spatial representation, e.g. by means of trees or graphs.

InfoVis purposely provides a spatial representation to data that are not inherently of spatial origin, reinforcing the human cognition. Only after a transformation into a spatial presentation is it possible to gain benefit from this data as cognitive amplification i.e. facilitating the comparison, the pattern recognition or the change detection.

The selection of the spatial representation of the data is performed during the operation of mapping in the visualization process (c.f. Fig. 2.3). Note that this selection is not necessary in SciVis, as the spatial representation is a priori given, and this actually resembles the mental image the user already has (e.g. Fig. 2.5). In addition, InfoVis has to target generally a large audience with generally limited mathematical knowledge, therefore the design has to follow the conventions accepted by the field of application. There are numerous applications of InfoVis in a large range of sectors, such as information technology, telecommunications, banking and logistics.

The most important visualization methods of InfoVis are [120, 210]:

- *Data visualization* represents quantitative data with or without axes in a schematic forms. Some of the diagrams used are basic, e.g. table, pie chart, bar chart, and scatter plot. Chord diagram (Fig. 2.6a) is a radial technique for visually exploring pairwise relations in categorical data [161]. The design of such kind of visualizations depends on the data properties and the performed processing based on the purpose of the visualization, i.e. by determining its editorial focus and persuasive power [121, 170].

- *Multivariate data visualization* focuses on data which present three or more variables or attributes, in which methods indicated in the previous heading are not enough. There is an extensive number of techniques for multivariate data visualization techniques [134, 62], parallel coordinates being the most representative [115](Fig. 2.6b). In this technique, each data point is represented as a set of connected points along different vertical axes, each representing a variable. Latest works on the topic aim to improve the discernibility of patterns in the representation of large data sets, e.g. [178].

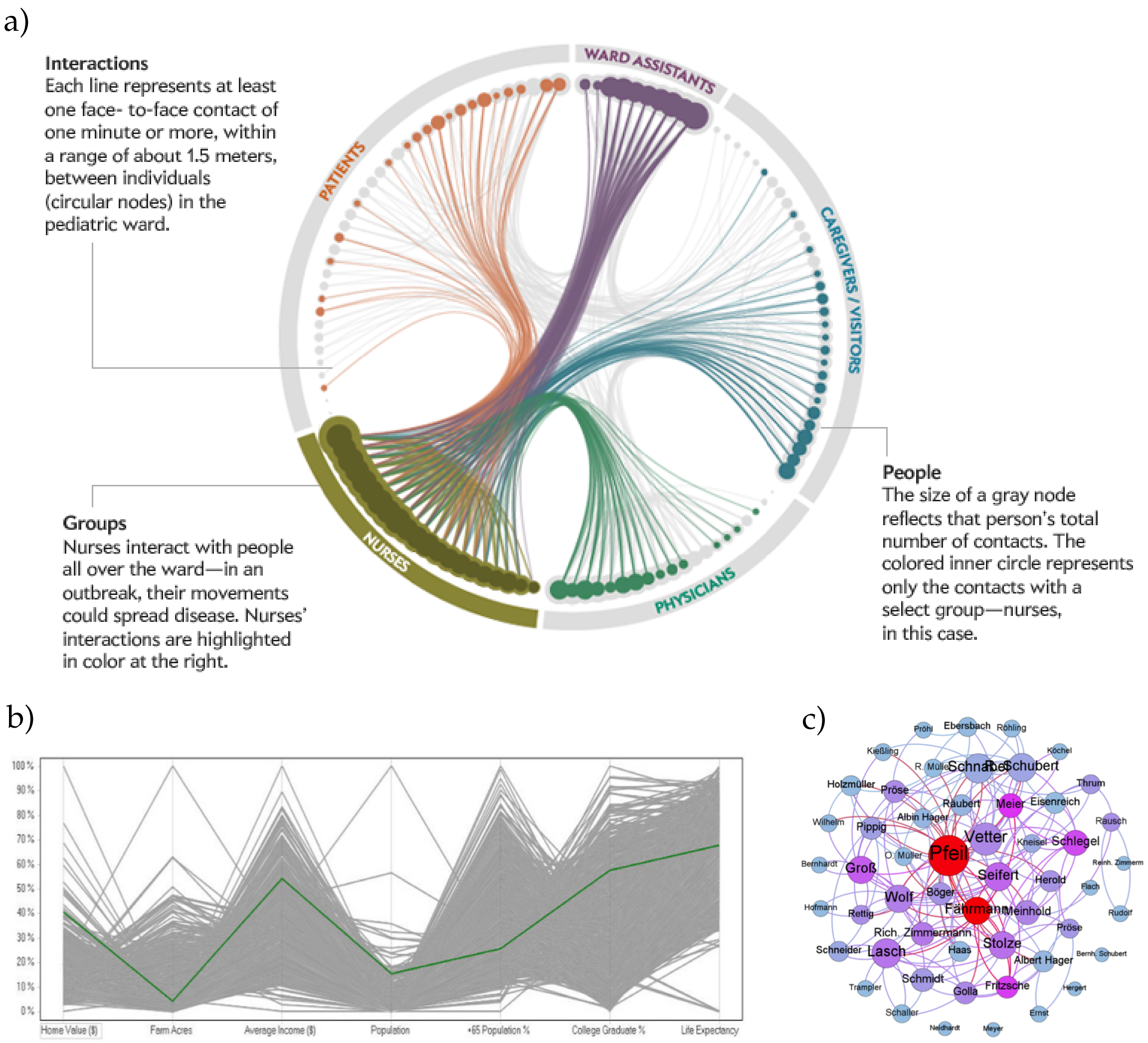
- *Tree visualization* encompasses specific relational data, i.e. data whose information is located not in the data value, but in the association of such data values. Specifically, tree visualization focuses on relational data which have a unique relation among two items. Formally, a tree is defined as a set of nodes and edges. Several main visualization methods exist for its representation:

  - *Node-link visualization* maps the tree nodes to glyphs, and the edges to lines that connect the related nodes. The position of the glyphs and their appearance are parameters to be defined depending on the application. Radial, bubble and cone-tree are some examples.
  - *Treemap* constitutes a method in order to display the tree structures in the form of nested rectangles [196]. Every rectangle represents a subtree, which is partitioned into smaller rectangles which represents its children (see Fig. 2.25a). Color and size of the rectangles are attributes to define.

    The aforementioned visualization methods can be combined in order to amplify cognition regarding relational data. For instance, both node-link and treemap views are used for the description of sequential patterns of human motion [113]. While the node-link view facilitates the temporal representation of pose sequences, the treemap allows a more intuitive encoding of motion pattern frequencies by employing the size of nested rectangles.

- *Graph visualization* focuses on relational data which may have more than one relation among two items. In contrast to trees, loops are allowed in the graphs. *Hierarchical graph visualization* is similar to the node-link visualization, drawing the nodes and edges with the same kind of constraints as the trees. *Non-hierarchical graph visualization* can employ force-directed algohrithms in order to create a lay-out according to several aesthethic criteria, e.g. uniform edge length, uniform vertex distribution (Fig. 2.6c). There are other visualizations methods in concrete applications:

- *Semantic network* is a graphical representation of semantic relations between concepts. It also uses a graph consisting of nodes and edges, representing concepts and semantic relations, respectively, being often used as a representation of knowledge (see Sec. 2.6.2).
- *Flow chart* is a symbolic representation of steps involved in a process, e.g. clinical processes. Basic 2D shapes and arrows represent concepts such as process, alternative process, decision or connector.



Interactions
Each line represents at least one face- to-face contact of one minute or more, within a range of about 1.5 meters, between individuals (circular nodes) in the pediatric ward.

Groups
Nurses interact with people all over the ward—in an outbreak, their movements could spread disease. Nurses' interactions are highlighted in color at the right.

People
The size of a gray node reflects that person's total number of contacts. The colored inner circle represents only the contacts with a select group—nurses, in this case.

Figure 2.6: Examples of InfoVis techniques: a) chord diagram for the control of hospital outbreaks, representing close encounters among the different groups in a pediatric ward (source [31]), b) parallel coordinates visualization analyzing aspects of several counties in a country (source [120]), c) hierarchical graph visualization of social networks employing the tool Gephi [46].

  - *Data flow diagram (DFD)* describes the transformation of information by a system, e.g. the exchange of data in a medical store management system. Basic 2D shapes and arrows represent concepts as process, input, output, file or database.

  Graph visualization can highlight several aspects from the relational data, such as the grouping of nodes, their attributes, the graph spatialization or its temporal evolution. A classification of graph visualizations based on these categories can be found in [95].

- *Text visualization* encompasses visualization methods for analysis of text documents, including: abstraction and representation of statistics of a high number of documents, parallel analysis between two documents, and retrieval and categorization in single documents. These methods allow the meaningful interpretation of narrative texts in digital humanities [114] and the analysis of source code in software engineering [72].

Without making the traditional distinction between SciVis and InfoVis described above, visualization can be defined as any technique for creating images in order to represent phenomena. In fact, several authors have begun to recognize that conventional definitions of SciVis and InfoVis are mistaken as delimiting the utilization of techniques from the other subfield [182, 183, 149] (Fig. 2.7). This criticism can be proven due to the proposal of new classifications. An example is a new classification scheme of visualization algorithms called A-space [96], in which there is no reference to the mentioned distinction: new visualizations are considered a blend of algorithms and are placed in this space. Another example is a new taxonomy proposed based on characteristics of data models rather than on data features [214]. In addition, some visualization techniques developed in parallel in the SciVis and InfoVis field start to converge. An example is

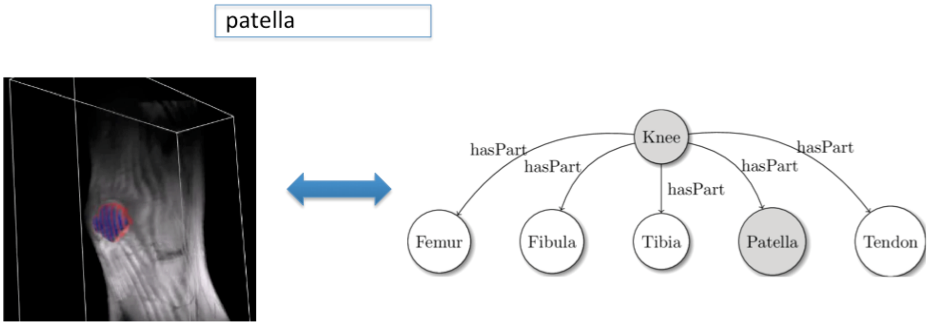


Figure 2.7: Proposal of combination of SciVis and InfoVis for the visualization of the human anatomy (source [149]), as one subfield provides only limited information. The user introduces queries as text, and SciVis and InfoVis views are both obtained from the system.

the F+C technique, which was generalized for both subfields [102]. Another example of this combination is the visualization of the human anatomical hierarchy integrated with volume visualization of skeletal substructures [43].

2.2 MULTI-SCALE VISUALIZATION

Multi-scale visualization aims to couple data coming from different spatio-temporal scales in a simultaneous presentation. Currently, multi-scale visualization appears in many fields: cartography, engineering, physics and medicine. Independent of the field of application all visualizations share the common need to merge data, which belongs to a range of scales that exceeds the resolution of the display or the human eye for appropriate presentation and exploration. In this section, the most relevant **multi-scale techniques** required to perform such a visualization are described, as well as examples of **applications** in different fields.

2.2.1 *Multi-scale techniques*

A wide and heteregenous variety of multi-scale techniques are involved in a multi-scale visualization [145, 146]. Some of them define the interaction mode, others the mode of magnification of sub-scale data or handle numerical precision problems. Note that these techniques are not exclusive. A combination according to the purpose of the visualization and the chosen basic visualization style is required. The most relevant of these techniques are:

- *Click-and-zoom* is used when sub-scale data is too small to be resolved on the display screen and it is therefore marked by a placeholder token (i.e. labels, landmarks or other symbols). Clicking the mouse on the placeholder implies the magnification of the target. The variant *look-and-fly* allows the user to freely change the direction of zooming if the mouse cursor is moved during this process from the screen center to another position [143].

- *Click-and-fly* is used when the camera position does not provide the desired view. Clicking the mouse implies the motion of the camera position through the scene and does not necessarily imply a change of scale, e.g. the Street view mode of Google Earth [5].

- *Call-out* is an enlarged sub-region that links to a point of the parent visualization. This technique appears mainly in static illustrations and allows simultaneous views of detailed and global content. The call-out can have several appearances, as the link can be represented by means of lines, arrows, or geometric figures (Fig. 2.8a).

- *Lensing* allows an interactive magnification of a region for the observation of details that cannot be seen with the human eye alone (Fig. 2.8b).

Similarly to the previous technique, it allows a simultaneous view of detailed and global content. *Magic Lenses* constitutes a generalization of the classic magnification lense, which provides an alternative visual representation, by means of alteration, supression or enrichment of the content in the selected region of the scene [213].

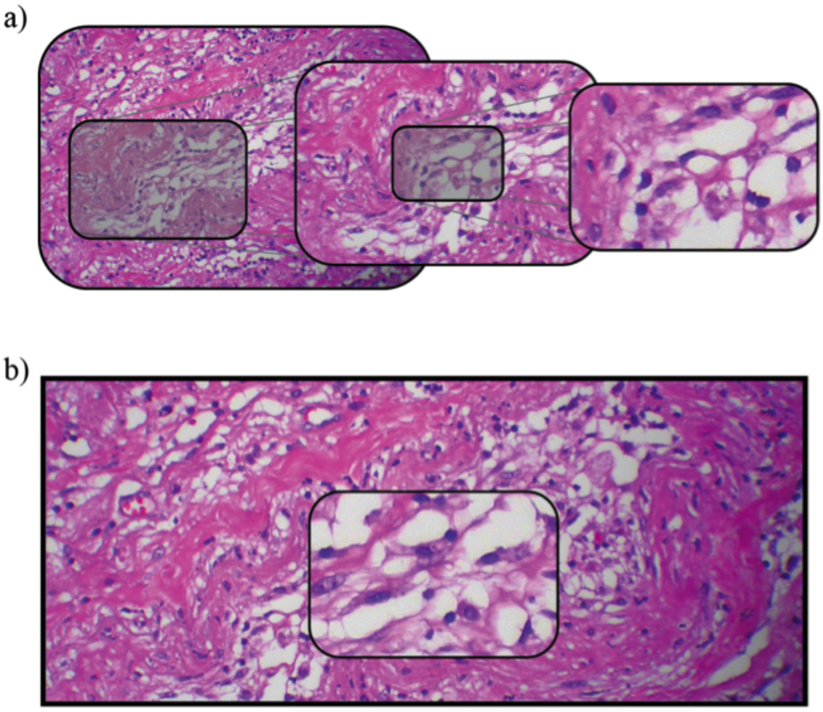


Figure 2.8: Examples of multi-scale visualization techniques applied to a histological image of cartilage: a) call-out technique, b) lensing technique (source [152]).

- *Power scaled coordinates* pursue the rescaling of the real space for visualization in order to integrate objects placed at vast distances that otherwise would not be visible or would be limited by the numerical precision of the global coordinate system. This technique utilizes the substitution of ordinary homogeneous coordinates by logarithmic scale of homogeneous coordinates, with the fourth coordinate representing the logarithm of the current scale in the chosen base, therefore allowing the representation of data in scale independent form. This technique is widely used in astrophysis [99].

  Another similar case is when objects are very small compared to their distance from the origin of the reference system. In such a case, the resolution of the objects geometry can be lower than the numerical precision of the computer. This problem, often called ill-conditioning, is solved by registering the positions of small objects with respect to their local parents [146].

- *Level of Detail (LoD):* This technique represents an object in a scene with different grades of complexity depending on its relevance in the visualization. The relevance of the object can be measured according to factors such as position, camera speed or user focus. At a concrete state, data need to be re-rendered, marked by a placeholder or simply disappear. As data sets grow in size and complexity, the importance of LoD techniques is also increasing [138].
- *Out-of-core visualization:* A collection of different approaches allow to handle data sets that are larger than the available memory for its visualization. External-memory techniques are grouped into a) batched computations, involving streaming data into internal memory and process them in passes, and b) on-line techniques, in which data are pre-processed according to possible queries and results are stored in a specific structure that facilitates the access [66].

The design of a multi-scale visualization application consists of choosing the appropriate aforementioned techniques. The choice of those techniques depends on the following factors [145, 146]:

- *Type of data and visualization techniques* used for their representation, e.g. isosurfaces, volume rendering, vector field, tensor field visualization (c.f. Sec. 2.1.3).
- *Nature of multi-scale*: Considerations to be taken into account are based on the relations between the different types of data, i.e. the order of magnitude and the relation between scales presented in the data sets. For instance, the absence of spatial or temporal continuity in the data sets to visualize requires the use of techniques, such as visual aids for indicating transitions (e.g. see Sec. 2.4.2) or data fusion for filling those spatiotemporal gaps (e.g. [76]).
- *Style of interaction*: The design of the interactions modes (e.g. click-and-zoom or click-and-fly, previously described in this section) depends also on the selection of the human computer interaction interfaces for the application, such as haptic or gesture interaction (see Sec. 2.5).

2.2.2 *Applications*

Multi-scale visualization is becoming more frequent in many fields of applications. Independent of the field and the purpose of the visualization, all applications requires massive data sets that comprise different orders of magnitude apart in scale. The main fields of applications of multi-scale visualization [146] are:

- *Cartography:* The multi-scale visualization used in cartography is based on the navigation through information through different levels of terrains and meteorological systems [143]. The most well-known example

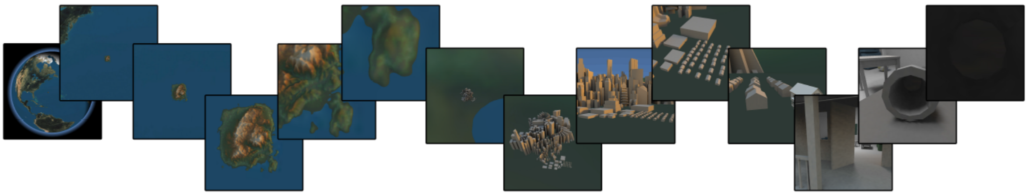


Figure 2.9: Cartographic multi-scale 3D navigation based on cubemaps (source [143]). The automatic sensing of scale allows the user to make a seamless transition from a 2D cartographic view to 3D street level.

of a multi-scale visualization is Google Earth [5]. While the 2D cartographic view mode provides an approach combining click-and-zoom and LoD techniques, the Street view mode offers at street level a 3D visualization with a click-and-fly interaction.

Challenges of navigation in a multi-scale cartographic are described in McCrae et al. [143], who, for instance, make use of an image-based environment representation called cubemap. The scene is rendered with a camera that faces each of the six canonical directions whose projection planes correspond to the faces of a cube. The application senses the size of the environment and adjusts the viewing and travel parameters, preventing the collision with the environment (Fig. 2.9).

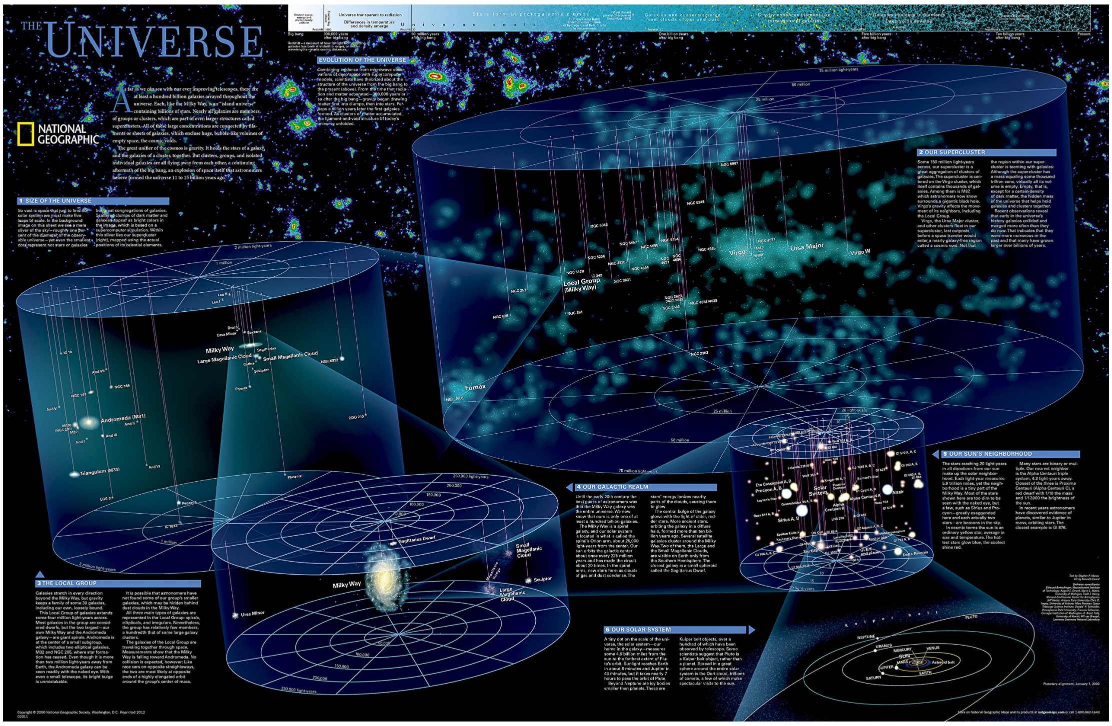


Figure 2.10: Visualization of the known universe with the call-out technique, allowing the observation from the solar system to the most distant super-clusters (source [21]).

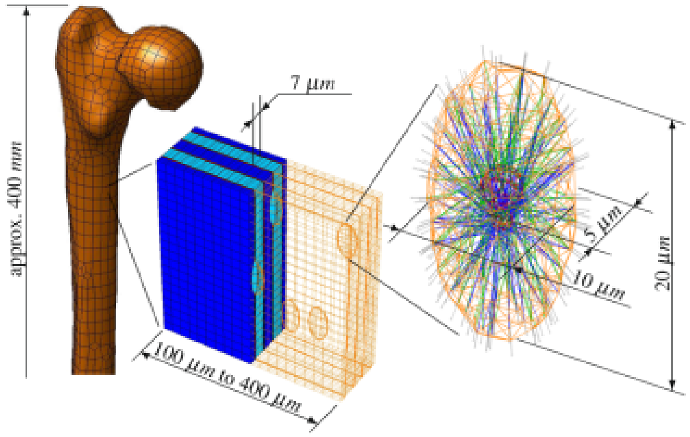


Figure 2.11: Multi-scale modeling of cortical bone tissue (source [160]). Several length scales are considered for simulating material behavior.

- *Astrophysics:* Data in astrophysics encompass an enormous range of spatial data. A single scene could comprise visual objects from sizes ranging 10^{25} m down to 10^{-15}m [89]. The main aspect to take into consideration is to mantain visually the difference of distances among the different objects. For this purpose, current visualization platforms in astrophysics use techniques such as call-out (Fig. 2.10) and power scaled coordinates.

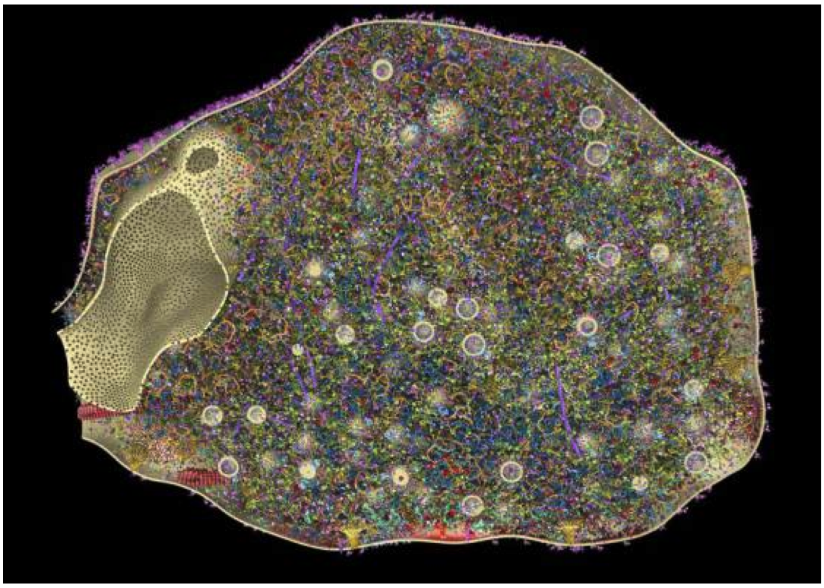


Figure 2.12: 3D model of a synapse (source [237]). After processing the data acquired via stimulated emission depletion (STED) microscopy, this model represents through super-resolution images a nanomap of presynaptic nerve terminals describing the localization of around 200 synaptic proteins.

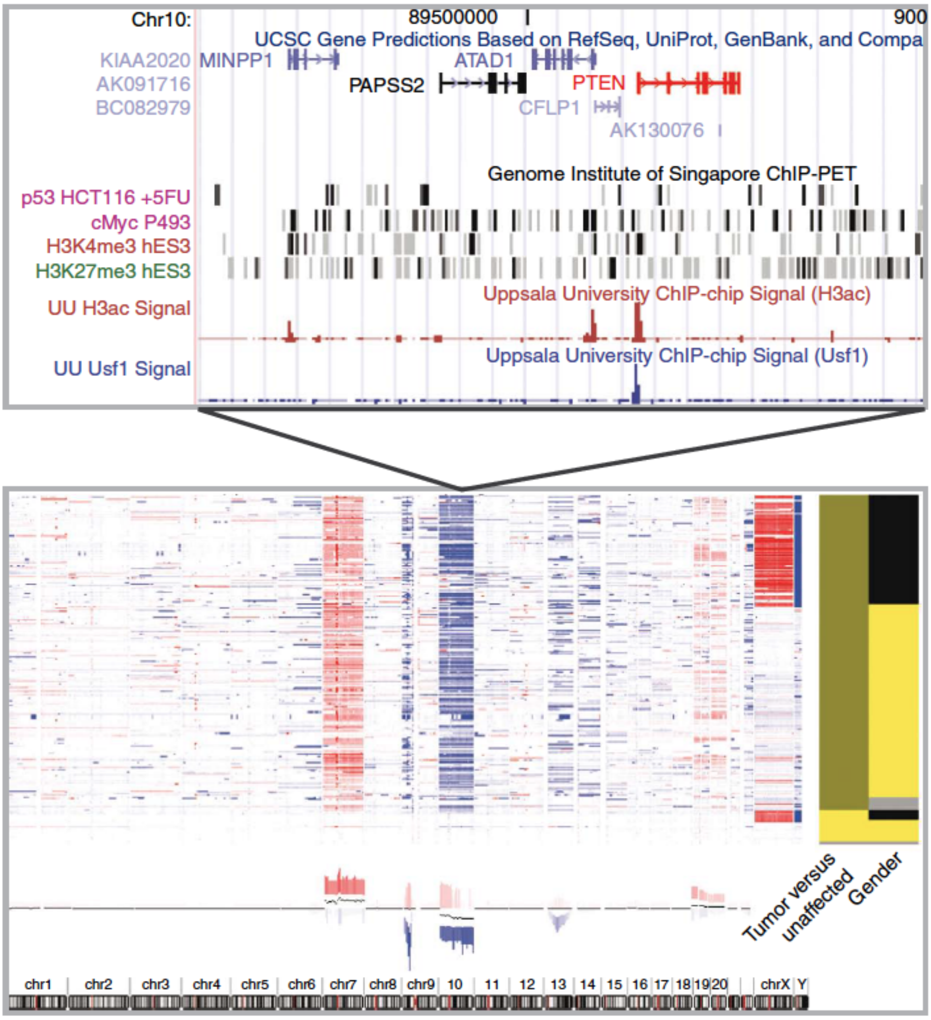


Figure 2.13: Examples of genomics visualization: The UCSC Genome and Cancer Genomics Browsers (source [162]) displaying several clinical parameters, e.g. on the right side, tumor (olive) versus unaffected (yellow), and male (yellow) versus female (black) – gray, data unavailable.

- *Engineering and physics:* Multi-scale modeling [206] refers to the field of solving physical problems that have important features at multiple (spatial or temporal) scales. Areas as computational analysis of materials (Fig. 2.11), computational fluid dynamics, computational combustion and computational mechanichs need the analysis of complex, large-scale, multidimensional data. This visualization uses in each scale scalar (colormaps), vector or tensor visualization (streamlines) (c.f. Sec. 2.1.3.1), depending on the atribute of data they operate on. Regarding the multi-scale technique, it usually makes use of techniques as call-out or lensing, which allows to simultanenously observe the calculations at different scales.

- *Biomedicine:* In the last decades there has been an exponential growth in the complexity of biomedical data visualization. This difficulty is due to the large amounts of data available from a wide variety of sources. If the purpose of the visualization requires data at different spatial scales (e.g. from microscopic level, see Fig. 2.12, up to MRI level), the complexity increases. The visualization of biomedical data is described separately in Sec. 2.3 due to its importance in this work.

- *Genomics:* The human genome contains almost 3 billion base pairs, requiring therefore a huge range of visualization scales. The analysis, interpretation and manipulation of such data requires visualization that can handle high-dimensional information, rather than preserving spatial representations. Thus, genomics is a concrete discipline of biomedicine that makes use of InfoVis techniques (c.f. Sec. 2.1.3.2) rather than SciVis ones. This is the reason why its description has been separated from the next section. There are a lot of tools for comparing genomes, e.g. Fig. 2.13 [162].

2.3 VISUALIZATION OF BIOMEDICAL DATA

The visualization of biomedical data has become more challenging due to the increasing **complexity** of the data sets. In order to succeed with a complete view of a biological phenomenon, it needs to fullfill both the **multimodal and multi-scale requirements**. Current **biomedical multi-scale visualizations** illustrate that no considerable advances in terms of visualization have been made in order to exploit multi-scale approaches that could solve multidisciplinary biomedical problems.

2.3.1 *Complexity of visualization of biomedical data*

The complexity of data is due to the following factors:

- *Variety of sources*: Biomedical data can be acquired through a broad range of modalities, e.g. CT, MRI, motion capturing and microscopy. Even sources of the same modality might have problems as they might not share fully a common standard. DICOM [28] is the standard for storing and transmitting information in medical imaging from different clinical scanners. However, emerging imaging techniques are sometimes not fully standardized with DICOM; in other cases, implementation of the standard varies by manufacturers [233]. Another example is microscopic imaging, in which no format has been adopted as a universal standard, leading to a loss of metadata during format conversion, or problems by organizing images from time-lapse experiments [233].

- *Large amounts of data*: Experiments in every kind of domain provide complex and large data sets, which are difficult to manage due to the memory limitations, e.g. microscopy [171]. Even though the amount of available memory is increasing and out-of-core techniques have been developed [66], data memory requirements increase due to a more detailed data collection. This creates another challenge: representing data sets in a user intuitive manner is more difficult in correlation to the increasing amount of data.

- *High-dimensional image data*: The aforementioned experiments provide currently a large number of attributes for each physical point, being possible to represent these attributes in a high-dimensional space. For instance, multispectral imaging (acquisition of spectrally resolved information at each pixel of an imaged scene) has become widely offered by microscopy manufacturers [132]. Visual encoding is required for the human perception of such data. Therefore, images carry implicitly more information beside x- and y-resolution.

3D reconstruction and projection techniques are important when dealing with high-dimensional image data [77]. This can be illustrated in an example of tomographic mineralogical data analysis [83]. The software used [82] allowed the experts from mineralogy to understand the geometric spatial structure intuitively, which was not observed in the respective 2D slice images used before. This can certainly be applied in the context of biomedical multi-scale visualization, where reconstruction of cartilage micro-CT data clearly exhibits tissue structure (Fig. 2.16c).

2.3.2 *Multimodal and multi-scale requirements*

A complete visualization of biomedical data requires not only the integration of all data from different modalities in the same reference system for a specific domain of knowledge (multimodal requirement), but also to consider the merging of several domains across scales (multi-scale requirement) as another constraint in the biomedical environment (Fig. 2.14).

The *multimodal requirement* is born by the variety of data properties: multiple imaging sources provide vast amounts of data with heterogeneous dimensionality that should be merged. This requirement is needed to help

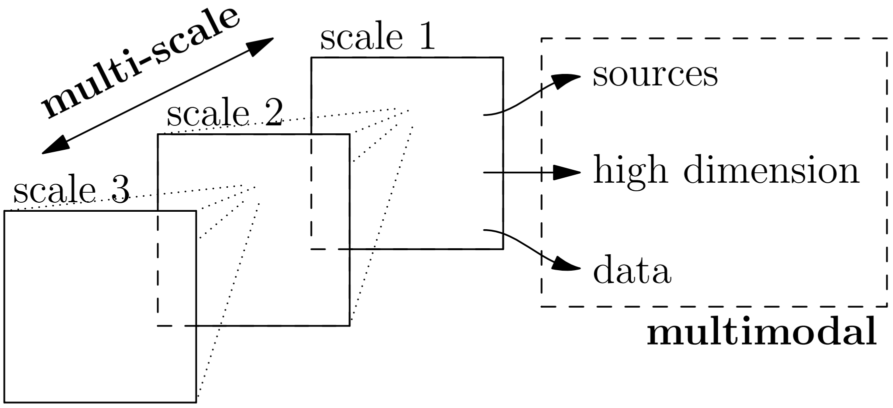


Figure 2.14: Multimodal and multi-scale requirements visualizing biomedical data (source [152]).

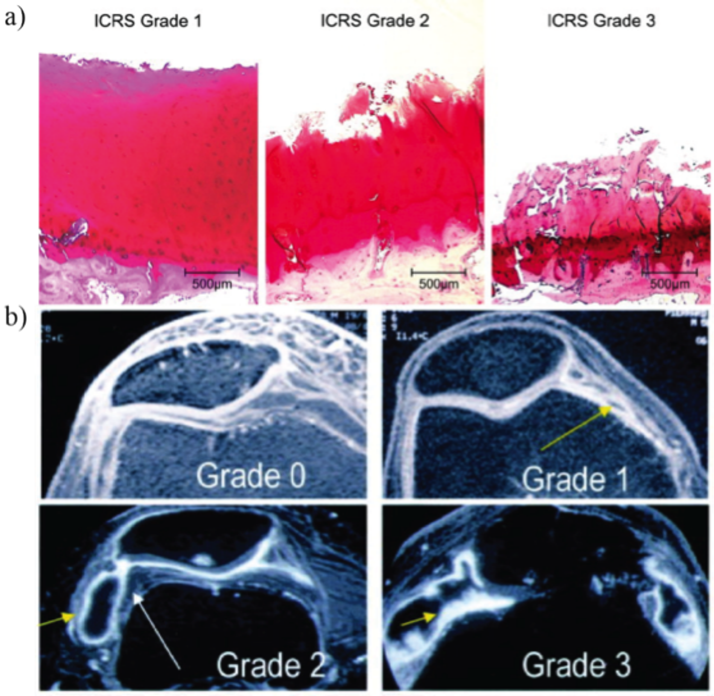


Figure 2.15: Example of propagation of pathologies across diferent spatial scales (source [152]). Different grades of osteoarthritis disease obtained using a) microscopic imaging [122], b) MRI imaging [136].

physicians and scientists of the same domain interpret the wide range of collected data [39].

For example, the extraction of information from both the hard and the soft tissues, acquired with different imaging modalities (CT and MRI), is essential in an anatomical study. It can be used to obtain information in many musculoskeletal clinical applications [80].

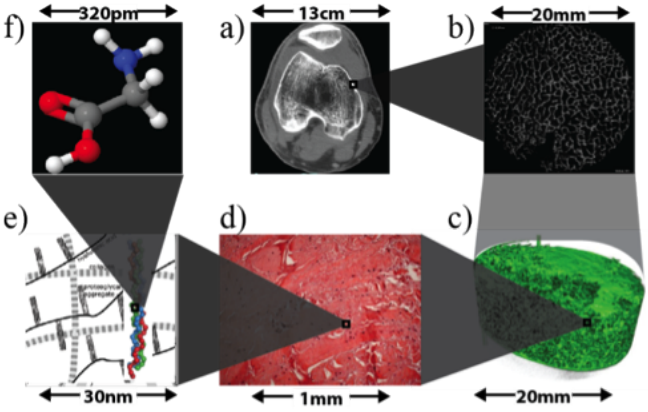


Figure 2.16: Example of knee joint multi-scale data set (source [152]): a) cross-section of knee CT scan, b) micro-CT slice of cartilage tissue, c) 3D reconstruction of micro-CT scan of cartilage tissue, d) histological image of meniscus, e) schematic of extracellular components of cartilage tissue, f) visualization of glycine particle.

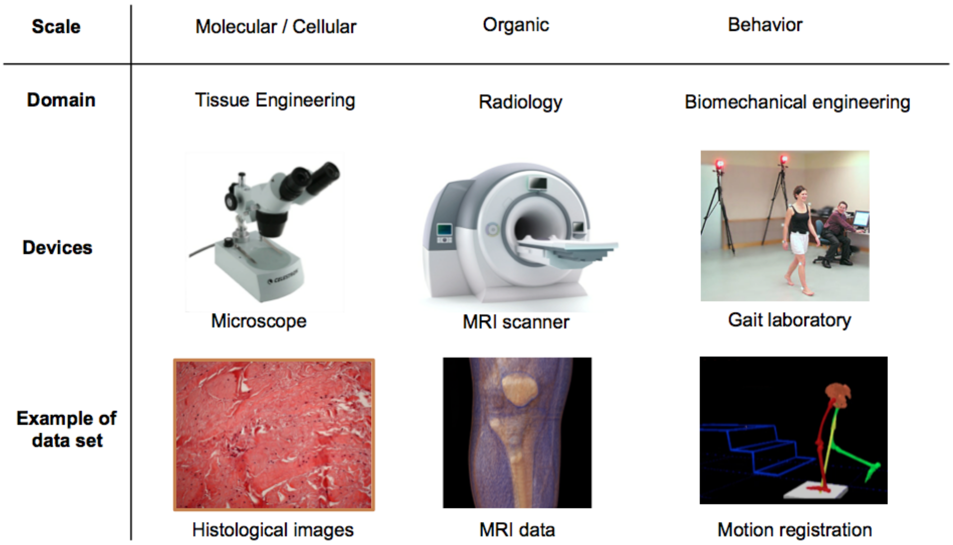


Figure 2.17: Example of several scales, domains, devices and data sets involved in the study of musculoskeletal diseases. Musculoskeletal diseases are a clear example that need to satisfy both the multimodal and multi-scale requirements.

On the other hand, the *multi-scale requirement*, i.e. mixing information between scales, is needed because systems and pathologies in the human body are often hierarchical. Cumulative events on the molecular and cellular scales propagate upwards to the tissue and organ levels (Fig. 2.15). In this work, these kinds of disease are going be denominated *multi-scale pathologies* (alternatively, pathologies of multi-scale nature). In some cases, a complete evaluation of medical risks can only be obtained if data from different scales are available [163].

For example, musculoskeletal diseases depend on several factors from multiple scales (Fig. 2.16). For a complete study, information sources from different scales and diferent domains of science have to be considered. Specifically, studies of cartilage [97] have shown the impact of extracellular matrix (molecular) components on macroscale elements. The degradation of their nanoscale structure greatly influences the behavior of the tissue. This causes degeneration with age, injury, or diseases such as osteoarthritis. Sources of information to be used range from cross-sectional histology at the cellular level, to body motion captures at the behavior scale, with additional data on the tissue and organ level in between. This analysis involves experts from domains ranging from biology to biomechanical engineering (Fig. 2.17). Recent research projects prove that the integration of multi scale data can lead to deeper understanding with practical consequences [15, 212, 223].

Another example is the study of the cardiovascular system. A multi-scale conception of the human blood circulation system, from molecular to organ level, can enhance the understanding of diseases, such as vascular atherogenesis [135].

2.3.3 *Biomedical multi-scale visualization*

Multi-scale visualization is necessary due to the division of science into domains, each one investigating the nature on a specific spatiotemporal scale and working with its own type of data. This specialization can even prevent scientific progress if phenomena are analyzed in strongly separated scales. This fact is considered the "tyranny of the scales" [163]. The observation and quantification of natural processes occurring at multiple scales is not possible without a multi-scale framework, resulting from a multi-disciplinary conception among scientists and visualization researchers [32].

The main challenge for multi-scale visualization of biomedical data is: "how to simultaneously display multiple visual features that map to very different space-time regions?" [116]. Detailed and global content information are usually distributed at different scale levels, and also small scales should have visibility in large scales.

Recent projects enable collaborative investigation of the human body as a single complex system. The development of data fusion and multimodal visualization demonstrates that the interplay of domains of science across spatial scales is beneficial for a complete analysis of a biological phenomenon. Thus, research groups and current projects highlight this approach for providing scientists with new knowledge in order to solve their challenges, e.g. projects under the framework of the *Virtual Physiological Human (VPH)* [22, 32].

The *Multi-scale Spatiotemporal Visualisation (MSV) Project* [14] is a VPH project which aims to cover the lack of specific interactive visualization for biomedical multi-scale data, proposing the use of placeholders as means of interaction for changing the LoD [212]. In the example of the visualization depicted in Fig. 2.18, this way of interaction allows the navigation across CT scans at different scales.

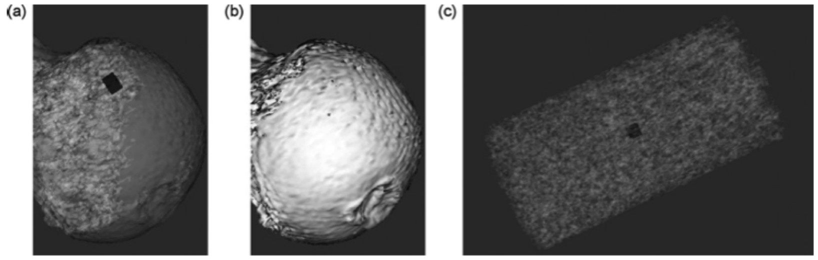


Figure 2.18: Multimodal fusion of different scales of CT data of femur, based on placeholder tokens, which indicate the location of data at different scales (source [222]): (a) CT data and micro-CT token without transparency; (b) CT data and micro-CT token with transparency; (c) micro-CT data and nano-CT token with transparency.

Another example is the *Multimod Application Framework (MAF)* [223], which supports the combination of biomedical time-varying data from several sources, allowing for instance the analysis of human motion (Fig. 2.19) [130].

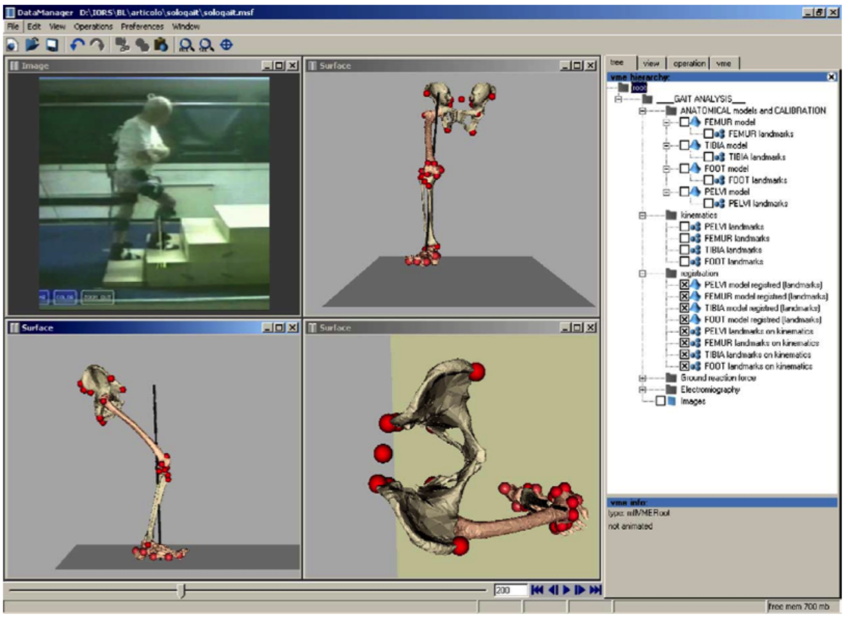


Figure 2.19: Multimodal visualization of clinical gait analysis in the assessment of total knee replacement (source [130]). This screenshot depicts original video sequence collected in the motion analysis laboratory, (top-right) frontal, (bottom-left) sagittal and (bottom-right) transverse plane views of the bony segment poses after 3D reconstruction by spatial registration.

This project and others use open-source systems and libraries for image processing and visualization for rapid development of medical imaging applications, such as the *Visualization Tool Kit (VTK)* [23]. VTK is an open-source toolkit written in C++ that supports a wide variety of visualization methods, including scalar, vector, tensor and volumetric ones. Open-source libraries constitute the basis of many advanced tools and are suitable for a rapid development of a multi-scale environment [58].

Biodigital Human [1] and *Zygote Body* [27] are examples of web visualizations for a general audience, allowing exploring models of body organs using a navigation widget and different level of transparencies. However, data are not multi-scale, as it is possible to navigate only the organic scale.

However, the aforementioned works exemplify that further improvements in terms of visualization are needed in order to substantially facilitate scientists' tasks during multi-scale biomedical exploration. For instance, standard graphical user interfaces (GUI) do not provide a simple method for transition between scales, and traditional approaches that conserve spatial dimensions often prevent important small scale data to have an adequate visibility in large scale views. Traditional approaches used in multi-scale biological visualizations are summarized in Table 2.1.

Many authors [64, 137, 164] have called for efforts to create a multidisciplinary work in an integrated visualization of biological data: "the revolution in biological data visualization hasn't started yet" [164]. Except in the domains of genomics and proteomics, with the help of InfoVis sub-

Table 2.1: Conventional approaches regarding multi-scale biological visualizations (e.g. [130, 212, 223]).

Exploration features	**Conventional approaches**
Representation of data sets based on	Tree list structure
Visualization scenario	Flat desktop
Superposition of data sets	Overlapping
Focus and Context technique	Preserving spatial dimensions (placeholders)
Visual semantic means among data sets	None
Rendering of data sets	Single data sets
Amount of rendered data sets	Few

field (c.f. Sec. 2.2.2), it is considered that no considerable advances have been made in multi-scale biomedical visualization [145]. Biologists aspire to soon have an integration of biological data in frameworks that allow a simultaneous presentation and navigation across linked data from tissue, cellular and molecular scales [165]. Visual links which preserve the context are needed in complex visualizations for finding elements with high user comfort [205]. This kind of visualization environments, as proposed in [165], would facilitate a collaborative and multidisciplinary investigation approach for analyzing multi-scale biomedical data (Fig. 2.20).

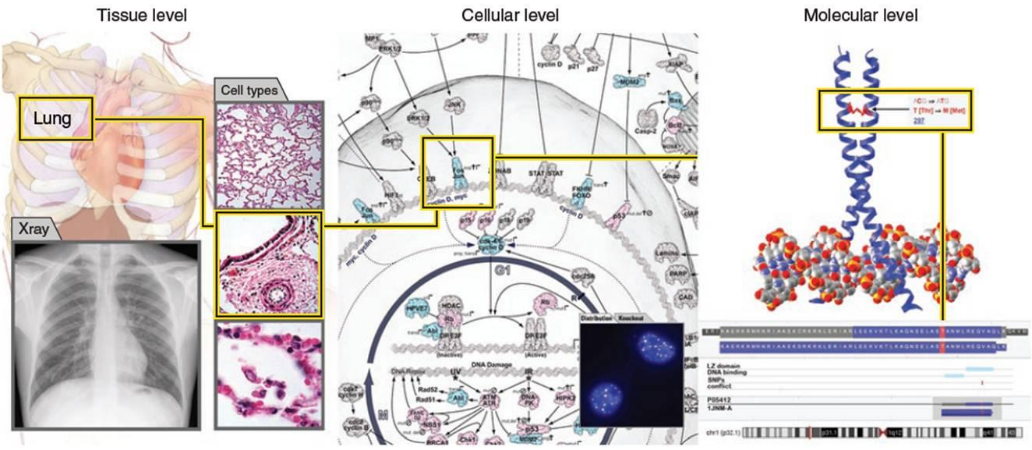


Figure 2.20: Integrated visualization environment described as desired (source [165]).

2.4 DESIGN OF VISUALIZATION FOR SCIENTISTS

Visualization is a powerful tool for *scientists* in the process of understanding data and their context. Visualization researchers try to give meaning to visual data for scientists in order they to gain systematic insights into many domains [233]. Therefore the creation of scientist-centered tools focused on the scientific process of data analysis is needed [203].

Moreover, the study of the *user* experience is an established procedure that analyzes the behavior of the user facing a man-machine interface [147].

Based on user feedback, the design of the interface is polished or modified. Although user experience can be applied universally to the design of every machine, it is gaining importance in the context of designing scientific visualization systems [116].

In this section, aspects proposed in recent literature regarding the design of a visualization are reviewed, taking account the double dimension of the perceiver of a scientific visualization, as a **scientist** and generally as a **user**.

2.4.1 *Scientist-centered visualization*

Visualization researchers try to provide a visualization tool to a scientist in order to help him or her in the understanding of complex data. The effectiveness on the creation of a visualization encompasses a set of steps, involving an initial analysis, frequent evaluation and validation.

Development of a new visualization

The analysis of a creation of a new visualization has to be wide, considering very different alternatives:

- The first option is no creation of a new visualization. Wijk states that "visualization is not good by definition" [221]. Visualization researchers should avoid visualizing information for scientists that could be extracted by automated data analysis and does not require direct human interpretation.
- The reuse of existing visualization software can also be a viable solution. For instance, several open-sources viewers of the standard DICOM are available, allowing the development of own modules or plugins for concrete purposes, e.g. YaDiV [82] and OsiriX [188].
- Third, the creation of a novel visualization has to involve doubts regarding its effectiveness against the costs to develop it. The cost associated with using a visualization system falls on the user and the initial development [221]. The user cost is related to the time required for learning how to use the new tool, converting the user data to the system format and interpreting the presented results, which can be minimized by user experience factors. The high price of the initial development costs, encompassing to have a novel idea and develop it, constitute the major factor.

In this context, the requirements analysis, the review of state of the art and the development of a new idea accordingly are not enough to achieve success. The preparation of a study on advantages and limitations is crucial before starting to work on a new visualization application.

Evaluation of visualization methods with the help of users

Studies analyzing users' feedback are an important instrument for evaluating a visualization (e.g.[85, 126]). This kind of studies can improve the quality of the performed visualizations as it aims to analyze their strengths and weakness.

Frequent evaluation during the design process

Working closely with the scientists is the best way to develop a visualization tool. In practice, visualization researchers have limited sources of information about the application required to be designed. Therefore, it is necessary to answer very soon if the visualization is really giving the scientist the information needed. In order to provide concrete usability to the visualization, a frequent evaluation has to be done during the design cycle, e.g. by testing isolated and specific usability hypotheses [232]. Johnson goes further, expressing that visualization researchers should use the scientific method during the design process of a visualization, including phenomena observation, hypothesis formulation, results prediction and evaluation [116]. This would ensure the creation of a tool that is attached from the scientific meaning.

2.4.2 *User-centered visualization*

Innovative visualization tools can be difficult to learn due to the complexity of data and tasks. In this context, as users are part of the visualization process (c.f. Sec. 2.1), perception factors and software usability principles are essential to successfully support the understanding required in any visualization tool.

2.4.2.1 *Perception factors*

Human factors are strongly suggested to be considered in order to improve the visualization design [215, 235]. Visualization can go beyond a faithful representation incorporating information by means of different features that human perception can decode, taking advantages of the mechanisms in the human visual system, as illustrated by the following examples:

- Use of color: Considerations about color theory (distance, linear separation, categories) by means of performed analysis on perception can help choosing the optimal color scheme that facilitates the understanding on a particular application, e.g. an intuitive blending color between two given colors [85], or an instinctive color scheme for tree visualization (node-link visualizations and treemaps, c.f. Sec. 2.1.3.2) [211].
- Shape: The humans' ability to distinguish between shapes can be used in order to encode different features. For instance, the use of shape primitives in node-link diagrams instead of nodes and links can facilitate the interpretation of software design diagrams [215]. Even the fundamental selection between cartesian or radial diagram as the basic shape for visual data mapping has been questioned and analyzed, considering factors such as aesthetics, efficient use of spatial

space and circular behavior of data, as relevant for the user preference [57].

- Texture: The use of perceptual texture elements also known as pexels, characterized by color, density, height or orientation can help users in shape perception [125].
- Pre-attentive processing: A limited group of visual features can be processed unconsciously by obtaining information from the visualization without the need for focused attention, independently of the number of data elements and the display size [103].

Other relevant aspects are size, contour and sharpness [215]. However, a combination in a specific application should be evaluated, as these features together are not always favorable.

An example which shows the importance of the perception factors is depicted in Figs. 2.21, 2.22. These figures represent the femoral cartilage thickness by using different colormaps (c.f. Sec. 2.1.3.1), tested during the development of a visualization tool for its representation [176]. In this example two aspects have been analyzed to evaluate both visualizations:

- Injective mapping functions: The visualization pipeline, depicted in Fig. 2.3 has the mapping function as the most important factor in the process chain. In order to design effective visualizations, a required property of this mapping function is that this function must be injective, i.e. different values of data can not be mapped as the same value of a visual attribute [210]. In this example, colormap functions are used as mapping functions. In Fig. 2.21, the visualization was designed to have $\mathtt{data} = 0$ and $\mathtt{nodata}$ the same value of a visual attribute (*red color*), leading to confusion. Instead, in Fig. 2.22 the mapping function is injective: $\mathtt{data} = 0$ and $\mathtt{nodata}$ values have different color values (*red and white, respectively*).
- Color selection: In the colormap of Fig. 2.21, red areas represent thinner cartilage while blue areas represent thicker cartilage, going through yellow and green colors (i.e. combination RYGB). Instead, in the map of Fig. 2.22, red areas represent thinner cartilage, green areas represent thicker cartilage, going through yellow (RYG), while white areas represent `nodata`. First, note that Fig. 2.21 wastes part of the interval color (red) to represent `nodata`, stretching the use of the other colors for areas with data. This is alleviated by the use of the combination RYGB, which gives a wider interval of colors. However, analysis on perception (e.g. [84, 85]) have revealed that the combination RYGB is not an intuitive blending color between RB, as lila color is considered better in studies with users than yellow and green. Instead, Fig. 2.22 has a more effective colormap, as yellow is an intuitive color for blending between the extreme values red and blue. In addition, in this case, as previously indicated, red color naturally highlights the abnormality of cartilage thickness (thinning).

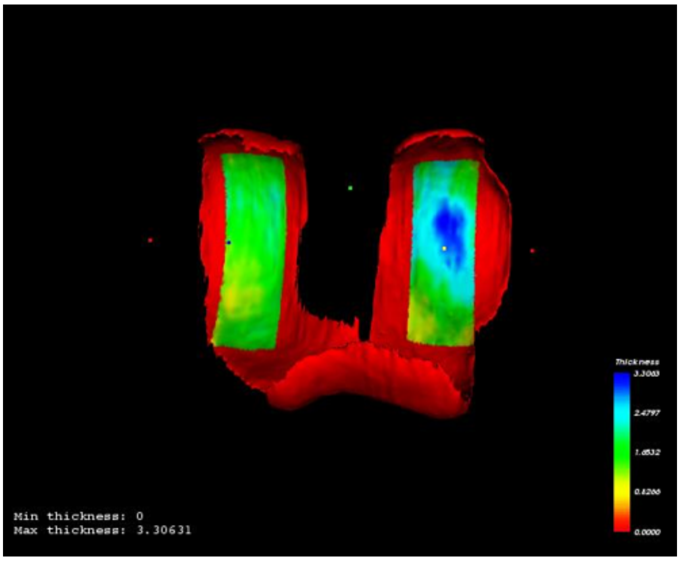


Figure 2.21: Example of ineffective color coding for visualizing femoral cartilage thickness.

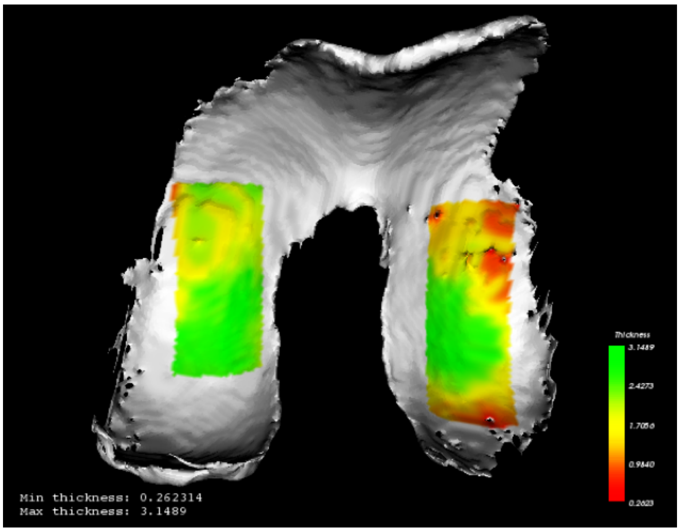


Figure 2.22: Example of effective color coding for visualizing femoral cartilage thickness, which has been applied in a visualization tool [176].

Learning process for new visualizations

The appearance of new representations conduces users to complain because of standards in representations. The perception of information depends strongly on the viewer's understanding of the given symbol system, e.g. hard tissues are represented with white color, soft tissues with black. Educating viewers may improve their understanding of data, helping them to gain new insights [70]. This learning process can be simplified if the visualization tool involves the following features [152]:

- Integration: Merging tools in the same program eliminates unnecessary navigation and reduces manual interaction times.

- Interoperability: A complete integration in the same visualization software might be not effective due to the high cost, as previously described in this section. For instance, if a data format is not supported, it should at least be possible to process or convert it with an external program, requiring clear software protocols, as described in [223].
- Navigation aids: In a complex visualization, it is easy to lose track of the current position and context. Navigation aids like an overview map, colored floating labels or other semantic information can help to keep track of the zone the user is currently exploring. The starting screen of such a system should enable the navigation across all the structures [109].

The achievement of these improvements in the biological visualization tools is a slow process. Authors recognize that working on usability enhancements is less rewarding in science than inventing new ideas and approaches [164].

2.5 USER INTERACTION

Interaction constitutes the fundamental auxiliary channel for visualization, as it is the way to control its flow. The exploration of a phenomenon is facilitated by using interfaces in which the perceiver can both observe a representation of the phenomenon and also interact with it (c.f. Fig. 2.1), satisfying the concrete enquiries of the perceiver during the exploration.

This section is aiming to illustrate the user interaction concepts regarding the coupling visualization-interaction, which have been introduced in Sec. 2.1. First, this section briefly describes the **basic principles** of the Human Computer Interaction (HCI) field, its definition and terminology, categorizing different HCI approaches. Second, it summarizes **related work** of the current main lines of research.

2.5.1 *Basic principles*

Definition of Human Computer Interaction

Human Computer Interaction (HCI) is a multidisciplinary subfield of research of computer science, which focuses on the design of the interfaces between the users and computers [73]. HCI has its roots in the pre-computer era, when this research went under the name man-machine interaction. Nowadays, the importance falls on an individual or a group of users interacting with any computer-based technology. Interaction means any kind of communication (or modality) between user and computer, such as feedback or control of a task. In order to tackle this research, expertise encompasses a variety of investigation areas besides computer science, such as engineering, human factors, cognitive science, psychology or sociology.

The design of a HCI interface has to keep the balance between functionality, usability and user experience [147]. *Functionality* defines all abilities of a system that HCI should provide access to. *Usability* evaluates if the user can accomplish with a given interface the functionality of the system. Therefore, the variation of realizations of interfaces can result in different ranges of functionality covered to different extent. Finally, *user experience*, already introduced in Sec. 2.4, investigates the behavior of the user about a particular interface.

Classification of Human Computer Interaction

HCI interfaces can be generally categorized based on the activities performed by the user [152]:

- *Physical:* This category encompasses interaction which makes direct use of senses and muscle actions [118], being possible to distinguish three subcategories related to the diverse human senses [159]:
  - *Vision:* Many input devices rely on human vision as the quickest and widest channel for interpreting information of the human, highlighting therefore the importance of visualization, e.g. screens, graphic tablets, printers.
  - *Audition* includes all means where hearing, human speech, audio signalization is involved, e.g. sound clue when pressing a button.
  - *Touch* encompasses all interfaces involving passing forces and sensations to human skin and muscles but also controlling objects with variable force actuated by human, e.g: mice, trackballs, keyboards or haptic devices (see Sec. 2.5.2).
- *Cognitive*: This category involves the analysis of the mental capabilities of user, such as understanding, learning, reasoning via cognitive models [204], or in a more direct manner in brain computer interfaces [69]. Affective computing focuses on the emotional state, allowing the system to have influence on and be influenced by user's emotions and allowing a system to sense emotional feedback [174]. Those lines of research are still relatively new fields in HCI.

Note that the majority of developed interfaces involves more than one of the aforementioned groups, even though the interaction is usually based on one concrete aspect.

In a more detailed analysis, it is necessary to introduce the concept of *modality*. A modality is any input or output that enables users to interact with the computer [118]. This concept allows to separate interfaces as unimodal (if it has only one modality) and multimodal (if it has more).

2.5.2 *Related work in user interaction*

In this section, the current main lines of research in HCI are briefly described. This classification, presented with some illustrative examples, is based on the different number and nature of the modalities which are involved in the design of the interface [118, 152].

2.5.2.1 *Unimodal systems*

Visual systems constitute the widest area in HCI research, and is intrinsically related with the image processing field. Face expression recognition constitutes one of the most active research topics for the development of responsive and affective HCI interfaces [50]. Moreover, body expression recognition gained more interest due to the increasing reability of whole-body sensing technology and its decreasing costs [123]. Another relevant line of research is eye tracking [106], which is commonly used as a form of communication for disabled people, e.g. [139], and whose analysis requires visualization techniques based on data visualization, timelines and scalar maps (c.f. Sec. 2.1.3) [54].

Hand gesture interaction [179] allows a direct manipulation and exploration of virtual objects, freeing the users from a demanding preparation of learning how to interact, if supported by understandable feedback. This kind of interaction was, until recently, expensive and had to deal with computationally intensive computer vision algorithms, a high latency and an uncomfortable work area for the user [124]. In the recent years, constant technological growth made intuitive, flexible and robust alternatives, such as the Leap Motion device [9, 236]. Moderate pricing allowed access to high quality interfaces, opening new perspectives for elaborated systems for medical imaging exploration. As a result, many new applications of hand gestures in the medical field have emerged [231].

Audio systems are growing in popularity since robust cloud-based voice recognition systems have been introduced [48]. On the other hand, traditional desktop voice recognition systems started offering ways to recognize speaker, from a prelearned database of voices [246]. Another approach is human-made sign detection, extracting from audio signal the speaker's mood [230].

Sensor systems encompass a large number and variety of applications that use at least one physical sensor. Basic examples are keyboard, mouse, joystick and pen-based sensors. Other more complex realizations include pressure sensors, motion tracking sensors and haptic interaction.

Haptic interaction focuses on devices which allow the user to both manipulate a virtual object and feel force feedback reactions, such as forces, vibrations or motions. Haptic devices are useful in a wide variety of domains, such as medicine, robotics, military applications or Computer-Aided Design (CAD) systems [227]. In medicine, haptic interfaces play a significant role in medical simulation and training. For instance, the utilization of sensor systems during surgeries keeping the natural feel of operations, while working through robotic equipment on organs in small scale and rescaling visual image along with a level of touch sensation [166]. Another example of a haptic environment is presented in Fig. 2.23a. The ability to obtain haptic feedback while preparing pre-operational planning is crucial for achieving success in medical procedures, e.g. assembling fragments of fractured bones. Vlasov et al. have described different methods for computing the forces in haptic interaction, denominated haptic rendering [226, 229].

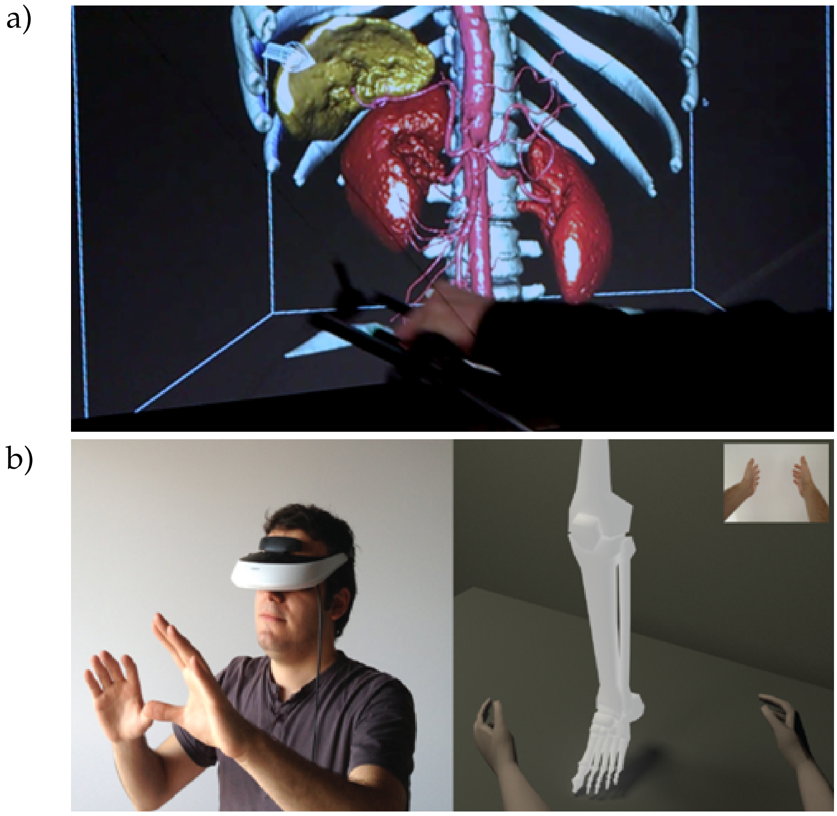


Figure 2.23: (a) Example of haptic interaction: Virtual reality room with a Haption INCA 6D device [7] at Welfenlab. (b) Example of augmented reality interaction: The user is wearing a VR helmet and is interacting with VR content together with a reference image of reality (source [152]).

2.5.2.2 *Multimodal systems*

Multimodal systems combine the strengths of several unimodal systems, working analogously as human beings, who process information from the environment and in parallel using different senses [112]. The multimodal human-computer interaction is based on the premise that effective interaction is likely to take place when different input devices are combined, allowing a natural communication with the computer. As huge advances in unimodal systems have been done, multimodal systems has as a main key technical challenge the way of integrate all those unimodal inputs [217].

Multimodal interaction allows alternative communication methods for different situations and environments. For instance, hand gestures can replace mouse interaction by mimicking it and following the same interaction strategy (simple pointing, dragging, etc.) [36], but replacing the mouse completely could lead to lack of interaction tangibility [111]. Advantages and disadvantages of each visualization-interaction application lead to propose diverse new integrated interfaces.

The design of environment based on virtual or augmented reality motivates the use of multimodal systems. *Virtual Reality* (VR) [245] is an immersive environment that simulates a physical world, in which the user can interact with their objects. *Augmented reality* [60] aims to enhance the view of the physical world by including computer-generated data to it (Fig. 2.23b).

2.6 KNOWLEDGE FORMALIZATION

Knowledge formalization pursues the description and representation of the knowledge in a domain, e.g. a specialty in medicine. Ontology constitutes a rich form of database systems that firstly describes the domain [79] and secondly provides this information to another knowledge technology entity such as a visualization system [154]. The visualization techniques used for the representation of the knowledge stored in ontologies are generally borrowed from the information visualization subfield (c.f. Sec. 2.1.3.2).

2.6.1 *Ontology as formalization of knowledge*

The aim of knowledge formalization is to represent knowledge about a certain domain in such a way that a computer could perform the process of reasoning on objects of that domain as a human would [200, 150]. Its applicability in a computational context for structuring and organizing data is given by ontologies.

Ontologies provide a set of well-defined terms for communicating knowledge about a domain with a set of relationships that hold among the terms. This well-formed and machine-readable terminology facilitates the construction of inference statements (automated reasoning) from the information at hand [154]. The uses of ontologies are mainly two:

- (i) structuring knowledge when capturing and modeling, and
- (ii) information fusion, filtering and presentation.

An ontology is "a formally explicit specification of a shared conceptualization" [207], being necessary to define the aforementioned terms:

- *Formal*: The meaning of terms is unambiguously defined and stated using mathematical axioms and formal definitions, guaranteeing machine-readability and thus, allowing automated reasoning.
- *Explicit*: Concepts and restrictions are explicitly defined. They allow creating domain assumptions explicit for reasoning and support human understanding of a domain.
- *Shared conceptualization*: Regarding conceptualization, the abstract model of a phenomenon is formed by identifying their relevant concepts. In addition, this conceptualization has to capture a consensual knowledge, rather than an individual view. According to Schulz et al. [193], a good ontology has to be adequate to the domain to be represented and thus has to reflect current scientific knowledge available about the domain to be modeled.

Ontologies are used to define concepts, relationships, and other distinctions that are relevant for modeling a domain [92]. The representational primitives of an ontology [93] are:

- *Classes (or entities)*: Objects that have properties in common and autonomous existence, which usually are positioned in hierarchies, i.e. classes may have superclasses and subclasses. For instance, "Tibia", "Femur", "Patella", "Femoral Cartilage", "Muscle", "Extensor" are examples of entities for a knee joint. "Extensor" is a subclass of "Muscle".
- *Relationships*: Logical links between two or more entities, i.e. the ways in which concepts are associated with another one. For instance, "belongs to" is an example of a relationship that can exist between the entities "Femoral cartilage" and "Cartilage".
- *Attributes*: They describe the elementary properties of entities or relationships. In the case of attributes of entities, they are the general properties of concepts. For example, "Mean thickness", "Maximal thickness" and "Minimal thickness" are possible attributes of the "Femoral cartilage" entity.

Modeling the aforementioned primitives depends on the domain under formalization. Criteria about the ontology design can be found in the literature, e.g. [157, 193].

Individual is an object in the class represented by the entity, i.e. it constitutes an instance of an entity. For instance, "a tibia" of a given "patient 1" is an example of instance of the entity "Tibia", and "a femoral cartilage" of the "patient 2" is an example of instance of the "Femoral cartilage" entity.

In the same way, *an instance of a relationship* is an n-tuple made up of instances of entities, one for each of the entities involved [61]. For example, considering the aforementioned relationship "belongs to" between "Femoral Cartilage" and "Cartilage", an instance of a relationship would be the double "(femoral of patient 1, cartilage of patient 1)".

Note that ontology does not need to include any individuals. This property actually makes the difference between ontology and knowledge base, altough it is difficult to separate their denominations in the literature [61]: a knowledge base is a technology used to store information, adding concrete instances to the ontology [128]. Ontology provides the "skeletal structure for a knowledge base" [208]. In more detail, there are different classes of knowledge and the corresponding information artefacts for the representation of that knowledge [193]: an inventory stores only knowledge about individuals; background knowledge conserves what is typically true in certain contexts; a thesaurus collects vocabulary terms; and an ontology is an artefact for representing classes of entities and the properties they have in common.

In an ontology, *axioms* also may be expressed [61]. Axioms are model sentences that are always true. They define general knowledge pertaining the elements in the ontology. For example, an axiom would be "a mean thickness of cartilage less than a specified value is medically considered

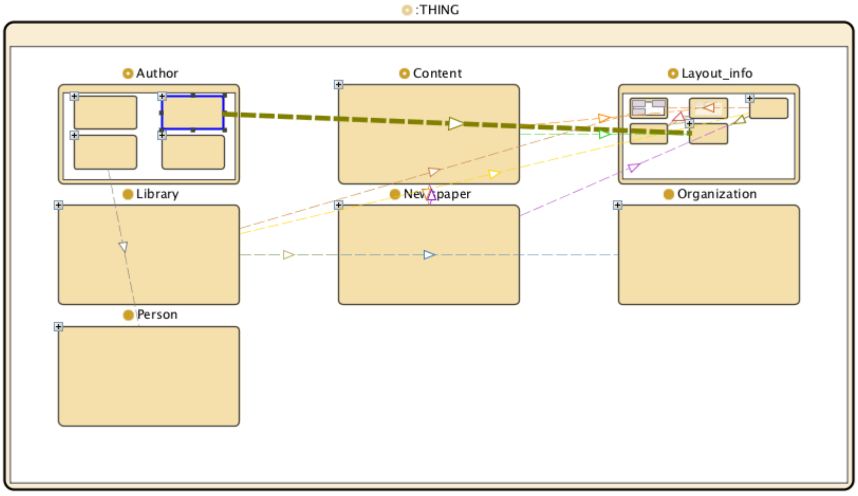


Figure 2.24: Ontology visualization of the organization of a publishing house with the Jambalaya plugin for Protégé [190], the most widely used ontology editor and knowledge base framework.

cartilage thinning". These axioms are formalized in a logical language and they are essential in order to get automatic reasoning, and then, to design good ontologies [193]. Following up with the example, if the "patient 1's cartilage has a mean thickness less than this value", then with the axiom, the reasoner can infer that "patient 1 suffers cartilage thinning". The *reasoner* is a program that infers logical consequences from a set of explicitly asserted facts and axioms, and typically provides automated support for tasks such as classification.

Formalisms are needed so that not only humans may be able to agree upon a shared non-ambiguous conceptualization, but also the machines, may be able to parse it, interpret it and communicate between them. For that purpose, Description Logics (DL) [40, 149], a decidable fragment of First-Order Logics was created and allows ontologies to be expressed in a structured, computer-interpretable and formally well-understood way. They form the core of the ontology language OWL 2 (Web Ontology Language)[45], arguably the most popular language to express ontologies. The Semantic Web provides a "common framework that allows data to be shared and reused across application, enterprise, and community boundaries" [25].

The ontology approach constitutes an integral part of many successful knowledge technologies [154]. Those technologies are computer-based techniques whose aim are to manage knowledge, i.e. embedding knowledge in computer systems, storing in an easy-access way to be able to identify its relevance for a specific problem. They use the information technology from a practical perspective combining ideas from different fields, such as psychology, philosophy, artificial intelligence, engineering, business studies, computer science and web technologies.

2.6.2 *Ontology visualization*

Ontology by definition is an abstract conceptualization and there is no one single, clear and generic way to visualize it. Techniques borrowed from the InfoVis subfield (c.f. Sec. 2.1.3.2, [119]) help to explore and interact with an ontology, detailing its topological information (Fig. 2.24). Some representative examples [149] are:

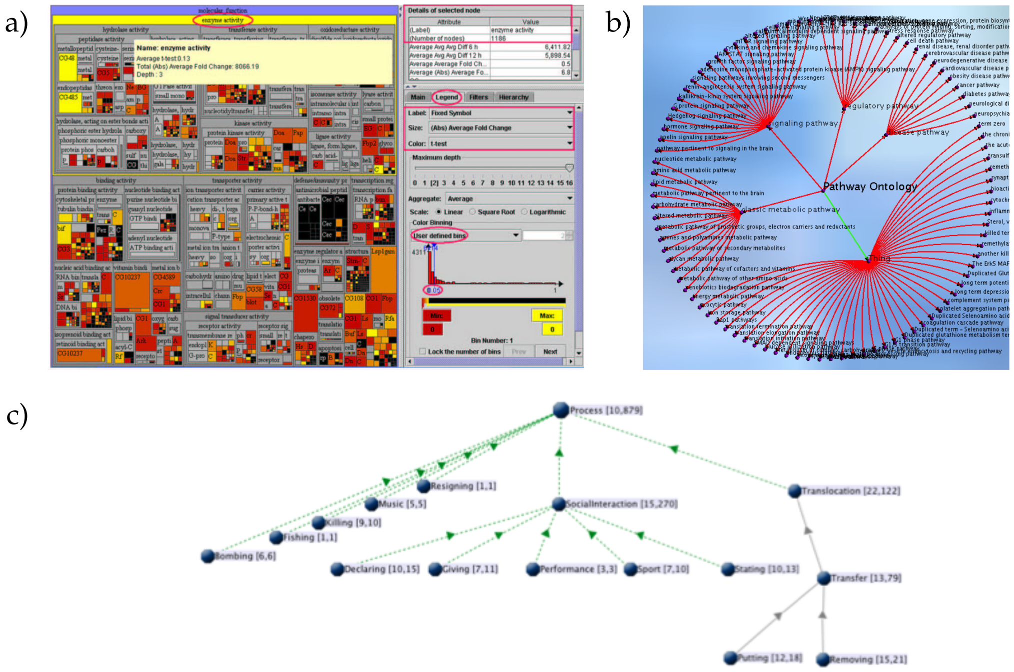


Figure 2.25: Examples of InfoVis techniques for ontology visualization: (a) treemaps (source [41]), (b) node-link diagrams (source [74]) and (c) Key-Concept Visualization (source [156]).

Treemaps have been proposed as a tool for visualizing the Gene Ontology [41, 4] (Fig. 2.25a) Treemaps are appropriate at giving a quick overview of the proportions of complex abstract data. Size and color are used to provide a mechanism to evaluate details about genes of interest.

Node-link diagrams represent ontologies as a set of interconnected nodes, presenting the taxonomy with a top-down or left to right layout. The user is generally allowed to expand and retract nodes and their subtrees, in order to adjust the detail of information shown and avoid display clutter. An example is a node-link diagram based on a hyperbolic tree (Fig. 2.25b). The node of focus is usually the central one and the rest of the nodes are presented around it, reduced in size until they reach a point that they are no longer visible. In order to combine important and additional information, those are based on the notion of distorting the view of the presented graph.

Key-Concept Visualization (KC-Viz) [156] relies mainly on topological properties of the ontology as criteria of the selection of the most information rich (key) concepts to show (Fig. 2.25c).

2.6.3 *Ontologies in the biomedical domain*

Ontologies are omnipresent in the biomedical domain [35]. They are usually found under the group of the ontologies denominated application ontologies. Application ontologies are domain specific and cover directly domain-specific terms and relations, helping to organize heterogeneous data into semantically sensible chunks of information, or to document background knowledge for further reuse and integration. On the other hand, domain-independent ontologies serve to establish a common framework in which application ontologies may reside and be integrated [91].

Applications of ontologies in the biomedical domain encompass definitions and classifications of common medical terms to explicit specifications for a focused domain [44]. Regarding the first group, SNOMED CT [201] is one of the most evident usages of ontologies in medicine for the definition of common medical terms. For specific domains, examples are Gene Ontology (description of gene products) [4, 37], FMA (human anatomy model) [187] and Radlex (unified language in radiology) [129].

Some recent tools use more complex visualization techniques for representing information contained in biomedical ontologies than the examples illustrated above. For instance, Phenoblocks [87] creates radial layouts in order to analyze phenotypes between patients using the Human Phenotype Ontology [185]. Network2Canvas [209] employs visual patterns of enriched canvases to present gene-set libraries from the Gene Ontology.

2.7 SHORTCOMINGS

Although there have been an extensive number of developments regarding exploration and organization of biomedical data, only limited attention has been given to some essential aspects that can certainly improve the understanding and analysis of multi-scale biomedical data. In the previous sections, basic principles of visualization and related work regarding exploration of biomedical data have been described. The current section aims to give an overview of the disadvantages found along this chapter, which constitute the motivation of this work.

The shortcomings for the exploration of multi-scale biomedical data are summarized in Table 2.2.

Table 2.2: Summary of shortcomings for exploration of multi-scale biomedical data.

Shortcomings
Visualization research has only partially contributed tools for facilitating major scientific insight
Standardized visualization systems do not allow a complete study of biomedical phenomena
Current multi-scale visualization frameworks are insufficient for understanding biomedical phenomena
Limited attention has been given to scientists' and users' experiences
Innovation in multi-scale exploration lacks a coupled interaction
Ontology visualization does not provide realistic representations needed for a multi-scale biomedical data exploration

Visualization research has only partially contributed tools for facilitating major scientific insight

Visualization is a method of presenting experimental and computational results, enabling users to observe their simulations and computations through visual methods in a wide amount of fields, e.g. technology and science. In a more general definition, visualization constitutes a synonym of understanding. Research in visualization can be approached from different points of view, such as cognition and perception issues [235] or the development of many algorithms in the fields of scientific and information visualization. An incremental loop of investigation on methods has caused specialization of visualization techniques. These methods as well as the foundations of visualization were summarized in Sec. 2.1.

Despite huge developments in visualization research, it is necessary to emphasize that more attention has been given to analyze the imperfections of the developed methods rather than analyze demands of new potential users of visualization. Several authors, e.g. Johnson or Van Wijk [116, 221], have reflected that visualization research has focused on the aforementioned incremental loop of investigation and has paid less attention to serve as a tool for getting a major scientific insight. It is necessary to remind the goal of visualization: to facilitate the cognitive process of their users for comprehending information and discovering new features (c.f. Sec. 2.1.1).

Standardized visualization systems do not allow a complete study of biomedical phenomena

The study of a system or pathology in the biomedical field involves processes that are occurring at very different spatial dimensions. Related information are acquired via multiple sources and are currently analyzed separately under specialized medical domains (c.f. Sec. 2.3). This specialization allows to deepen in concrete details, but constitutes a double-edged sword [163], as it fails to analyze the relations among such analyses and the overall meaning.

Experts of these domains use on a daily basis isolated systems, allowing only the exploration of features involving a concrete specialty and scale. Many visualization tools integrate data from multiple sources [77], supporting a rich local visualization. However, tools are not ready to observe the complete picture of a biomedical phenomenon. A global analysis of the impact of such phenomena requires a multi-scale framework [32], where the different spatial scales studied by different specialties could coexist and be examined.

Current multi-scale visualization frameworks are insufficient for understanding biomedical phenomena

Authors have recently been very critical with the current state of biomedical multi-scale modeling and visualization. According to Gehlenborg, "truly integrated visualization of systems biology data across the entire range of possible data types is still very much in its infancy" [86]. The existing multimodal exploratory systems (c.f Sec. 2.3.3) do not allow a flexible exploration of multi-scale data. An example was depicted in Fig. 2.19, showing a multimodal visualization of clinical gait analysis in the assessment of total knee replacement. Similarly to other current systems, this visualization provides a standard GUI, composed of a set of opaque windows, dialog boxes and list structures in order to configure viewports, which do not allow a flexible exploration of all available data (e.g. overlap of data sets, lack of semantic information regarding the data sets).

Multi-scale visualization offers techniques and methods for dealing with data at different spatial dimensions, whose techniques and applications were summarized in Sec. 2.2. However, understanding a biomedical multi-scale process requires adaptation of the current techniques on multi-scale visualization. An example was depicted in Fig. 2.18, showing the multi-scale visualization of different scales of CT data of femur. This visualization preserves the conservation of spatial dimensions and uses placeholders as a focus and context technique, based on a realistic point of view. However, small scale data do not have visibility in a large scale view, avoiding a global view of all the data sets.

Current approaches used in biological visualizations were summarized in Table 2.1. In order to facilitate the exploration of multi- scale biomedical data, flexible multi-scale visualization tools are needed. Among other features, they should integrate information independently of the spatial dimensions and highlight important relations among data sets.

Limited attention has been given to scientists' and users' experiences

A main reason why visualization has restricted its role for providing understanding in science is based on the limited attention given to the users of visualization [137]. Visualization researchers have not spent enough time with potential users analyzing their demands and their underlying fields. As there has not been an alliance between visualization researchers and the fields of application of visualization (in this case, biomedical scientists), this fact hinders the creation of techniques and tools which increase the potential of researchers for solving challenging scientific problems.

Several dispersed claims and proposals have been appearing in recent literature, e.g. [215, 221]. These features, which were described in Sec. 2.4, take into consideration the double dimension of the perceiver of a scientific visualization, as a scientist and more generally as a user. The design of a biomedical visualization tool should take into account both the scientific purpose of the visualization (c.f. Sec. 2.4.1) and also aspects regarding user experience (c.f. Sec. 2.4.2). This interplay of working with and for the scientists would provide a more complete meaningful analysis, leading to solutions that would provide scientists with new knowledge [152].

Innovation in multi-scale exploration lacks a coupled interaction

Interaction constitutes a fundamental channel for visualization acting as control flow between the user and the phenomenon under analysis in the computer (c.f. Sec. 2.5). Interaction facilitates the exploration process, as questions that follow the premises "what if" are solved with the coupled system composed of visualization and interaction. The importance of interaction increases due to the complexity of visualization of multiple biomedical data sets (c.f. Sec. 2.3). It is even more necessary to implement the visual-information-seeking mantra "overview first, zoom and filter, then details-on-demand" [197].

Although innovation in interaction is not the scope of this work, an innovative solution regarding visualization (whose need has been described) strongly requires a coupled interaction system in order to obtain an intuitive and user friendly data space exploration of multi-scale data. Therefore, both visualization and interaction features for the exploratory system have to be designed with a common strategy.

For the exploration of complex scenarios the use of conventional interaction systems (e.g. 2D screen, keyboard and mouse) appears to be insufficient for providing access to the exploration of multi-scale data. In the recent years, constant technological progress in HCI technology allowed access to high quality interfaces (c.f. Sec. 2.5.2), opening new roads for interaction in visualization systems.

Ontology visualization does not provide realistic representations needed for a multi-scale biomedical data exploration

Ontologies constitute an essential part of technologies which manage knowledge about a domain (c.f. Sec. 2.6). The applicability of ontologies in the biomedical domain is proven due to the large number of tools that make use of them, including classifications of medical terms and organization of heterogeneous data. Therefore, ontologies can support efficiently the storage of knowledge regarding multi-scale biomedical data.

However, traditional visualization techniques for representing the knowledge encoded in ontologies do not provide a realistic representation. The focus has been to represent the concepts in text formats and the relations among the entities (c.f. Sec. 2.6.2). The visualization techniques applied are mainly from the InfoVis subfield, as the spatial domain for representing such information (text) is not inherent and therefore is artificially given (c.f. Sec. 2.1.3.2).

Thus, ontologies alone are not enough to provide both medical background knowledge and exploration of multi-scale biomedical data. The ontology visualization based on InfoVis allows only to explore the concepts attached to the data, but not to observe the data *per se*. Although ontology can be important for efficiently storing knowledge, its visualization is not enough for a multi-scale data exploration, as the data in biomedicine is substantially based on physical measurements, and therefore suitable for techniques of SciVis subfield (c.f. Sec. 2.1.3.1).

3

METHODOLOGY

As in the review of the state of the art in Chapter 2 exposed several shortcomings in the biomedical multi-scale exploration (c.f. Sec. 2.7), the current chapter describes the proposed approach to overcome them. Section 3.1 introduces the new contributions, comparing them with the state of the art. The proposed methodology is subsequently described in detail in the next sections.

3.1 INTRODUCTION

The presentation and exploration of biomedical multi-scale data are complex due to the variety of data formats, a massive amount of information and diverse levels of abstraction (c.f. Sec. 2.3). A visualization which separately improves the understanding of each spatial scale is not enough, as for the multi-scale exploration the importance lies in coupling the spatial scales. Despite of the requests of authors for improving the exploration of biological data across the complete range of scales [86, 164], the latest works have shown that no major advances have been made to facilitate this task, which is still in its "infancy" [86]. Multi-scale visualization offers techniques and methods for dealing with data at different spatial dimensions (c.f. Sec. 2.2). However, the current systems which deal with the multi-scale exploration are insufficient for understanding biomedical phenomena. Among other aspects, there is no visibility of small scales in large scale view [212], there is no simple method for a transition between scales [223] or they do not provide sufficient semantic means to visually understand internal relations between data sets.

Understanding a biomedical multi-scale process requires adaptation of the current techniques, therefore a **novel multi-scale visualization approach** is proposed in Sec. 3.2 addressing the importance of all scales and emphasizing the relationships among data sets.

The data sets in a multi-scale biomedical scenario are collected from multiple simulations and experiments from different domains. Therefore, the presentation of such hetereogeneous information has very different visualization properties. In this context, visual abstractions can help to represent such data [116]. Coming from the foundational goal of visualization (considering visualization as a synonim of understanding), the use of techniques in visualization for understanding science might not make a distinction between SciVis and InfoVis methods [182, 183], outlined in Sec. 2.1.3. Effective visual abstractions based on InfoVis can indeed facilitate the multi-scale exploration. However, as the major part of the data collected is based on physical measurements, SciVis visualizations are needed as well.

Therefore, exploring multi-scale biological data sets requires both a realistic visualization of data sets and an effective visual abstraction for visualizing extracted information from them and relations among the data sets. A **combination of scientific visualization and information visualization techniques** addressing these requirements is proposed in Sec. 3.3.

Knowledge formalization can organize biomedical data sets into semantically connected pieces of information, as ontologies provide precise formulations of the properties and relations of certain types of defined entities (c.f. Sec. 2.6). Note that the traditional representation of knowledge encoded in ontologies is based on InfoVis techniques. The organization provided by ontologies is potentially relevant in a multi-scale scenario, as they could store the organization of hetereogeneous information sources from several scales. Furthermore, a complete analysis of a biological phenomenon (e.g. a disease flow) requires the preservation of the known relations among the data sets during the data exploration, which can be efficiently saved with ontologies through the definition of relationships that hold among the terms.

The proposed **support of visualization based on knowledge formalization** addresses the aforementioned need of semantic means for the organization and presentation of the data to be given to the user of the visualization (Sec. 3.4).

There is a large amount of self-criticism among visualization scientists because they have not spent enough time with potential users analyzing their demands and their underlying fields [116, 221] ("Too often, creators of visualization technology do not spend enough (or indeed any) time endeavoring to understand the underlying science they are trying to represent" [116]. "There is a gap between our prospective users and the research community. Both do not have the proper stimuli to bridge this gap: individual researchers are too busy increasing the number of publications they are judged on, and for the end-users implementing new methods is far too costly" [221]. Only building bridges between visualization researchers and users is it possible to create better techniques and tools to provide to users, thereby increasing their potential for solving challenging scientific problems. In biomedical domains, this interplay among visualization researchers and scientists can provide a meaningful analysis and lead to solutions that provide scientists with new knowledge that would not have been previously possible.

In the present work, processing methods and visualization techniques have been developed for accurately characterizing and interpreting data on concrete spatial scales. In order to achieve this, the analysis of specialists' needs, their data and the development of adequate tools have been performed. Those methods are encompassed under the title **enhanced intra-scale visualizations**, outlined in Sec. 3.5. In this context, the overall visualization system (Secs. 3.2, 3.3, 3.4) constitutes a framework in which intra-scale developments facilitate the study of processes of multi- scale nature.

Understanding the needs of scientists is not enough for a visualization tool. An optimal design requires to address both the scientific purpose of the visualization (user as a scientist) and also aspects regarding user experience (scientist as a user). Several dispersed claims and proposals have been appearing in recent literature (c.f. Sec. 2.4).

In Sec. 3.6, the present work addresses the importance of these aspects under the title **aspects regarding the design of scientist-centered visualization tools**. The proposed exploratory environment has been developed optimizing a tight interplay with domain researchers, starting with the analysis of the visualization requirements and continuing during the development of the visualizations, performing also a preliminary evaluation of the visualization environment. A coupled interaction with visualization also facilitates the creation of scientist-centered tools [191, 192].

The proposed exploratory system is intended to be usable by a broad group of users with expertise in different disciplines of medicine working collaboratively on the same scenario. In that scenario, the experts analyze a large set of data sets of multi-scale nature, discuss their conclusions, and obtain insight from this process.

3.2 APPROACH FOR MULTI-SCALE VISUALIZATION OF BIOMEDICAL DATA

A complete study of biological processes involves biomedical data acquired from different acquisition modalities and distributed over multiple spatial scales. For instance, a phenomenon that occurs on the cellular level can have its results propagated to tissue or even organ level (for a detailed example, see Sec. 4.6). Those data have different spatial dimensions, diverse levels of abstraction, and therefore diverse visualization properties. The analysis of such multi-scale phenomena requires a simultaneous presentation of data from different scales, thus, coupling scales in a multi-scale exploratory environment. In order to overcome the shortcomings of the previous approaches

Table 3.1: Conventional approaches (c.f. Table 2.1) and proposed approach for exploration of multi-scale biomedical data.

Exploration features	**Conventional approach**	**Proposed approach**
Representation of data sets based on	Tree list structure	Nodes displaying data sets
Visualization scenario	Flat desktop	3D workspace
Superposition of data sets	Overlapping	Overlaying
Focus and Context technique	Preserving spatial dimensions (placeholders)	Multilayered workspace with non-linear depth
Visual semantic means among data sets	None: inferred by the experience of users	Visual links thanks to an underlying ontology
Rendering of data sets	Single data sets	Multiple data sets
Amount of rendered data sets	Few	Many, by distributed rendering

regarding the presentation and exploration of these heterogeneous data for facilitating scientists' tasks in the multi-scale biomedical exploration (c.f. Sec. 2.7), this work proposes an integrated visualization for multi-scale visualization of biomedical data with the following exploration features (Table 3.1).

Nodes displaying data sets

The proposed approach is based on the data sets as the main actors of visualization. Each data set from a different acquisition modality is displayed as an independent entity, called *node* (Fig. 3.1b). Each node is displayed as a hollow cube or half-sphere that encompasses 3D or 2D content and semantic information. The nodes allow for a direct inspection of the data sets, as they are attached with their semantic information. In addition, the nodes also provide a natural and flexible way to explore the contained data, as they have the capability to be moved, to be observed from different sides, i.e. observing them as they would be real objects.

The nodes constitute the basis for an intuitive and user-friendly data space exploration. The exploration environment makes use of 3D stereographic visualization for the representation of the nodes, as well as their data sets, as most acquired biomedical data has a 3D representation, i.e. volumetric objects. The interaction channel takes also benefit of the nodes, as it uses gesture interaction for a natural exploration of the nodes and their contents (see Sec. 3.6).

Conventional approaches are based on standard GUI and mouse and keyboard as way of interaction, e.g. [223] (Fig. 3.1a). They usually are composed of a set of windows and dialog boxes to configure viewports. In such approaches, the information of data sets and their views are detached, and a direct and natural method for exploring data sets is not provided, i.e. it is necessary to configure viewports and to employ the keyboard and/or the mouse.

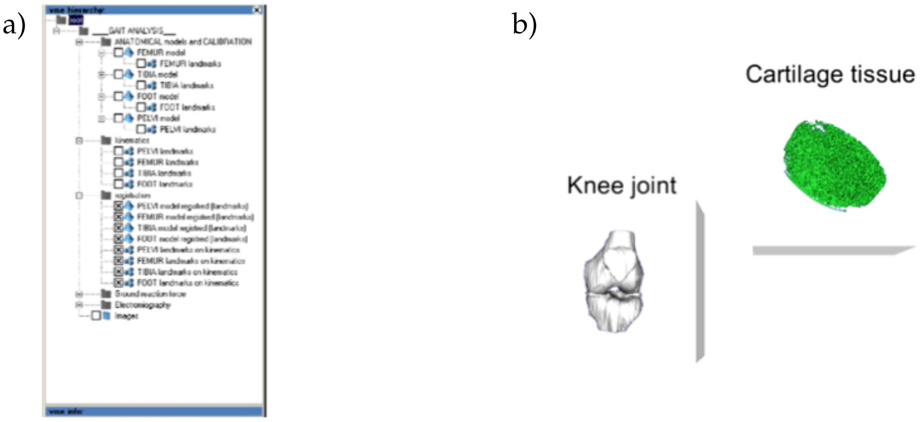


Figure 3.1: Representation of data sets based on a) tree list structure (source [223]), b) nodes displaying data sets (proposed).

3D multilayered workspace

The visualization scene consists of a 3D multilayered environment in which the nodes are distributed (Fig. 3.2b). The layers are distinguished mainly by the spatial depth (i.e. z-order), grouping the nodes with data of the same spatial scale. In order to achieve that, each node is classified according to the spatial range of the acquired data set, defining visualization properties for the nodes on the scene (see Sec. 4.3 for more details).

Conventional approaches are based on a visualization scenario with flat desktop (Fig. 3.2a) composed of a set of opaque windows and dialog boxes. The 3D multilayered workspace allows for obtaining more space in which the multi-scale data sets can be distributed and organized according to the spatial dimensions.

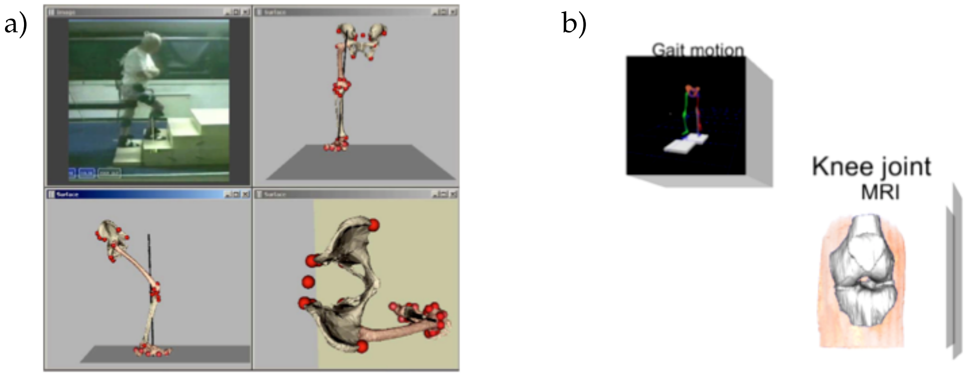


Figure 3.2: Visualization scenario based on a) flat desktop (source [223]), b) 3D workspace (proposed).

In the environment proposed, the data sets are encompassed in the nodes having a high grade of transparence, minimizing overlays among content (Fig. 3.3b). As the nodes constitute the main actors of visualization and interaction, the use of opaque dialog boxes is avoided (Fig. 3.3a), alleviating the overlap of data contents.

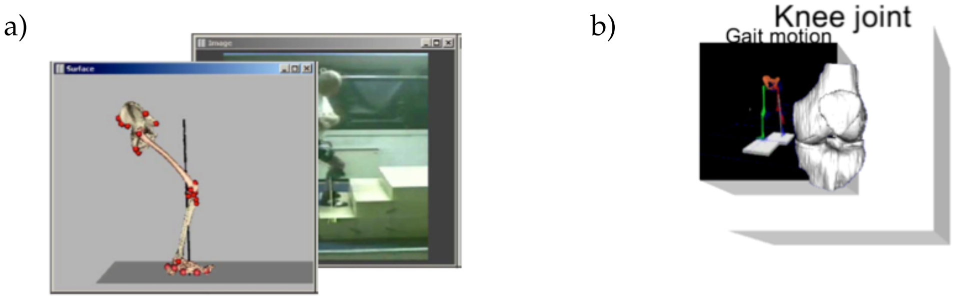


Figure 3.3: Superposition of data sets: a) overlapped data sets (source [223]), b) overlayed data sets in the multilayered workspace (proposed).

Data sets are organized and structured according to their properties, such as the spatial scale they belong to, and the visualization technique to be represented (see Secs. 4.2, 4.4). Those properties determine the appearance and location of the data sets in the workspace.

Workspace with non-linear depth

The 3D multilayered workspace is composed of layers whose distance between each other is uniform. Such layers encompass nodes with contents belonging to the same spatial scale but they do not preserve accurately the spatial dimensions of the data sets. Therefore the depth of the multilayered workspace does not preserve a linear relation with respect to the spatial dimension, assuring an augmented representation of the smallest scales (Fig. 3.4b). This approach allows for the exploration of all data sets, independently of their dimensions, being important for the analysis of data in a multi-scale scenario.

Multi-scale exploratory systems have focused on preserving the spatial dimensions [144, 212], in which small scale data do not have visibility in large scale view, avoiding a global view, as depicted in Fig. 3.4a. Instead, the proposed approach allows for a direct extraction of information from the context, alleviating the differences in the order of magnitude of data in a multi-scale scenario.

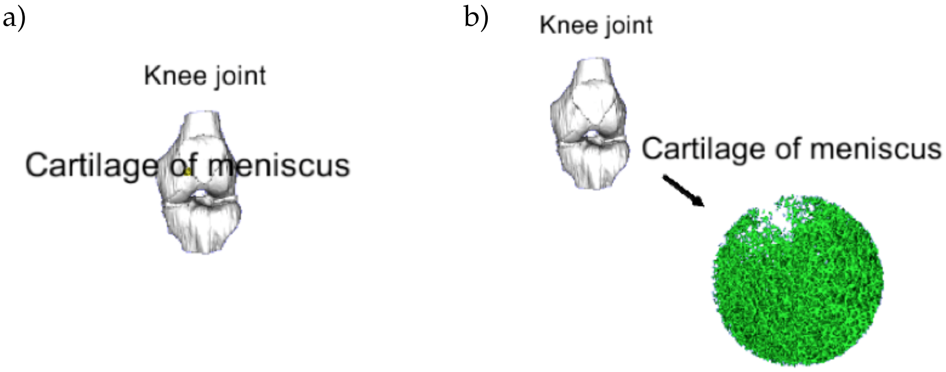


Figure 3.4: Representation of data sets a) preserving spatial dimensions, b) with non-linear depth (proposed). The cartilage of meniscus is not visible in a), as the spatial dimensions are preserved. Instead, the approach depicted in b) allows for a direct exploration of all data sets in the context of a multi-scale scenario.

Visual semantic links

Semantic means to visually understand internal relations between data sets are provided in the visualization scene. The presentation of the data sets is enhanced by perceptual cues in the relations between nodes, e.g. labels, colored lines, arrows, enriching the understanding of the complete collection of data. For instance, nodes which encompass data sets are interconnected by arrows, highlighting well-known or established relationships about them, such as spatial origin of sources, anatomical structures or hierarchy of evidences in a pathology (Fig. 3.5b).

This feature alleviates the complexity of presentation and exploration of data in a multi-scale scenario due to the heterogeneity of the data (c.f. Sec. 2.3.1). Current multimodal systems have not provided semantic means to visually understand internal relations between data sets (e.g. Fig. 3.5a). Applying those systems in a multi-scale scenario, the user of the visualization could feel overwhelmed due to the amount of data; this fact can be aggravated because users are not a priori familiar with all the multi-scale data as they are coming from different areas of expertise.

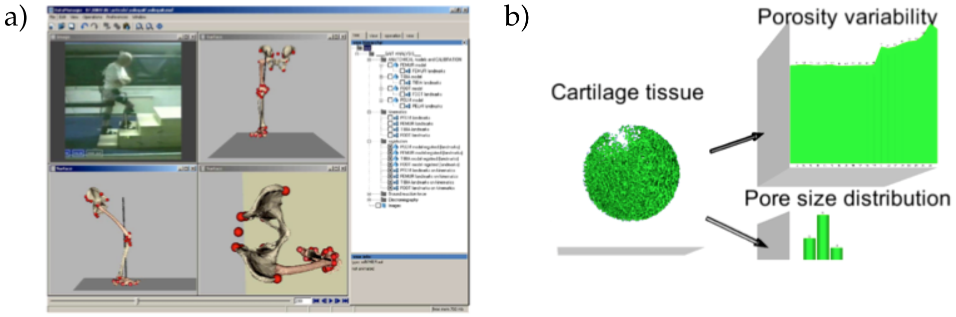


Figure 3.5: a) Example of absence of visual semantic means among data sets (source [223]). b) Presence of visual semantic means among data sets (proposed), indicating in this case the data source of the InfoVis visualizations.

The semantic-driven visualization is supported by knowledge formalization (c.f. Sec. 2.6). In this work, an underlying ontology [13] provides a set of well-defined terms for storing and communicating such knowledge about the relationships that hold among the data sets in a multi-scale domain. This ontology has been supplied with visualization aspects, such as node features and their dependencies, providing semantic means to identify relevant items during the presentation and exploration. More details of this methodology are described in Sec. 3.4.

Distributed rendering

The architecture of the visualization environment makes use of a distributed rendering scheme for the composition of the scene. The distributed rendering architecture performs the composition of the visualization scene from several data sets rendered on different machines (Fig. 3.6). The exploration of a data set can require a lot of renderings of intense data sets structures such as the cartilage tissue of Fig. 3.4b. This designed scheme can assure a smooth rendering of the data sets when they are being explored, as it avoids unfeasible cases when rendering large size of data sets in one single machine.

The rendering scheme is designed in such a way that each machine performs the entire rendering of a data set. This scheme is based on the premise that a single machine is currently sufficiently performant to render the most complex data set for the purpose of this work (e.g. a complete biomedical volume DICOM file). Therefore, traditional approaches for distributed rendering [198] have not been considered. The architecture, which addresses also issues of scalability and multi-platform design, is described in detail in Sec. 4.5.

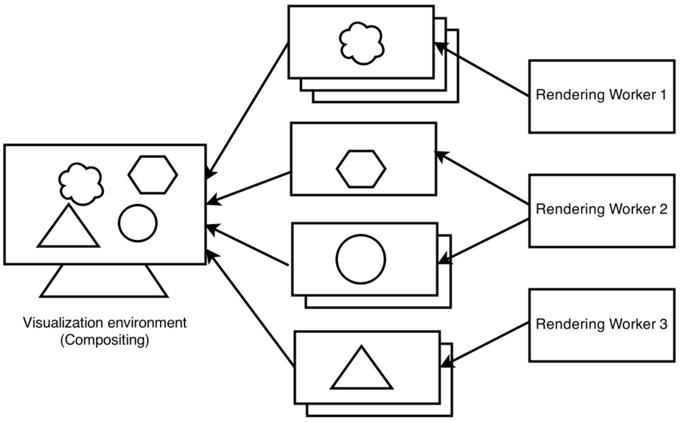


Figure 3.6: Illustrative schema of the distributed rendering and composition of the visualization scene. The schema establishes dynamically that each data set is rendered by a rendering worker entity, satisfying the rendering requirements given by each data set. Subsequently, the visualization scene, composed of several data sets is performed.

3.3 COMBINATION OF SCIENTIFIC VISUALIZATION AND INFORMATION VISUALIZATION TECHNIQUES

The relevant types of biomedical data in a multi-scale scenario are very heteregenous and use visualization techniques from both main subfields of visualization, SciVis and InfoVis:

SciVis focuses primarily on physical data and provides realistic representations. This subfield presents types of data that are inherently spatial in a visual form, and those are based on physical measurements, e.g. CT-scanning, light microscopy. Some of those techniques are equipped with sophisticated mathematical computations evaluating the respective physical measurements for presenting an appropriate visualization of the respective spatial data, e.g. volume and image visualization (c.f. Sec. 2.1.3.1).

On the other hand, InfoVis uses data that is mainly not inherently of spatial origin. The techniques from this subfield transform data into a spatial presentation being graphically intuitively accessible, e.g. via charts or graphs. After such a process that includes the selection of the spatial representation of information, it is possible to get benefit from this data as a means to amplify cognition (c.f. Sec. 2.1.3.2).

The presentation of relevant features of heteregenous multi-scale data requires visualization techniques from both main subfields of visualization. This conclusion came from an initial analysis of the requirements for the design of the visualization systems which had been performed (see Sec. 3.6). Some data such as the measurements extracted from the nanoindentation of cartilage, or the relations between data and evidences analyzed during the investigation of osteoarthritis (Fig. 3.7) cannot been represented by means of SciVis techniques, as those techniques require data that are inherently spatial in a visual form. Instead, these kinds of data need to be processed with the help of InfoVis techniques, which purposely provide a spatial representation to those data that are not inherently of spatial origin (e.g. by means of graphs or trees). This information complements the data that are inherently spatial in a visual form, therefore representable by SciVis techniques (e.g. volume visualization of cartilage thickness from MRI-scanning).

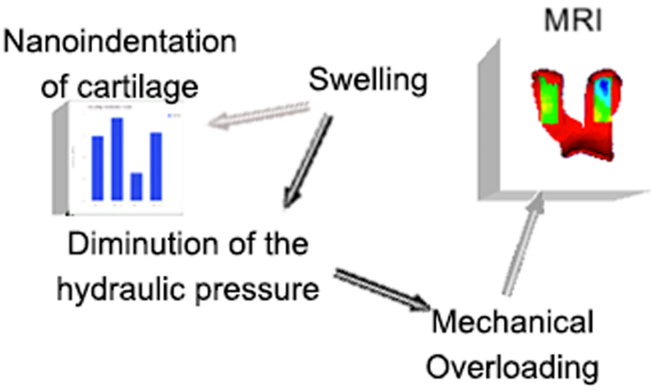


Figure 3.7: Combination of SciVis and InfoVis techniques proposed. Nodes encompass SciVis as well as InfoVis suitable data (source [150]).

The proposed approach for the presentation of multi-scale biomedical data combines both InfoVis and SciVis techniques. Each node, displayed as a hollow cube or half-sphere, encapsulates a data set which is presented with the most suitable visualization technique, either SciVis or InfoVis technique. This combination allows for both a consistent representation of heteregenous data as well as the preservation of the optimal choice of the representation of each data set.

The data structure and the architecture of the system are designed in order to perform the aforementioned feature. First, visualization properties are taken into account for the organization of the data (see Sec. 4.2). Such properties are encoded in the underlying ontology, exploiting the knowledge formalization for facilitating the collection and obtaining of information from each data set (see Sec. 4.4). After the retrieval, the distributed rendering scheme creates the scene. This scheme supports types of rendering for representing SciVis as well as InfoVis contents (see Sec. 4.5).

3.4 SUPPORT OF VISUALIZATION BASED ON KNOWLEDGE FORMALIZATION

The difficulty of exploring heterogeneous data sets increases if means to understand the meaning of such data sets and their relations are not provided. Taking into consideration that the aim of visualization is to get insight from a phenomenon (c.f. Sec. 2.1.1), an exploratory scene composed by merging data sets of multi-scale nature might not be enough to obtain valuable knowledge (c.f. Sec. 2.3.2). The need of semantic means gains even more importance in a multidisciplinary environment, in which medical experts try to analyze collaborately a multi-scale pathology. They have depth expertise in one concrete specialty, but they lack the big picture.

Therefore, semantically relevant information is intended to be visualized together in the multi-scale workspace. Providing visual semantic means in the data sets to understand relations between them (e.g. pathological relation between data sets) facilitates the exploration across all the multi-scale data. In addition, functionalities and visual properties of the data sets can be encoded in the ontology, automating and customizing the creation of the visualization scene.

The representation of meaningful data sets in a multi-scale scenario requires the acquisition of such information from some a priori knowledge. This multi-scale biomedical knowledge encompasses information sources that come from different scales, their relationships and data representing or accompanying them. Such multi-scale knowledge is obtained from all the domain specialists, which contribute with their data and expertise (e.g. tissue, biomechanical engineers) [13].

In this context, knowledge formalization can represent knowledge about several domains, as medical ontologies demonstrate (c.f. Sec. 2.6). Computer-based techniques can perform the process of reasoning on concepts of those domains, facilitating the presentation of data sets enriched with semantic meaning. In order to specify explicitly that conceptualization, an ontology can formally define what are the properties or attributes necessary to document them and the means to identify relevant items.

Current ontology visualization tools, based on InfoVis techniques, are not sufficient to give a cognitively rich and interactive exploration of the multi-scale biomedical knowledge (c.f. Sec. 2.6.2). This fact would hinder formalized semantic description and therefore the use of ontologies in a multi-scale exploration of medical data.

In this work, knowledge formalization supports the storage of the multi-scale biomedical knowledge and the relationships among multi-scale biomedical data for visualization purposes. Instead that the visualization for each specific profile, data type and need is explicitly encoded in the visualization system, roles and functionalities and relations of different visual contents can be obtained from information previously encoded in the ontology. Therefore, the development of a unifying conceptual framework controls the presentation of the data. Particular relevant features of the support of visualization based on knowledge formalization are:

- Extraction of visualization parameters for the creation of visualization scene: Parameters of each data set as the spatiotemporal scale it belongs to, the suitable visualization technique, as well as other visualization parameters are encoded in the ontology, allowing for an automatic creation of the visualization scene. This allows to automatize, among others, the positioning of the nodes and the proper use of a worker rendering entity to use for rendering a data set.

- Semantic links among multi-scale data sets: Data sets presented in a multi-scale scenario have inherent semantic properties (e.g. properties and features are being measured or investigated when obtaining and presenting a data set) as well as internal semantic relations (e.g. the relations among the different data sets in a flow of features evidenced when exploring a multi-scale pathology, see Sec. 4.6). Those data sets do not have per se such those semantic properties, but they have a critical relevance for comprehending the multi-scale scenario. The extraction of such abstract information is obtained from the multi-scale biomedical knowledge via the underlying ontology. Such information is represented in the visualization scene by a 3D immersive visual display of semantic features showing connections with related data sets.

- Customization of the visualization scene: Medical experts coming from different fields have different backgrounds, perspectives and interests in the different data sets of the scene. Therefore it is natural that the mode to show the different data sets depends on the profile of the specialist - user of the visualization system. Terms for this customization are encoding in the ontology, such as "user profile" and

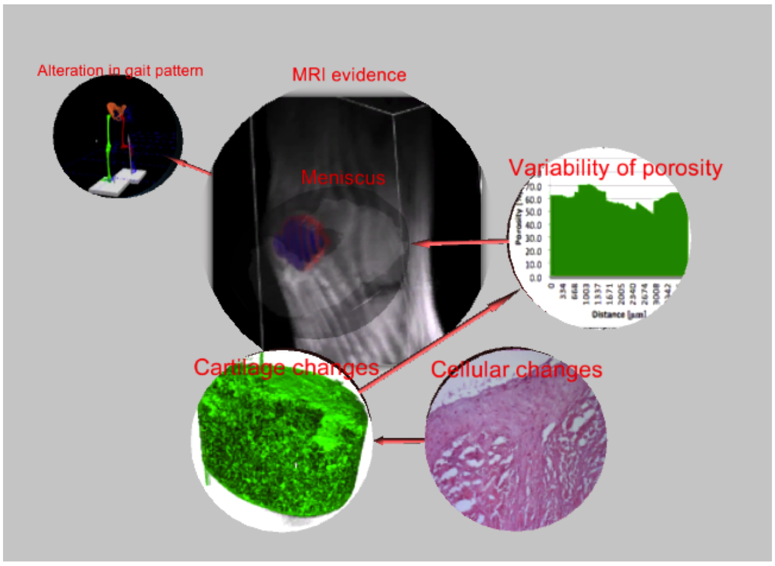


Figure 3.8: Example of links among nodes showing hierarchy of evidences in a pathology.

"interest" of the different profiles in the existing medical data sets and concepts.

The underlying ontology, denominated in the following as *multi-scale ontology*, serves as knowledge formalization of the multi-scale biomedical knowledge. The multi-scale ontology constitutes the multi-scale biomedical data management [13], which has been developed by IMATI within the framework of the MultiScaleHuman Project [15]. The introduction of the visualization components into the multi-scale ontology (e.g.[35]) allows its use for automating, customizing and supplying semantic means in the presentation of the biomedical data sets.

Following up with the current design of the multi-scale environment (c.f. Secs. 3.2, 3.3), this section enriches the visualization system previously described with semantic meaning. Knowledge from the multi-scale ontology (e.g. classification of data, user profile, location of resources) is applied to create the scene (e.g. the position of the nodes on the layers and their appearance, visual links among nodes indicating semantic relationships among the data sets they present, Fig. 3.8). The details of this development are found in Sec. 4.4.

Figure 3.9 depicts the interconnection which has been designed and developed between the multi-scale ontology and the exploratory system. The multi-scale ontology, acting as a driver for data management, receives requests and yields all relevant multi-scale biomedical information previously encoded to the visualization system. Such information is used for the rendering of the visualization scene, allowing for a customized and meaningful presentation of the data sets.

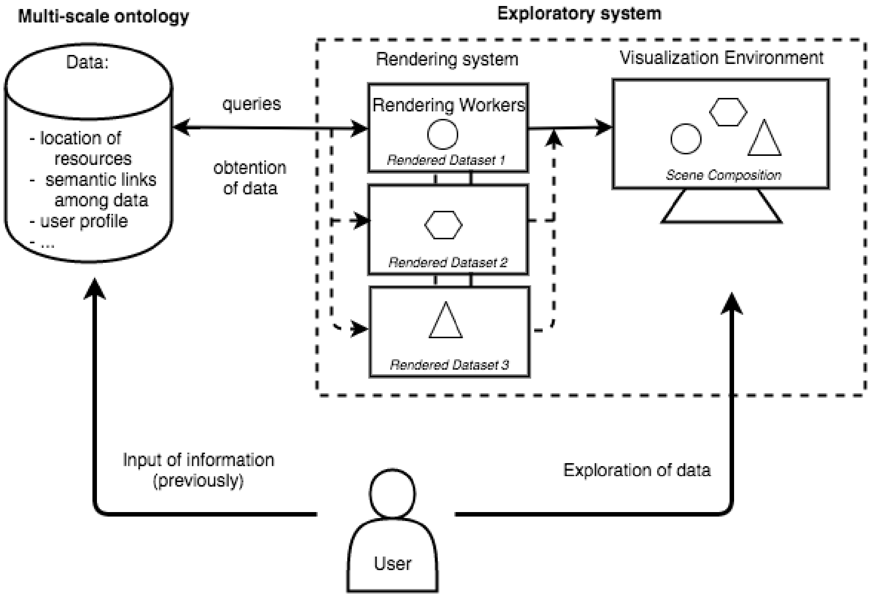


Figure 3.9: Simplified schema of interconnection of the multi-scale ontology [13] with the exploratory system.

3.5 ENHANCED INTRA-SCALE VISUALIZATIONS

In addition to the introduced strategy for multi-scale visualization of biomedical data, efforts have been made in this work in order to develop enhanced intra-scale representations (Table 3.2). The aim of the intra-scale visualizations is to get an in-depth characterization, presentation and analysis of data within the considered scale. Thus, the presented work also describes processing methods and visualization techniques which enhance the characterization and analysis of data available in concrete spatial scales. Each of those methods facilitate experts from a concrete biomedical domain to be equipped with a new procedure for understanding their data. Those intra-scale visualizations, together with the multi-scale visualization environment lead to a new way of analysis of biological phenomena of multi-scale nature.

Table 3.2: Summary of efforts towards the development of intra-scale visualizations, indicating the involved domain and scale.

Development	**Domain**	**Scale**
Anatomical visualization of helical axis data	Biomechanical engineering	Behavioral scale
Overall similarity visualization for comparison of helical axis data	Biomechanical engineering	Behavioral scale
Organization and exploration of micro-scale data	Biology	Micro-scale

In all those cases, a same procedure has been performed. Initially, the demand of the experts have been analyzed, taking into considerations their requeriments. Then, data have been carefully analyzed and solutions have been performed, combining concepts from different fields. Subsequently, adequate tools have been developed, providing experts solutions which contribute for the improvement of their respective workflows analyzing data.

Anatomical visualization of helical axis data

In biomechanical engineering, the axis of rotation about the knee joint performing a motion (e.g. flexion-extension motion) is commonly discussed in order to improve joint functionality and increase prosthesis longevity. The generally adopted method to define this axis is widely considered as a fixed axis throughout motion [75]. However, the description of motion based on helical axes has been verified to be superior as it removes repeatability errors [49, 218]. In contrast to the fixed axis of rotation, the description of a bone motion in three-dimensional space can be more faithfully captured in terms of a temporal sequence of helical axes and angles of flexion with respect to a reference bone [202]. However, the existing applications (see Sec. 5.2.2) used to represent helical axes lack an intuitive visualization to analyze states and conditions (e.g. Fig. 3.10a).

In this work, an intra-scale visualization that enriches the joint motion representation based on a direct measurement of helical axes is introduced (Fig. 3.10b, see Sec. 5.5.1). The implemented approach visualizes the three-dimensional motion of patient specific bone segments and the representation of the spatial configuration of the helical axes intersecting the bone, focusing on the representation of the knee joint flexion-extension motion. The realistic visualization of bone motion incorporating helical axis data provides a more understandable representation of the knee joint functional articulation, facilitating the description of the flexion-extension motion for kinematical studies.

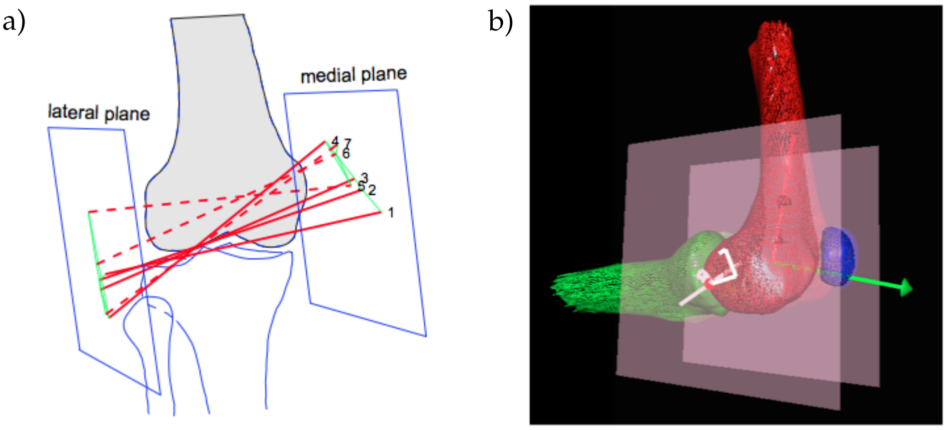


Figure 3.10: a) Traditional representation of helical axes during a knee joint flexion-extension motion (source [218]). b) Developed anatomical visualization of helical axis data.

Overall similarity visualization for comparison of helical axis data

Following up with the analysis of helical axis data, the description of the knee joint motion based on helical axes can refer either to Finite Helical Axis (FHA) [53] or Instantaneous Helical Axis (IHA) [240]. While the first method refers to a finite rigid body transformation between two distinct poses, the latter uses infinitesimal transformation, thereby characterizing the differential change along a curve of rigid body transformations.

Many, even recent recent biomechanical studies rely on the FHA approach [218, 100, 140]. Altough it provides a rough estimate of the IHA as the two poses approach each other, it is easier to compute. However, FHA is highly sensitive to noise in the two sample poses involved and its computation becomes numerically unstable for small differences, while on the other hand using too large a difference yields only a bad approximation to the IHA (see Sec. 5.2.1).

In this work, both the FHA and IHA are naturally discussed in the unifying mathematical framework based on the Lie group of rigid body motions, its Lie algebra and the exponential map relating those. This approach ensures the obtaining of only valid rigid body transformations, which by analytical differentiation effectively allows to calculate stable instantaneous helical axes for an accurate analysis (see Sec. 5.4). The output of this approach is used for accurately interpreting kinematical data of flexion-extension motion, which particularly leads to an efficient overall similarity visualization across several motion sequences in order to differentiate among several cases and states (Fig. 3.11b, see Sec. 5.5.2). Additionally, this also allows for an accurate analysis of the helical axes in terms of bone anatomy by using the anatomical visualization introduced above.

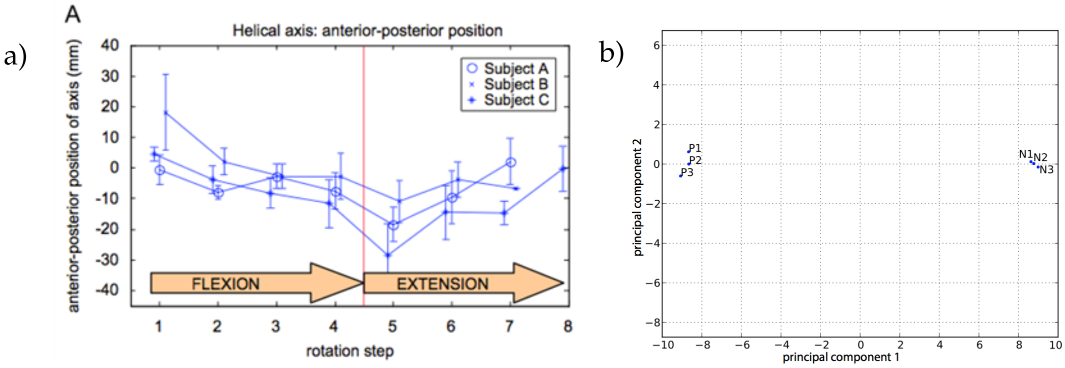


Figure 3.11: a) Traditional type of visualization of motion sequences by using FHA (source [218]), which makes difficult the analysis of overall differences. b) Developed overall similarity visualization of helical axis data based on IHA in terms of Lie algebra.

Organization and exploration of micro-scale data

The methodology of investigation and exploration by biologists when dealing with mainly micro-scale data has been also analyzed. This methodology of investigation is based on the formulation and validation of hypotheses using the evidences found in the data obtained in their experiments taking into consideration the established knowledge. However, the traditional exploration methodology does not facilitate this task, as the current work procedure for analysis mainly uses isolated visualization tools, avoiding to have the complete picture. The process of data collection and analysis is typically executed manually involving several steps, being extremely time-consuming. Data are stored in different machines as a stack of files, and metadata are saved in spreadsheets or in own researcher notes.

In this work, efforts have been done in order to improve the biologists' workflow for the investigation of micro-scale data (e.g. Fig. 3.12). Note that extending this methodology, it also allows for an overall study of the multi-scale data, capturing all information relevant of the involved domains (see Sec. 4.6 for more details).

All the efforts towards those enhanced visualizations are encompassed in the multi-scale visualization environment proposed in Secs. 3.2, 3.3. Note that, in Fig. 3.12, changes due to osteoarthritis at micro-scale lead to

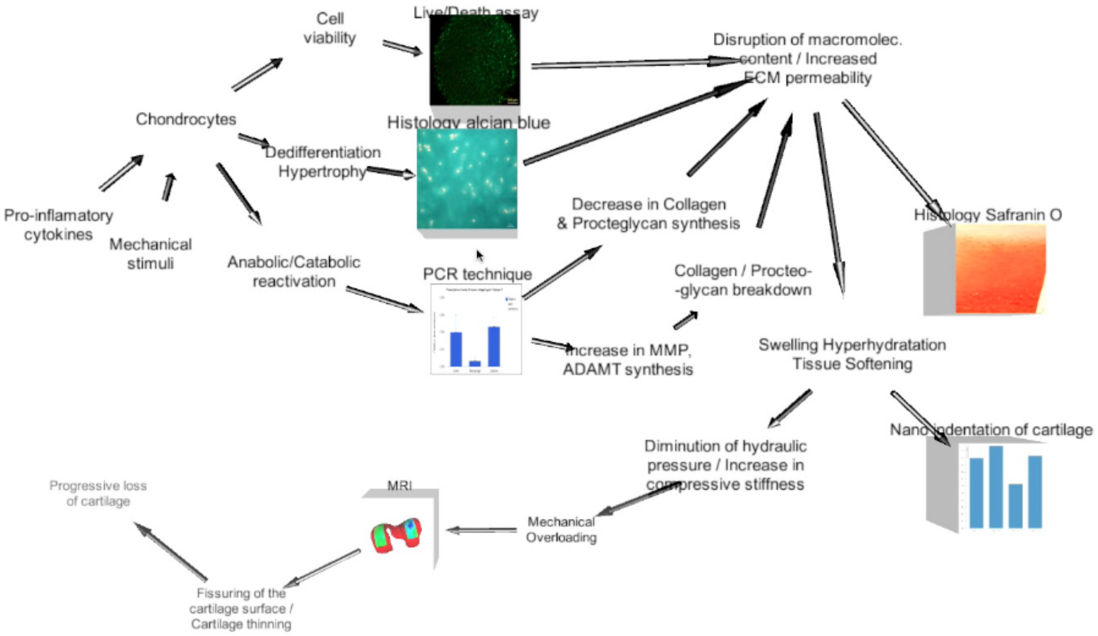


Figure 3.12: Proposed visualization for the organization and exploration of micro-scale data together with the scheme of cartilage degradation during osteoarthritis.

alterations on the range of motion of the knee at behavioral scale [38]. Thus, with all those intra-scale developments, the proposed general framework for the study of multi-scale data is enriched.

3.6 ASPECTS REGARDING THE DESIGN OF SCIENTIST-CENTERED VISUALIZATION TOOLS

The design of scientist-centered visualizations, i.e. adequate visualization tools for scientists to gain insight from the data they explore, depends on several aspects which have been proposed in the literature (c.f. Sec. 2.4). These aspects have been taken into consideration in this work and encompass: *analysis of scientists' requirements*, *evaluation of visualizations tools* and a *coupled interaction*.

The development of the different visualization tools has been performed taking into consideration the demands and requirements of the scientists/users following the same procedure: i) analysis of data and users' requirements, ii) proposal of solutions and iii) evaluation. In the case of the design of the multi-scale approach, the heterogeneity of data and the fields of the users involved has required not only the understanding of the data to be visualized, but also the identification of semantic and structural relations inside a multi-scale data set. In addition, it has been considered important to listen to the scientists – as authentic users of the tools – and query them about their desires and intuition about the visualization outcome as well as to know quickly their feedback during the development of the environment with the help of a preliminary evaluation.

Every visualization system is composed of two main components intrinsically connected: visualization and interaction systems (c.f. Sec. 2.5). In this work, the design of the visualization system has followed a common strategy with interaction: a natural interaction consistent with visualization. The aim has been to provide a human-computer interface that is perceived by the user to be compliant and coherent with the visualization sytem, facilitating them to gain insight from the data to explore. Thus, the approach towards the exploration of biomedical data in this work makes use of Virtual Reality (VR) techniques, such as 3D stereographic visualization, which also contribute to the design of scientist/user-centered visualizations.

Analysis of scientists' requirements

A visualization requirement analysis has been initially performed. Its aim has been to identify relevant aspects for the development of the multi-scale visualization environment from the perspective of the users that would use the system. This analysis has included the technical specification of data as well as wishes about the common multi-scale visualization environment.

The specification of data has included identification of devices, data and formats. A brief classification of the data is depicted in Table 3.3. The variability of data from multiple modalities in different biological scales has led to decide on features of the visualization platform, which should be light-weight, modular and plugin-based, consisting of several subsystems that exchange data via files.

Table 3.3: Classification of the data according to the scale and biomedical domain involved.

	Scenario: study of a knee joint multi-scale data set		
Scale	Molecular/cellular (Micro-scale)	Organic (Medium-scale)	Behavioral (Macro-scale)
Examples of data	Histological images, micro-CT, mechanical properties	PET, MRI, CT, segmentations	Gait pattern, EMG data, kinematical data for helical axes
Biomedical domain	Biology, tissue engineering	Radiology	Biomechanical engineering

Regarding the considerations about the multi-scale visualization environment, the collection of information was performed by a written query. The results have shown that there are two repeated main requests, which translating them to the vocabulary of the visualization field can be expressed as follows:

- Need for a tight integration not only scientific image visualization but also scientific visualization with information visualization.
- Need of highlighting partial information inside scientific visualization (like segments, relations between elements).

Those aspects have constituted a ground base for the design and development of the multi-scale environment, which have been taken into consideration for the approach proposed in Secs. 3.2,3.3.

Evaluation of visualizations tools

Following up with the analysis of the visualization requirements from the user's perspective, a preliminary evaluation of the multi-scale visualization environment was performed during an initial phase of the development (see Sec. 4.7, summarized and published in [192]). The aim of this analysis was to find out if the direction of the proposed approach for the visualization environment was appropriate. To this aim, the opinion of users after performing several tasks related to the exploration of multi-scale data in different scenarios was taken into consideration. The analysis had the following features:

- Participants belonged to the domains which were addressed in the design of the system, comprising users from the fields of computer graphics, physics and biomechanical engineering.
- During each scenario, participants were asked to perform tasks close to the real application. These tasks were related to the exploration of a (multi-scale) set of knee joint related data, therefore involving both data used on a daily basis as well as unfamiliar data.
- The aim of this preliminary evaluation was to analyze to what extent the proposed visualization features for the exploration of multi-scale data were comfortable to the user with respect to some traditional methods generally used (see Sec. 4.7 for further details).

Regarding the enhanced visualizations, a continuous evaluation of the tools has been performed during tight collaboration periods with specialists of the respective domains.

Coupled interaction

The analysis of the multi-scale data has indicated that the most acquired biomedical data have a 3D representation by means of volumetric objects. A natural way to interact with those objects is to make use of actions with the hands in order to adjust the view for their optimal observation, i.e. natural hand manipulation in order to rotate the objects or move them closer to gather information from different sides and distances. Therefore, a common strategy of the visualization and interaction approaches has been required in order to mimic these natural strategies for a more intuitive and user friendly data exploration. The proposed approach works towards an exploration of biomedical data employing a combination of 3D stereographic visualization and natural interaction.

The multi-scale visualization scene makes use of an immersive 3D multi-layered environment (c.f. Sec. 3.2), in which the representation of data is in the form of nodes displaying 3D content without the traditional GUI. In this environment, the proposed interaction with the data is mainly by means of natural hand manipulation, therefore reducing users' needs for high demands of learning how to interact with data by using devices [191, 192].

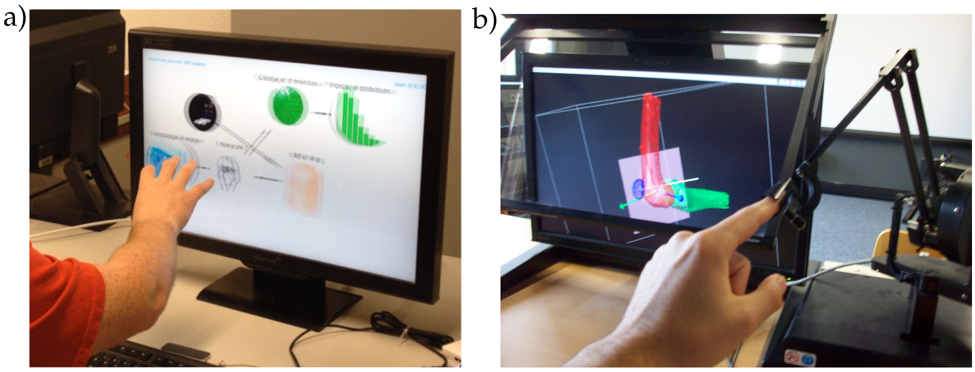


Figure 3.13: Coupled interaction: a) Hand gestures interact with nodes in the multi-scale environment. b) Haptic interaction [82] and exploration of CT data of knee joint.

A *multimodal interaction method* has been proposed for the interaction with the multi-scale visualization environment [191, 192]. This method constitutes an approach that integrates interfaces with different interaction qualities, similarly to the way humans communicate (c.f. Sec. 2.5.2.2). In this case, the multimodal interaction method involves a synergy of hand gestures, haptic interaction and traditional means of human-machine communication.

- Hand gesture interaction allows the manipulation of the nodes in the multi-scale environment. Several actions can be performed, e.g. a user grasping and moving the hand will move the grasped nodes (Fig. 3.13a).
- Haptic interaction (c.f. Sec. 2.5.2.1) allows the exploration of biomedical data while being able to feel underlying structures through a force feedback loop (e.g. Fig. 3.13b).
- Traditional interaction (i.e. mouse and keyboard) is ultimately allowed in order to prevent a lack of interaction tangibility due to unforeseen unavailability of the other interaction interfaces.

Note that the design, development and evaluation of the multimodal interaction system are not the scope of this work. Extended details of those features can be found in the work titled "Multimodal interaction with an integrated visualization system for the analysis of multiscale biomedical data", authored by J. Rzepecki [191]. A brief summary is described for completeness at the end of Chapter 4 (Sec. 4.9).

4

MULTI-SCALE VISUALIZATION ENVIRONMENT

The aim of this chapter is to describe the design and implementation of a multi-scale visualization system that enables the exploration of biomedical data related to diseases of multi-scale nature, focusing on the example of musculoskeletal diseases. This development (Table 4.1) addresses the importance of all spatial scales involved and emphasizes the relationships among data sets, combining techniques coming from SciVis and InfoVis fields in order to present realistic visualization of data sets as well as visual abstractions based on the relations of the data . The creation of the visualization scene including semantic aids among data sets is supported by knowledge formalization applied to the multi-scale scenario. Important aspects considered for the design of the environment have been the analysis of scientists' requirements, a preliminary evaluation of the proposed exploration features and a coupled interaction.

4.1 INTRODUCTION

An analysis of the biomedical data required for the study of musculoskeletal diseases has been initially performed. During this analysis, it has been found that for such a study an heterogeneous set of data sets is required, demanding both multimodal and multi-scale visualization needs (c.f. Sec. 2.3.2). The performed analysis has led to carry out the **classification of data** according to the related spatial scale, the visualization properties, and the user profile which specially is interested in, described in Sec. 4.2.

Table 4.1: Multi-scale visualization environment: Conventional approach vs. proposed approach.

Exploration features	**Conventional approach (c.f. Table 2.1)**	**Proposed approach**
Representation of data sets based on	Tree list structure	Nodes displaying data sets
Visualization scenario	Flat desktop	3D workspace
Superposition of data sets	Overlapping	Overlaying
Focus and Context technique	Preserving spatial dimensions (placeholders)	Multilayered workspace with non-linear depth
Visual semantic means among data sets	None: inferred by the experience of users	Visual links thanks to an underlying ontology
Visualization techniques	Usually either InfoVis or SciVis	Combined InfoVis and Scivis via visual links
Rendering of data sets	Single data sets	Multiple data sets
Amount of rendered data sets	Few	Many, by distributed rendering

The criticism found in the literature regarding the current multi-scale visualizations (c.f. Sec. 2.7) has motivated the design and development of a novel multi-scale visualization approach addressing the importance of all scales and emphasizing the relationships among data sets (c.f. Sec. 3.2). Details of the visual features of the **visualization environment** are described in Sec. 4.3.

The heterogeneity of the data sets and the consequent need to provide semantically relevant information has led to the exploitation of knowledge technologies. Ontologies can efficiently store biomedical knowledge and supply such semantic information, but the traditional visualization used for their representation, focused on the representation of information at a conceptual level, is not enough to provide a realistic and interactive exploration of data (c.f. Sec. 2.6). The proposed approach combining the exploratory system and the multi-scale ontology [13] controls the presentation of the data to appear in the visualization environment (c.f. Sec. 3.4). Details of the **support of visualization based on knowledge formalization** are explained in Sec. 4.4.

The multi-scale visualization environment requires a coupled **interaction** in order to obtain a resulting tool that facilitates the exploration process (c.f. Sec. 2.5). The aim of the interaction system is to provide a human-computer interface that is perceived by the user to be compliant and coherent with the visualization sytem, facilitating them to gain insight from the data to explore. To this aim, the multi-scale visualization environment employs a combination of 3D stereographic visualization and multimodal interaction [192], involving a synergy of hand gestures, haptic interaction and traditional means. A brief summary of the solution adopted for the multi-scale visualization environment is outlined in Sec. 4.9.

Next, details regarding the **architecture** and implementation of the overall exploratory system (Fig. 4.1) are indicated in Sec. 4.5, focusing on the visualization environment and the support of visualization based on knowledge formalization. The implementation of the visualization environment uses a distributed rendering scheme accesing network resources in order to

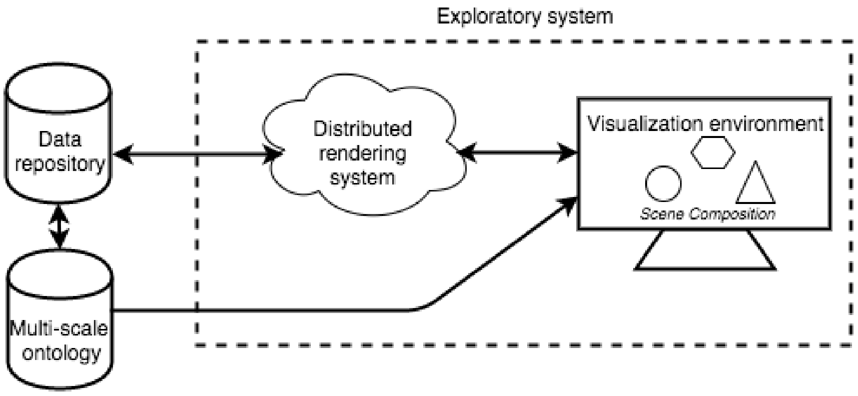


Figure 4.1: Big picture of the overall exploratory system.

make feasible the presentation of all data sets in a single view. The support of visualization based on knowledge formalization requires information from the multi-scale ontology to be extracted and processed in order to render the visualization scene.

An **example of use** of the system is presented in Sec. 4.6. Concretely, the proposed exploratory system is presented in a case of a biologist investigating osteoarthritis at the knee joint. In effect, specialists from different domains (biomechanical engineering, radiology and tissue engineering) contribute with their data and expertise. The set of data sets fulfils both the multimodal and multi-scale requirements: They belong to different spatial scales (cellular, organic and behavior scales) and have different visualization properties (adequate to be represented with SciVis or InfoVis techniques). The proposed framework allows a direct and meaningful exploration of all related data sets of interest to the biologist. The use of the system in this example is demonstrated by employing data sets of multi-scale nature, described in Table A.1. *Note that those data sets do not correspond to the same patient, but serve for illustration purposes.*

In order to know the feedback about the multi-scale environment by potential users, a preliminary **evaluation** was performed [192] and its description is extended in Sec. 4.7. An experiment involving scientists from the fields addressed in the design of the system was conducted in order to find out the user comfort with the visualization features of the proposed approach. This section includes the protocol, the data analysis and the results of this evaluation.

Finally, a **discussion** regarding the multi-scale visualization environment introducing additionally other considerations is presented in Sec. 4.8.

Note: The multi-scale environment constitutes a complex system which has been developed jointly by J. Rzepecki and the author of this thesis in the context of the MultiScaleHuman Project (interdisciplinary training network supported by the EU Marie Curie actions) [15]. The parts regarding classification of data, design of visualization environment, support of visualization based on knowledge formalization as well as the example of use are primary work performed by the author of this thesis [149, 35, 150]. The architecture, development as well as the performed evaluation of the system has been coauthored with J. Rzepecki [192]. The multimodal interaction system, which has been outlined in this thesis for completeness, is work of J. Rzepecki. Extended details can be found in the work titled "Multimodal interaction with an integrated visualization system for the analysis of multiscale biomedical data" [191].

The multi-scale ontology [13] has been developed by IMATI within the framework of the MultiScaleHuman Project [15]. The introduction of the visualization components into the multi-scale ontology and its application to uses related to the musculoskeletal diseases analysis, allowing its use for customizing and supplying semantic means in the presentation of the biomedical data sets within the multi-scale visualization environment [35, 150], has been the contribution of the author of this thesis. Note that extended details of the features of the multi-scale ontology system [13] are not the scope of this work. They can be found in the work titled "Multi-scale biological knowledge formalization: definition, properties, and applications" [34].

4.2 CLASSIFICATION OF DATA

The analysis of the technical specification of the data for the analysis of musculoskeletal diseases has found that an in-depth analysis of such diseases requires a large heterogeneity of data from different medical specialties.

The gathered data sets are not only acquired from different acquisition modalities (e.g. CT, MRI, gait pattern analysis), but are also distributed over multiple spatial scales (from data acquired or processed at ranges of micrometer to meter). They have several levels of abstraction, which lead to different grades of suitability to be represented by the large number of existing visualization techniques (e.g. volumetric representations, graphs or diagrams).

In addition, the analysis of all those data involves scientists from different domains, who contribute with their data and expertise. They usually work on individual features involving a concrete domain and spatial scale, contributing for the analysis of the multi-scale pathology. Examples of sources of data under investigation, devices used and domains involved are depicted in Fig. 4.2.

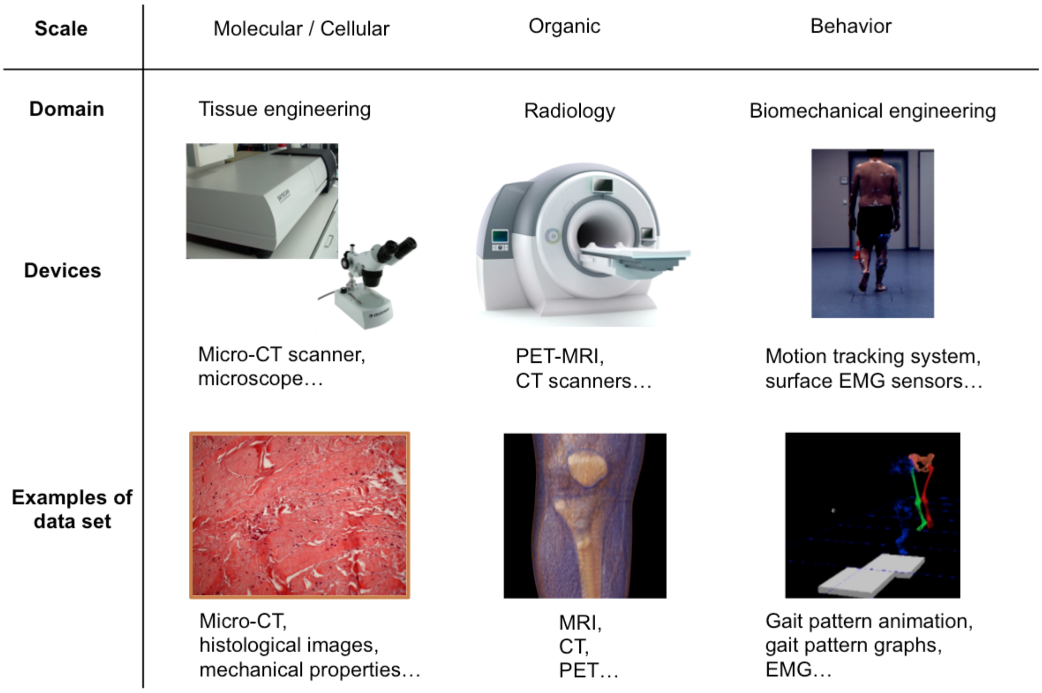


Figure 4.2: Example of scales, domains, devices and data sets involved in the study of musculoskeletal diseases.

The illustrated data sets range from a cross-sectional histology of the meniscus at the cellular scale, to graphics associated to the motion pattern of the knee at the behavior scale, with data on the organic scale in between, e.g. PET/MRI images, and their segmentations. Note that these examples have different levels of abstraction and diverse representation techniques. Physical data (e.g. PET/MRI, CT) are traditionally the focus of *SciVis* techniques (c.f. Sec. 2.1.3.1); and nonphysical, abstract data (e.g. meniscus properties, hierarchies, and statistical data) are more suitable for *InfoVis* (c.f. Sec. 2.1.3.2). Different specialists (e.g. tissue engineers, radiologists, biomechanical engineers) contribute for the exploration of musculoskeletal diseases by acquiring and analyzing data of a specific scale.

Data have been collected and analyzed in the framework of the MultiScaleHuman Project [15], in which specialists of the aforementioned domains have shared knowledge and data sets for this work. The development of the multi-scale visualization environment has been performed in order for these kind of specialists to be able to use the system for exploring multi-scale data. A complete list of the multi-scale data sets employed in this work is found in Table A.1.

Biological data sets have been classified according to their *scale of data*, *visualization suitability*. Scale of data classiffies data acquired or derived from different spatiotemporal ranges. Visualization suitability is the appropriateness of a given data set to be represented by using a concrete SciVis or InfoVis technique. In addition, *user profile* saves the main scale of interest of the specialist (Table 4.2):

- *Scale of data:* Four scales have been considered:
    - *Micro-scale:* Data acquired or derived from images whose pixel size ranges in the micrometer range, e.g. micro-CT , histological images, and mechanical properties of cartilage.
    - *Medium-scale:* (Medium: from Latin, *the middle, center*, i.e. intermediate scale). Data acquired or segmentations obtained from PET, MRI, CT imaging techniques.
    - *Macro-scale:* Data acquired and processed from the gait pattern analysis, which correspond to the highest spatial range.
    - *Abstract scale:* This scale encompasses all the nonspatiotemporal knowledge which cannot be directly implied from one of the previous scales. Those data include anatomical structure, relations between evidences in a multi-scale pathology or other derived knowledge.
- *Visualization suitability:* Appropriateness of data to be represented by using a concrete *InfoVis* or *SciVis* technique, measured according to the standard representation used by the specialists. For example, MRI is suitable for volume rendering - *SciVis* technique, the joint angle evolution in a gait pattern is suitable with a graph - *InfoVis* technique. Note that the abstract scale data are represented mainly by InfoVis techniques. Semantic relations and their structures have not inherently

a spatial representation and therefore it is necessary to supply it, e.g. by making use of tree or node-and link visualizations (c.f. Sec. 2.1.3.2).

Table 4.2: Classification of the data with respect to *scale of data*, *visualization suitability* and *user profiles*.

Visualization suitability / Scale of data	**SciVis technique**	**InfoVis technique**	**User profile**
Micro-scale	Molecular and histological images, micro-CT	Properties extracted at molecular, cellular and tissue level	Tissue engineer
Medium-scale	PET, MRI, CT and segmentations		Radiologist
Macro-scale	Gait pattern animation, original video sequence, helical axes of knee joint motion	Gait pattern graphics, e.g. joint angles, EMG signals	Biomechanical engineer
Abstract scale	-	Anatomical structure, relation among evidences, other derived knowledge	Computer scientist, Generic

The importance of the visualization suitability has emerged during the written query to the specialists (c.f. Sec. 3.6) regarding their wishes and considerations for a multi-scale environment. In such a query, specialists highlighted the need for a tight integration of scientific visualization with information visualization. Therefore it has been important to identify the data sets according to the visualization suitability.

Different kinds of specialists contribute with their data and expertise to the exploration of musculoskeletal diseases. All of them have their own *user profile* in the multi-scale environment. Thus, the users fall into five main groups, depending on their field or medical specialty:

- *Radiologist*,
- *tissue engineer*,
- *biomechanical engineer*,
- *computer scientist*, or
- *generic*.

The first three types of users contribute to the environment by supplying data of a specific scale. The computer scientist organizes the information and has an important role in the multi-scale visualization as well as in the inference of abstract knowledge. Generic is the profile of a physician interested in an overall view. The use of user profiles is required to reach the scientist-centered visualizations. The visualization environment has to satisfy not only the integration of data of any nature, but also the customization of the view according to the level of interest in a given data set of the user - scientist.

The aforementioned parameters, encoded in the multi-scale ontology (see Sec. 4.4), allow the positioning of the multi-scale data on the visualization scene in a suitable way according to their visualization properties as well as the user interests (see next section).

4.3 VISUALIZATION ENVIRONMENT

The proposed approach of visualization environment is based on the data sets as main actors. Each data set is encapsulated in a node which has a geometric shape as a hollow cube or half-sphere. The data set is presented inside the node with the most suitable visualization technique, independently of its SciVis or InfoVis nature, allowing for a consistent representation (Fig. 4.3).

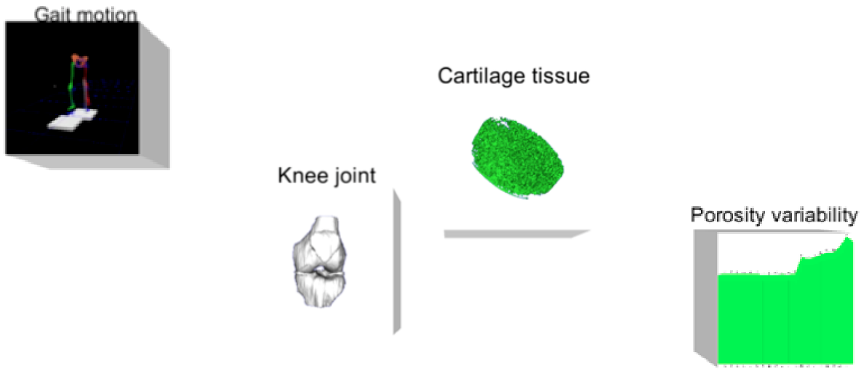


Figure 4.3: Diverse examples of representation of data sets by means of nodes, according to the most suitable visualization technique encoded in the visualization suitability parameter.

Those nodes are distributed in a *3D multilayered environment*, allowing for a direct exploration of all the data. Nodes provide perceptually semantic means to understand information contained in the nodes as well as their relationships. Visual cues play an important role in the presentation of relations among data sets. Thus, the nodes are positioned on one of these *layers* and are connected through *visual links*:

- The *3D multilayered environment* is composed of layers whose distance between each other is uniform. The *layers*, distinguished by their z-order, are *focus*, *context* and *background* (Fig. 4.4). They group the nodes with the same spatial scale, i.e. data from each spatial scale (i.e. *micro, medium* and *macro*) are positioned on one of these layers.

  - *Focus* constitutes the main scale of interest of the user. Data sets with InfoVis and SciVis suitabilities are linked and visualized on the foreground.
  - *Context* is placed behind and aims to provide context to the data on the focus layer with data coming from a contiguous spatial scale.
  - *Background* is the last layer, and completes the general view across all the spatial ranges.

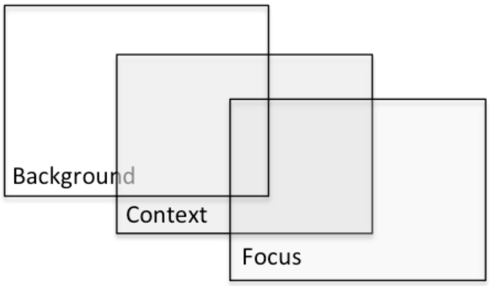


Figure 4.4: Focus, context and background layers.

  This approach allows the data sets to be presented and explored independently of their spatial dimensions, alleviating the differences in the order of magnitude of data.

- *Visual links* between nodes represent semantic relations across data sets, extracted by the *abstract scale* provided by the multi-scale ontology. These visual cues can take different forms by means of arrows.

The position of the nodes on these layers depends on the main scale of the *user profile*. Given the main scale for the user, the nodes corresponding to this scale are positioned on the *focus layer*, containing either *SciVis* or *InfoVis* data for the scale. The integration of the adjacent scales depends on their spatial proximity. Data belonging to the most adjacent scale is positioned on the *context layer*, and the data of the furthest scale is placed on the *background layer*.

The 3D multilayered environment is realized in a form of a thin-client based on the Unity software framework [104]. Unity is a cross-platform game engine with a built-in integrated development environment (IDE) for the development of visualization scenes. Each scene is composed of *objects* (e.g. camera, light, or every visible geometrical shape) which are configured by adding components and setting their properties to the appropriate values. The scripting of such configuration has been developed in C#.

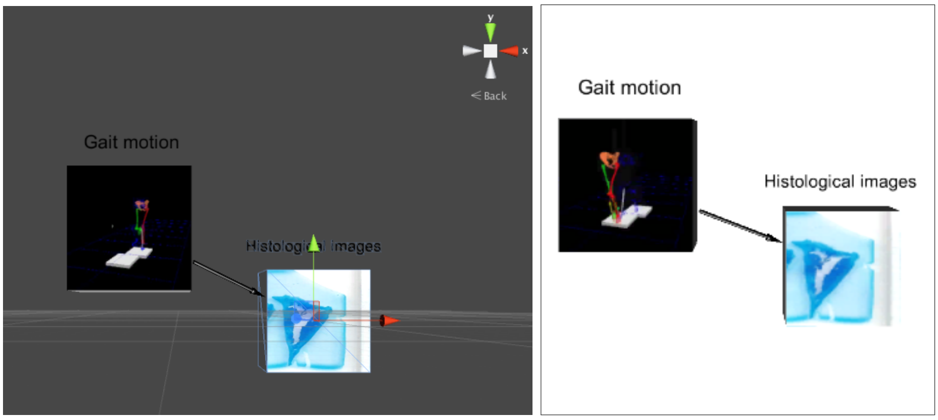


Figure 4.5: Examples of *TemporalNode*, *Arrow* and *ImageNode* in the Unity IDE and in the final scene.

The most representative objects in this environment are *nodes* and *arrows* (Fig. 4.5):

- *Node*: It contains an encapsulated data set. Physical appearance of those nodes can be hollow cube or half-sphere meshes (Fig. 4.6). The concrete selection of the shape will depend on the application (see Sec. 4.8). Node constitutes a super class for the following types of nodes:
  - *ImageNode* contains an encapsulated image.
  - *SetImageNode* contains a set of superimposed images, e.g. a set of histological images. Automatically or by interaction, the image can be changed to the next one.
  - *3DNode* encapsulates data for volume visualization, e.g. CT of knee joint.
  - *InfoVisNode* contains InfoVis data (e.g. gait pattern graphics). Graphs values can be interactivelly explored.

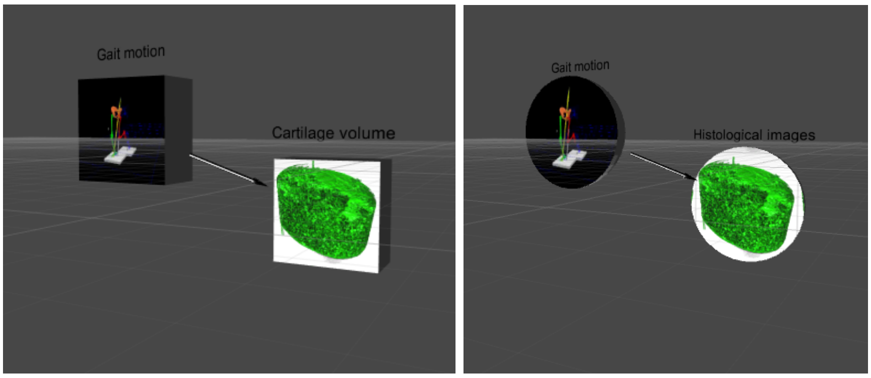


Figure 4.6: Different physical appearances of nodes: hollow cube and half-sphere.

  - *TemporalNode* contains a data set which has temporal dimension (e.g. video of motion capture). The node incorporates means to modify the speed of the representation.

- *Arrow* relates nodes. By using a mesh developed under the appearance of an arrow, it creates a relationship between the two nodes indicated.

Each of these objects have been developed in Unity3D by means of *prefabs*. A prefab acts a template from which new object instances can be created in the same scene. In such objects, the data sets already rendered by means of a distributed rendering system are inserted (see Sec. 4.5).

The creation of the scene, i.e. selection of the rendering worker entity to render a data set, positioning of nodes on the layers as well as arrows between nodes, is dynamically performed, and described in Sec. 4.5. The properties for the creation of the visualization scene are extracted from the ontology which supports the visualization (see next section).

4.4 SUPPORT OF VISUALIZATION BASED ON KNOWLEDGE FORMALIZATION

The proposed framework combining the exploratory system and the multi-scale ontology [13] (c.f. Sec. 3.4) controls the presentation of the data to appear in the multi-scale visualization environment. The multi-scale ontology leverages the multi-scale biomedical knowledge, which encodes the aforementioned parameters which classify the data (c.f. Sec. 4.2), as well as others (e.g. location of resources, pathological relations among data sets...). The information from the multi-scale ontology will subsequently allow the extraction of the necessary visualization parameters for the creation and customization of the visualization scene (see Sec. 4.5).

In the following subsections, the support provided by knowledge formalization is described. First, the multi-scale knowledge is defined, which contains information regarding the biomedical domains that study musculoskeletal articulation of a human body and the related musculoskeletal diseases. This knowledge is formalized and encoded by means of the multi-scale ontology, which focuses on the multi-scale degradation process features occuring at different scales. Third, the extraction of information by means of queries to the ontology determines semantically relevant data and information for the multi-scale visualization environment. Finally, the knowledge formalization support is demonstrated in an example related to the musculoskeletal diseases.

Multi-scale biomedical knowledge

The knowledge to be formalized focuses in this context on biomedical domains that study musculoskeletal articulation of a human body and related musculoskeletal diseases, restricted to the region around the knee. The multi-scale biomedical knowledge serves as *medical data repository* and *framework for storing common knowledge* [35, 149]:

- As a digital patient medical record, the multi-scale biomedical knowledge documents a medical case in which a patient underwent an operation on meniscus in a knee. Thus, it contains personal data (e.g. patient ID, sex, birthdate) as well as a plethora of information from different acquisition sessions and analysis. For instance, they can be the stack of MRI images before and after surgery, detailed information about the mechanical properties of the meniscus, a history of the gait pattern both pre- and post-operative as well as a simulation model of the knee articulation. All these data come from different spatial scales (cellular, molecular, organic, behavior) and reside in the multi-scale biomedical knowledge.

- The multi-scale biomedical knowledge also contains generic knowledge that is necessary for diagnostics and follow up reports, e.g. from *biomedical domains* such as tissue engineering, radiology and biomechanical engineering. The knowledge can be generic (e.g. anatomy) or established from given facts. A typical example would be the fact that bone erosion caused a pathology that resulted in an abnormal gait pattern. This knowledge serves as a common framework for knowledge discovery among different medical specialists working simultaneously on the same medical case.

  The users of the multi-scale biomedical knowledge fall into the 5 main groups already indicated: generic, radiologist, tissue engineer, biomechanical engineer, and computer scientist. Different users have different levels of interest in these data. For example, a radiologist is more interested in studying MRI images, a tissue engineer in studying mechanical properties of the meniscus, and a biomedical engineer specialized in human motion in analyzing the gait pattern.

  The representation of the multi-scale biomedical knowledge requires techniques coming from both subfields SciVis and InfoVis (c.f. Sec. 2.1.3). InfoVis techniques cover derived knowledge, anatomical structure, comparison and diagnosis procedures; while SciVis focuses on physical acquisitions.

  In this context, note that the *visualization* field also collaborates towards the analysis of the multi-scale data sets. Thus, this information is also included in the generic common knowledge. Clear examples are the suitability of visualization techniques of the multi-scale data and levels of users' interest in those data, used for the creation and customization of the scene in the multi-scale environment.

Multi-scale ontology

The formalization of the aforementioned multi-scale biomedical knowledge is encoded in the multi-scale ontology [13], which acts as a driver for data management. Thus, the ontology formalizes relationships between multi-scale data, patients, techniques, user profiles and relevant visualization parameters. The general structure of the ontology focuses on multi-scale degradation process features occuring at different scales. A general overview of the multi-scale ontology applied to the multi-scale visualization environment [35] is represented in Fig. 4.7.

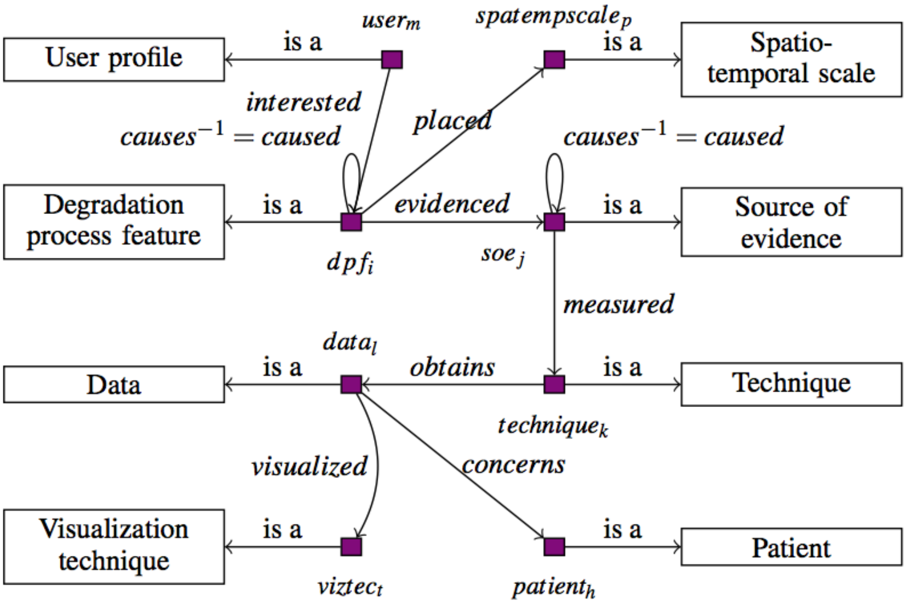


Figure 4.7: Graph representation of the multi-scale ontology (source [35]).

The representation of the ontology [35] is given by means of a labelled directed graph $G = \{V, E\}$, where nodes ($V = \{C, I\}$) are concepts (C) and instances (I) of concepts, and edges $E = \{R, is\ a\}$. R are relations between instances and "is a" represents a relation between instances and concepts. G is labeled with $l : V \mapsto L$, which maps nodes to the corresponding labels (L, labels of concepts, individuals and relations).

Concepts (C) include:

- Patient: Subject identifier.
- Data: Data set identifier (e.g. resource location).
- Spatiotemporal scale: Its instances (I) can be "micro-scale", "medium-scale", "macro-scale" or "abstract scale" (c.f. Sec. 4.2).
- Visualization technique: The appropriate technique to be used for the representation of a concrete data set (c.f. Sec. 4.2).
- User profile: Its instances can be "Radiologist", "Tissue engineer", "Biomechanical engineer", "Computer scientist", or "Generic" (c.f. Sec. 4.2).
- Degradation Process Feature (DPF): Characteristic evidenced in a pathology. For example, instances of a DPF in a musculoskeletal disease can be "Cellular change", "Loss of biomechanical function",

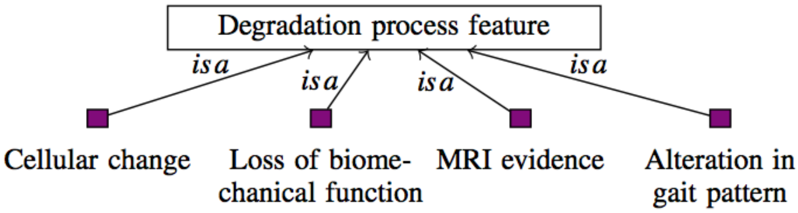


Figure 4.8: Instances of degradation process feature (source [35]).

"MRI evidence"" and "Alteration in gait pattern". Those instances are represented as a graph in Fig. 4.8.

- Source of evidence (SOE): Origin that reveals a DPF. For example, "Joint stiffness" and "Joint weakness" are instances of SOE. They evidence the DPF "Alteration in gait pattern".
- Technique: Procedure which obtains a data set and measures a SOE. For example, "EMG" (i.e. electromyography) is a technique, and is used for the measurement of the SOE "Joint stiffness".

The last three concepts listed fundamentally formalizes the propagation of degradation process features in hierarchical pathologies. Thus, multi-scale DPFs that may cause one another DPF ($\mathsf{cause}, \mathsf{caused}^{-1} \in \mathsf{R}$), are evidenced ($\mathsf{evidenced} \in \mathsf{R}$) by SOEs which in turn are measured ($\mathsf{measured} \in \mathsf{R}$) by different techniques. For a complete example, see Sec. 4.6.

Implementation and use

The extraction of information from the multi-scale ontology supports the presentation of the data in the multi-scale environment. In this approach, exploiting a graph representation of the ontology, relevant items are identified as results of queries to the ontology. In the following, the overall process starting from the generation of the ontology until the extraction of information for the multi-scale environment is briefly described [150]:

- First, *multi-scale biomedical knowledge is encoded* in an ontology [13], implemented in OWL [45]. It stores initially *common knowledge* consisting of:
  - Conceptual hierarchies, e.g. human anatomy, patient information, data, acquisition techniques, visualization properties, degradation process features and sources of evidence.
  - Relations between these concepts: patients undergoing acquisitions sessions, causal relationships between DPFs. The causality previously indicated between DPF and SOE is modeled as OWL axioms, which allows to interconnect concepts.

- Second, the ontology performs *the management of data*. The ontology starts to act as a medical data repository by instantiating the corresponding classes of the ontology. This allows to record systematically the knowledge and data about a given patient, e.g. the undergone acquisitions, the acquisitions protocols indicating which acquisition sessions were performed, the data sets which were acquired and the anatomical entities they represent, and relations of data sets to sources of evidence which they hint to.

- Third, *semantic querying* is performed to obtain information from the ontology. SPARQL (SPARQL Protocol and RDF Query Language) is an ontology querying language, which uses graph pattern matching techniques to evaluate answers [172, 194]. Another variant is to transform the populated ontology into a directed graph and then extract context information by using graph traversal techniques starting from the seed node provided by the user [150]. Finally, the graph representation of the query contains nodes instances as well as inferred relations between them.

  Queries to the ontology can retrieve all the relevant information of a given patient for the representation in the visualization environment. Examples (expressed in English language) are "Which are all the *Data* that concern a specific *patient*?"), and the techniques used ("Which is the *technique* that obtains specific *Data*?"). For a complete illustrative example, see the next subsection.

  Note that extended details of the features of the multi-scale ontology system are not the scope of this work. They can be found in the work titled "Multi-scale biological knowledge formalization: definition, properties, and applications" [34].

- Finally, the exploratory system carries out the *obtaining of requests for the visualization composition*. Answers to queries are represented as subgraphs, and are encoded as JSON documents (Fig. 4.9) [33]. They are served to the exploratory system in order to create the visualization scene (more details in Sec. 4.5).

Example

The support provided by the ontology allows for obtaining all necessary visualization parameters for positioning the different spatiotemporal data sets on the scene and their proper representation. Examples of those queries related to visualization (expressed in English language) are "In which *Spatiotemporal scale* a given *DPF* is placed?", "Which *Visualization technique* visualizes the given *Data*?"). Accordingly, in the visualization environment, the data sets are positioned on the corresponding layer and rendered by a concrete rendering worker type (c.f. Sec. 4.3).

In order to illustrate this support, consider that the knowledge depicted in Fig. 4.10 is formalized, as described previously in this section (c.f. Fig. 4.7).

```
{
    "directed": true,
    "graph": [],
    "links: [
        {
            "source": 0,
            "target": 1,
            "type": "is a"
            "uri": "http://www.w3.org/1999/02/22-rdf-syntax-ns#
                type"
        },
        ...
    ]
    "nodes": [
        {
            "id": 0,
            "abstract": "True"
            "label": "Femur",
            "uri": "http://www.multiscalehuman.ch/ontology/
                Femur"
        },
        ...
    ]
}
```

Figure 4.9: JSON representation of answer to the query (source [150]).

This figure represents some factors involved in the degradation of articular cartilage during osteoarthritis. As indicated previously, each DPF is evidenced by SOEs and those are measured by certain techniques. The data are also classified according its spatiotemporal scale.

Subsequently, data regarding a patient is provided to the ontology. For instance, "Patient 231086" has undergone different acquision sessions (e.g. MRI, gait pattern) and different analyses have been performed (e.g. molecular, celular and tissue analyses of his damaged meniscus). The techniques used to obtain the data are:

- Knee angle patterns during gait analysis.
- EMG during gait analysis.
- MRI scanning.
- Nano-indentation of cartilage of meniscus.
- Histological analysis of cartilage.
- Live/Dead cell analysis, for analyzing the metabolic activity.
- Polymerase chain reaction (PCR), for analyzing the gene profile, at molecular level.

Figure 4.10 indicates the SOEs measured with the aforementioned techniques, the DPFs evidenced with such SOEs, as well as the spatiotemporal scales in which those DPFs take place. For example, an excerpt of the multiscale knowledge is expressed in English as: "Patient 231086 is a patient which concerns the following Data: MRI 231086, EMG231086, KneeAngle231086, Histology231086...".

The query expressed in English as: "Which are all the Data that concerns Patient 231086?" is expressed in SPARQL, which evaluates queries by using graph pattern matching techniques (Fig. 4.11) [172]. The results of these queries are used to identify semantically relevant items to support visualization, shown in [35].

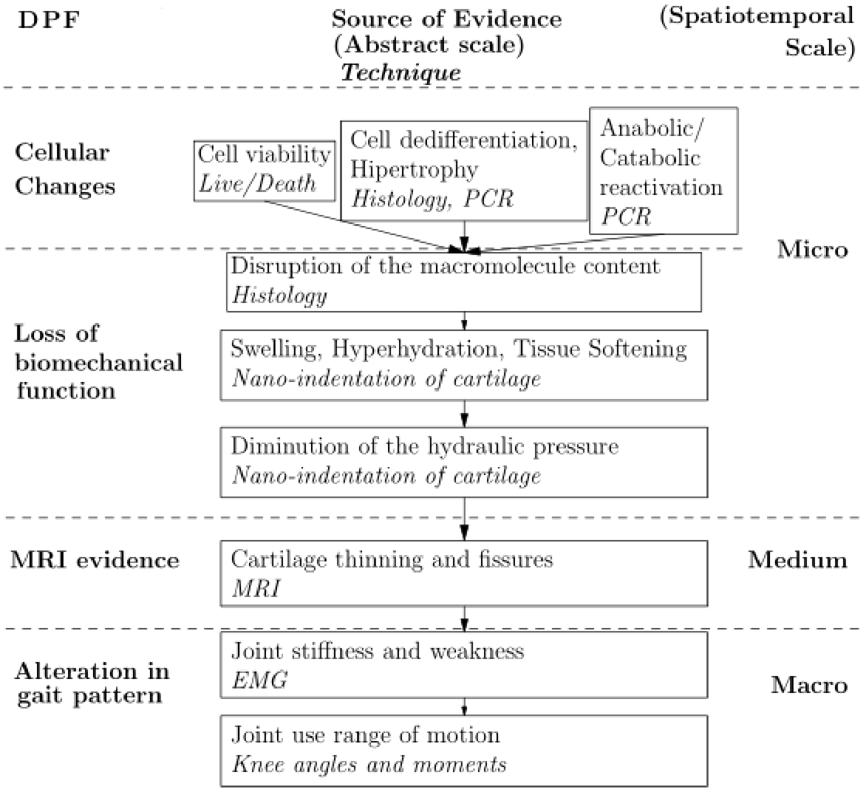


Figure 4.10: Some factors involved in the degradation of articular cartilage during osteoarthritis. Each DPF is placed on a corresponding spatiotemporal scale, and is evidenced by several SOEs, which are measured by certain technique (source [35]).

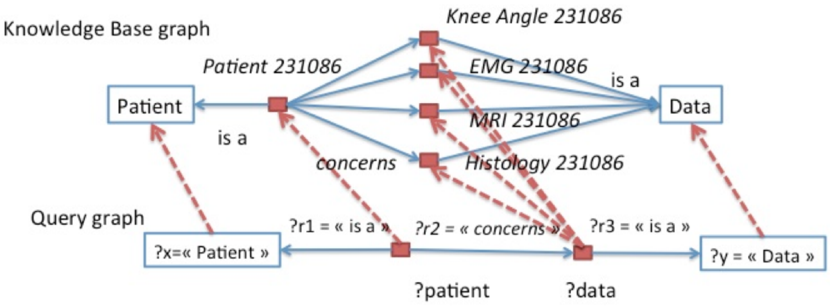


Figure 4.11: SPARQL evaluation of the query "Which are all the Data that concerns Patient 231086?" (source A. Agibetov in the context of [35]).

Figure 4.11 is an example of a graph pattern match from the "Query graph" to the "Knowledge Base graph". Note that bound variables were matched exactly ones and to the nodes with the same value. Also note that since the variable "?data" is unbound, then it could be matched to any of the "Knee Angle 231086", "EMG231086", "MRI231086", "Histology231086". Therefore there are four possible pattern matches. By means of this illustrative query, all the data regarding the patient have been retrieved for its visualization.

Consider a visualization scene of representing data of the patient "Patient 231086" by a user with the "Tissue Engineer" profile. In the following, queries are analogously matched and their visual results are presented during the visualization scene composition.

First, the data of the patient is obtained, as detailed above (Fig. 4.12). Next, the visualization techniques of the data are obtained (Fig. 4.13), therefore allowing the visualization system to process their presentation. Figures 4.14- 4.16 illustrate the obtaining of the corresponding SOE and DPF related to each data set, moving upward in the conceptual hierarchy by means of the relations of the ontology among these concepts depicted in Fig. 4.10. Subsequently, the spatiotemporal scale related to each data set is obtained. Thus, the visualization system can place the respective data sets on diferent layers, as described in Sec. 4.3. As the user profile is "Tissue Engineer", the focus layer is the micro-scale, the context layer corresponds with medium-scale and the background is the macro-scale. Finally, Figs. 4.17- 4.19 introduce by means of arrows the relations between the sources of evidences which proof the different cartilage degradation process features represented by the available data sets.

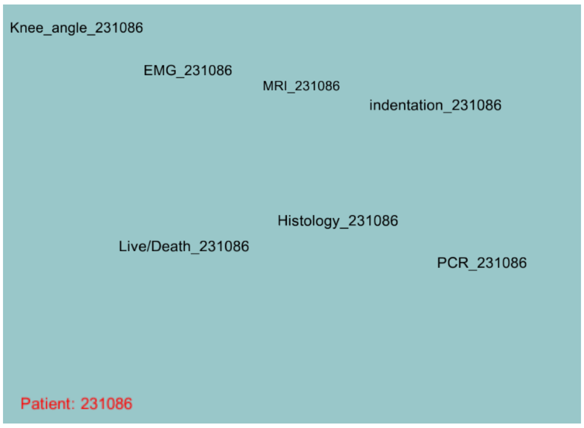


Figure 4.12: 1. - Which are all the data that concerns Patient 231086? (source [35])

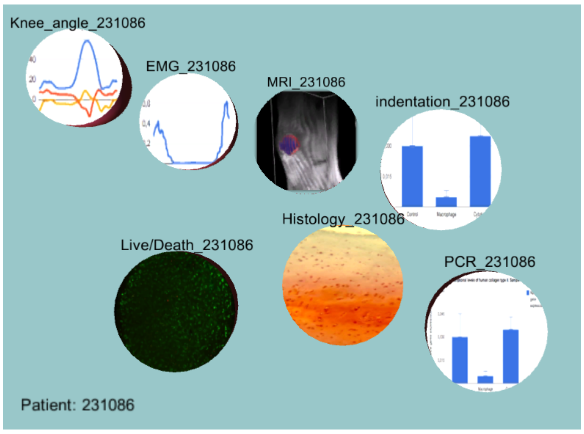


Figure 4.13: 2. - For the previously obtained data, what are the visualization techniques which visualize them? (source [35])

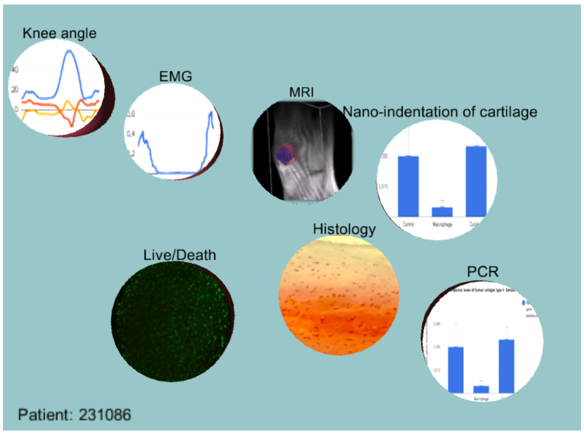


Figure 4.14: 3. - By which technique were the data in question obtained? (technique accordingly to Fig. 4.10) (source [35])

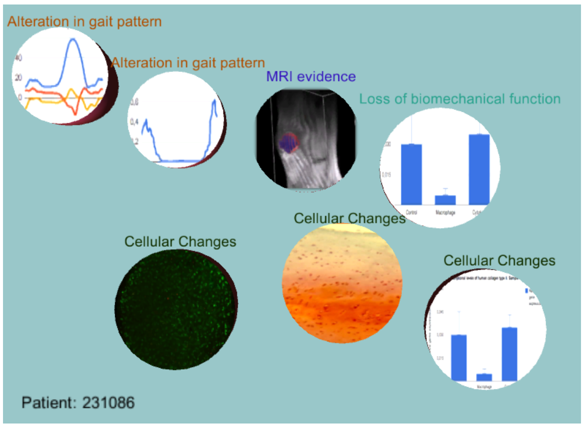


Figure 4.15: 4. - For the previously evaluated techniques, which SOEs did they measure? And for those SOEs, which DPFs did they evidence? (source [35])

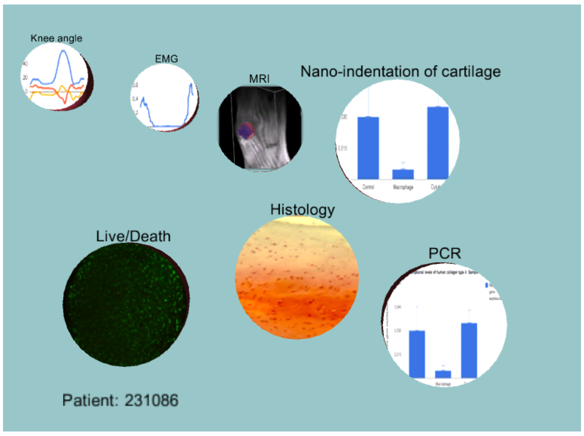


Figure 4.16: 5. - For the obtained DPFs, which are the spatiotemporal scales they are placed? (source [35])

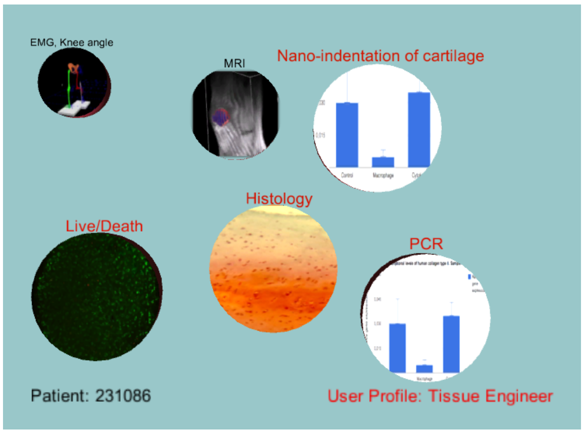


Figure 4.17: 6. - Filter only those DPFs that are of interest for a "Tissue Engineer" (source [35]).

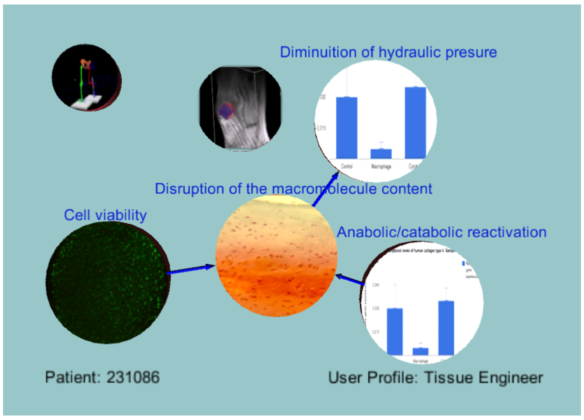


Figure 4.18: 7. - Extract the relationships "causes" between SOEs (c.f. Fig. 4.7) (source [35]).

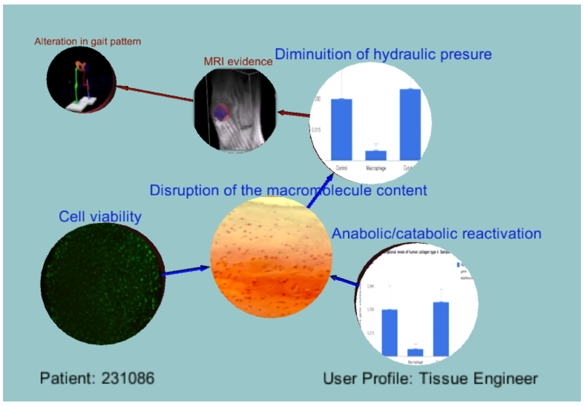


Figure 4.19: 8. - Extract the relationships "causes" between DPFs (c.f. Fig. 4.7) (source [35]).

4.5 ARCHITECTURE

The overall exploratory system is specifically designed to be used by several users working remotely with large amounts of biomedical data. Its underlying architecture addresses portability and multi-platform design requirements as well as network data transfer (streaming and caching) [192]. The distributed rendering scheme and the interconnection with the multi-scale ontology allows the subsequent composition of the visualization scene.

Overall architecture

The visualization environment accesses various network resources in order to provide the scene to the user. In order to perform the composition of the scene, the system connects with the multi-scale ontology, the data repository and the distributed rendering system (Fig. 4.20).

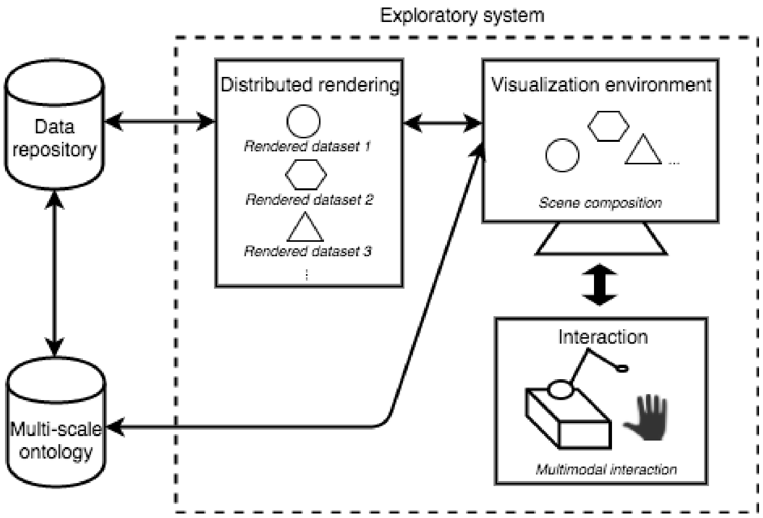


Figure 4.20: Overall architecture.

The *visualization environment system* has been realized by means of a thin client which connects network resources. Consequently, the system can remain scalable with respect to an increasing number of simultaneous users as well as with respect to the complexity of multi-scale data sets. The visualization environment, developed under the multi-platform Unity software framework [104], allows the user to employ it in different desktop platforms or other devices.

Requests to the *multi-scale ontology* yield all relevant multi-scale biomedical information (e.g. location of resources, visualization properties of resources) of a biomedical case to present to the user (c.f. Sec. 4.4). Those requests constitute the first step in order to create the visualization scene.

The *distributed rendering system* generates the visualization scene from several data sets rendered on separate rendering worker entities. Thus, the system is able to deal effectively with massive data sets. The visualization system connects to a rendering worker entity, which renders the data set and sends it to the multi-scale environment.

The *interaction system* provides the multimodal interaction involving a combination of hand gestures, haptic interaction and traditional input. It constitutes a part of the exploratory environment and is described briefly in Sec. 4.9.

Architecture of the exploratory system

In the following, the architecture of the exploratory system is described more in detail (Fig. 4.21). The *visualization environment* system connects with the *multi-scale ontology* through encrypted HTTPS protocol to ensure the security of the connection. As a result of each query, a JSON document is returned consisting of a list of data sets (each representing data from a single acquisition) together with, among other properties, the corresponding location of such resources in the *data repository*.

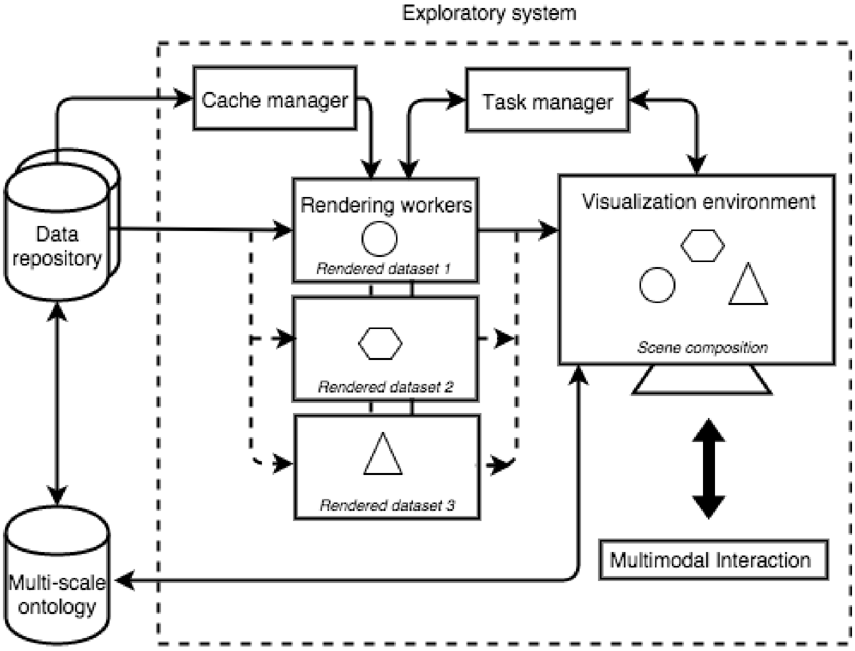


Figure 4.21: Architecture of the exploratory system.

Those data sets are going to be generated by means of the *distributed rendering system*. Thus, the visualization environment connects to a *rendering worker* entity, which acts as an active proxy between the visualization environment (client) and the data repository. An appropriate rendering worker according to the type of data set subsequently renders it and sends it to the environment for the composition of the visualization scene.

Rendering workers can support different types of rendering (Fig. 4.22):

- *3D workers* render volumetric representation of data sets. This group of workers receive as input the location of resources and visualization

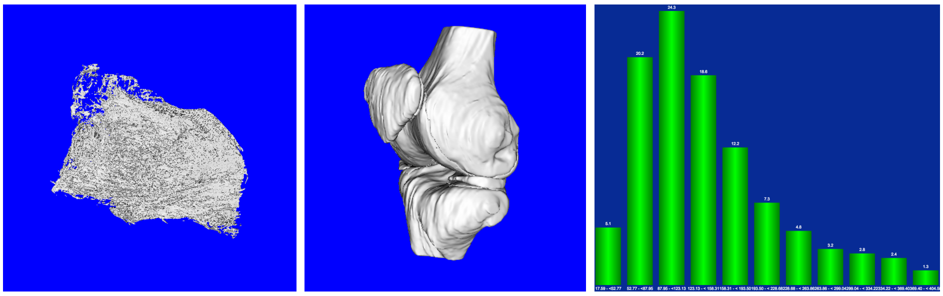


Figure 4.22: Examples of renders performed by several rendering workers: *STL worker* representing a part of the cartilage of meniscus, *VTK worker* representing a knee joint, *InfoVis worker* representing the pore size distribution of cartilage. Note that the background is going to be transparent when inserting those renders in nodes.

and view parameters, and returns the image of the file already rendered. Regarding their implementation, workers were developed by employing the open-source toolkit VTK [23] for Cocoa (native API for the OS X operating system) under the IDE XCode [26]. Three types of 3D workers have been developed so far:

  - *DICOM worker* reads the format file standard in medical imaging DICOM [28] and renders it. The worker is adapted for reading the stack of files from CT, MRI and for performing the ray casting algorithm.
  - *VTK worker* reads and renders VTK file formats. Those formats offer a consistent data representation scheme for a variety of data set types, including texture and volumetric data [24].
  - *STL worker* reads and renders the STL file format [20]. STL defines the surface geometry of 3D objects, and is widely used for producing models or prototypes in computer-aided manufacturing and 3D printing.

- *InfoVis workers* render files with InfoVis content. It has been developed under the InfoVis toolkit [78], and uses Chromium [2] as HTML rendering engine.

- Other workers are *Image, SetImage and Temporal workers*, rendering images, groups of them, and videos, respectively. These rendering workers, which do not require extensive computational power in comparison with the rendering of volumes, are directly integrated as a part of the visualization client.

The central part of the architecture is the *visualization environment* (c.f. Sec. 4.3). The decision to build upon the framework Unity was made in order to address multi-platform and scalability challenges. Unity is well known for its lightweightness, modularity and extendability [234]. In addition, the portability between platforms favors the use of the system in whatever environment where the different users are, independently from operating system (e.g. PC, Linux, Mac, iOS, Android) or hardware (e.g. 3D screen, 2D screen, portable tablet devices).

Note the correspondence between the types of rendering workers here described and the nodes - objects of the visualization environment (c.f. Sec. 4.3). The nodes of the scene request the rendering and subsequently encapsulate the results performed by the different rendering worker entities. The nodes generate the request by means of an Uniform Resource Identifier (URI) including location of resources and visualization properties (Code 4.1). With this approach, the visualization environment system does not try to download massive data sets from the data repository and render it. Instead, the processing power needed to render complex and large data sets is parallelized between different rendering workers, which can run on different machines.

```
scheme://host:port/path?query

http://localhost:8081/_stl/cartilage.stl?view_parameters;resolution_x;
    resolution_y
```

Code 4.1: Generic syntax of URI and application to a rendering request.

Following up with the description of the elements of Fig. 4.21, the *task manager* monitors the use of rendering workers' resources and balances the load of rendering requests from the visualization environment. This is especially relevant when interacting with contents. For instance, moving or applying zoom-in on a content or several contents might imply new renderings. Referring to the example depicted in Fig. 4.23, the manipulation of a node in the scene causes the generation of hundreds of new URL

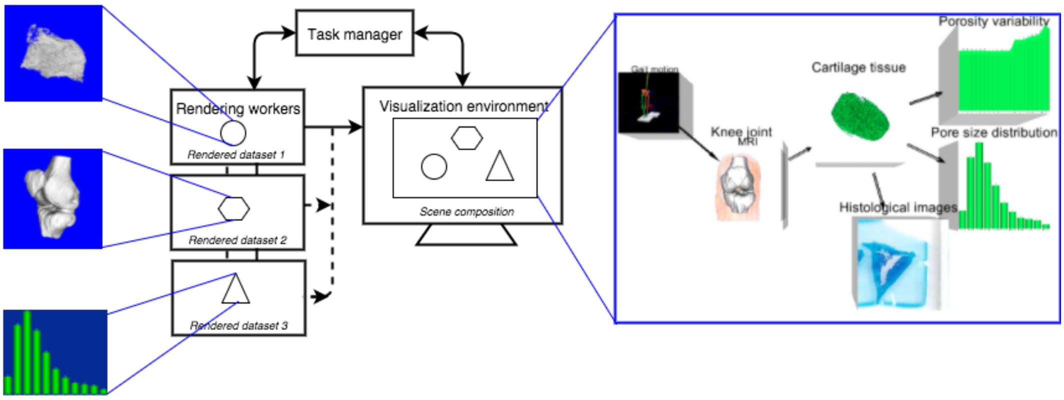


Figure 4.23: Rendering workers and visualization composition in the architecture of the exploratory system.

requests. This rendering is fast enough such that the user perceives an effective interaction (c.f. Sec. 2.1.1).

The *cache manager* stores data that had been requested by rendering workers before, in order to avoid the misuse of processing power. Data repositories can be spread geographically, so that data are stored as close to the rendering workers as possible, within the limit of the local area network, in the way similar to web proxy servers.

Composition of the visualization scene

In the previous subsection, the description has been focused on the distributed rendering process in the exploratory system. However, parameters which classify the data (c.f. Sec. 4.2) and have been saved in the multi-scale ontology (c.f. Sec. 4.4) participate also in the creation of the visualization scene (e.g. selection of the rendering technique, position of nodes on the layers). In the following, the whole process of composition of the scene from information obtained from the multi-scale ontology is described [150] (schematically depicted in Fig. 4.24).

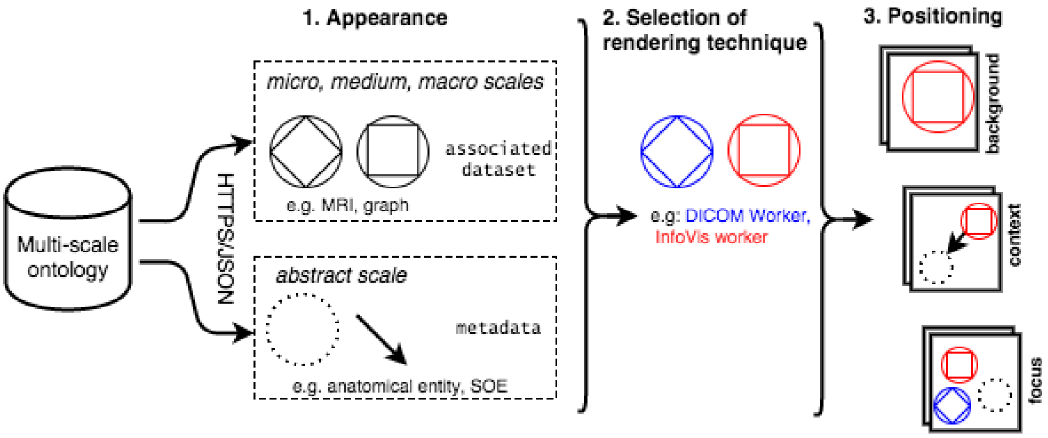


Figure 4.24: Process for the visualization composition (source [150]).

- *Appearance of multi-scale data sets*

  Initially, the collected information from ontology in the JSON document is visually displayed in the multi-scale visualization environment by means of nodes or visual links (c.f. Sec. 4.3) according to the attribute *spatiotemporal scale*. Data sets from *micro-scale*, *medium-scale* and *macro-scale* have a visual representation as nodes. Those diverse nodes encapsulate diverse types of data (2D, 3D, InfoVis...) consistently for a simultaneous exploration of heterogeneous data. Each node has an associated URI leading to a related data set, which is retrieved in the data repository and requested to be rendered by a rendering worker entity. On the other hand, information from the *abstract scale* can be used for representing nodes or for the creation of perceptual cues in the relations between such nodes in order to enrich the understanding of the complete collection of data. They can have a node representation, e.g. nodes with a neutral representation and a label are used to represent anatomical entities, or an arrow representation which links nodes in order to indicate semantic relations across data sets, e.g. causes between SOEs and DPFs (Fig. 4.25). Examples for visual cues include:

- Colored arrows between nodes indicate relations between nodes, e.g. causes between SOEs in the cartilage degradation process.
- Tooltips provide additional information, e.g. on the acquisition protocol performed to obtain the data set.

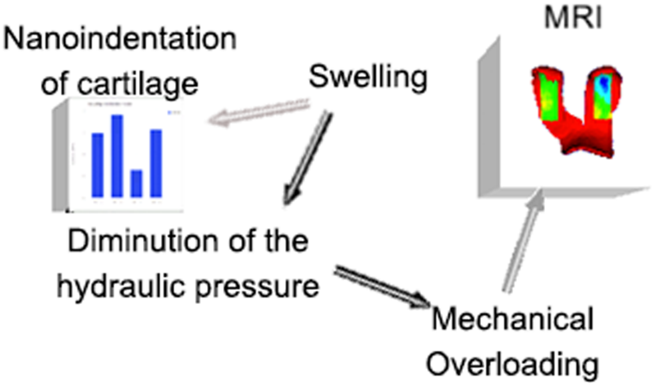


Figure 4.25: Extended view of the resulting visualization (source [150]).

- *Selection of the rendering technique*

  Subsequently, data nodes are rendered by an appropriate rendering worker entity (e.g. *3D, Infovis workers*) according to the visualization parameters. The visualization system identifies the visualization technique and settings to be used from the description of the data as inferred from the ontology.

  The obtaining of the visualization suitability of a given data set can be defined by the mapping [150]:

$$(AP, PD, CP, DR) \mapsto (VT, S),$$

  where the entries in the tuple on the left denote the acquisition protocol, the processed data, the calculated parameter values and the data representation, respectively. Similarly, the tuple on the right hand side denotes the visualization technique and settings.

  For instance, in Fig. 4.25, the femoral cartilage thickness is visualized as a manifold surface mesh obtained after processing a MRI scan. Here DR=*ManifoldSurfaceMesh* and PR=*CartilageThickness* leads to VT=*VTKViewer* and S=*Colormap*. Therefore, a *VTK worker* is employed with visual settings for using a color map to indicate thickness in the cartilage.

- *Positioning of data sets*

  Finally, the visualization scene is created and nodes are positioned on the multilayered environment (c.f. Sec. 4.3). The layers encompasses nodes with the same spatial scale. The allocation of a node on a layer depends on the spatiotemporal scale of the data set and the interest of the user in that scale (attributes *spatiotemporal scale* and *user profile*) (c.f. Sec. 4.4). Nodes on focus layer are visualized on the foreground, constituting the main scale of interest for the user; nodes on the context layer are placed behind, aiming to provide context to the data on the focus layer; and nodes on the background complete the general view across all the spatial ranges.

4.6 EXAMPLE OF USE: ANALYSIS OF MUSCULOSKELETAL DISEASES

The study of diseases affecting the musculoskeletal articulation, such as osteoarthritis of the knee joint, requires a challenging visualization of biomedical data (c.f. Sec. 2.3.1), demanding both the multimodal and multi-scale requirements (c.f. Sec. 2.3.2). Data are acquired from different acquisition modalities and distributed over multiple spatial scales: The gathered data sets can contain, among others, chondrocytes death analyses of the meniscus (cellular scale), MRI and CT images of the knee joint (organic scale) and gait pattern analyses (behavior scale). The data extracted from such acquisitions has not only different spatial dimensions, but also diverse visualization properties: Some of these are presented as 3D models, images or through InfoVis representations, such as graphs or diagrams. The data collection and analysis require experts from different specialties: Biomechanical engineers, radiologists and tissue engineers contribute with their data and expertise.

The presentation and exploration of this plethora of information quickly becomes complex for any specialist working on the biomedical case. First, experts use isolated systems allowing only the exploration of features involving a concrete specialty and scale but not the complete picture. Second, the existing multimodal exploratory systems are based on traditional standard interfaces, which do not allow a flexible exploration of multi-scale data. For instance, radiologists analyze the MRI by using 3D volumetric viewers, and separately tissue engineers make use of data analysis tools. And finally, specialists lack of an exploratory environment to efficiently support the analysis of causality across evidences from different scales (c.f. Secs. 2.3.3, 2.7).

The example focuses on the workflow of the biologist investigating osteoarthritis. Based on established knowledge about the pathology, the biologist formulates and validates hypotheses using the evidences obtained in the experiments by means of quantitative methods and statistics. However, the visualization employed during the traditional exploration methodology (described later in this section) does not facilitate this task, as after performing such experiments and statistical analyses, current visualizations to explore data do not constitute an effective tool for the observation of the complete collection of evidences and results encompassing all the data involved.

In the following sections, the example of use is described. First, the essential features of osteoarthritis are described. Second, the traditional methodology of investigation applied by biologists is summarized. Finally, the aforementioned methodology will motivate the proposal for an integrated exploratory system for automatizing the organization and exploration of experimental data applied to the example [150].

Osteoarthritis as a multi-scale pathology

Osteoarthritis is an example of hierarchical pathology of multi-scale nature (c.f. Sec. 2.3.2). Degradation features at the cellular level propagate upwards through molecular, macromolecular, and tissue level, causing finally the alteration in gait pattern [38, 88]. It firstly and mostly affects the articular cartilage, causing its complete degeneration [88, 107].

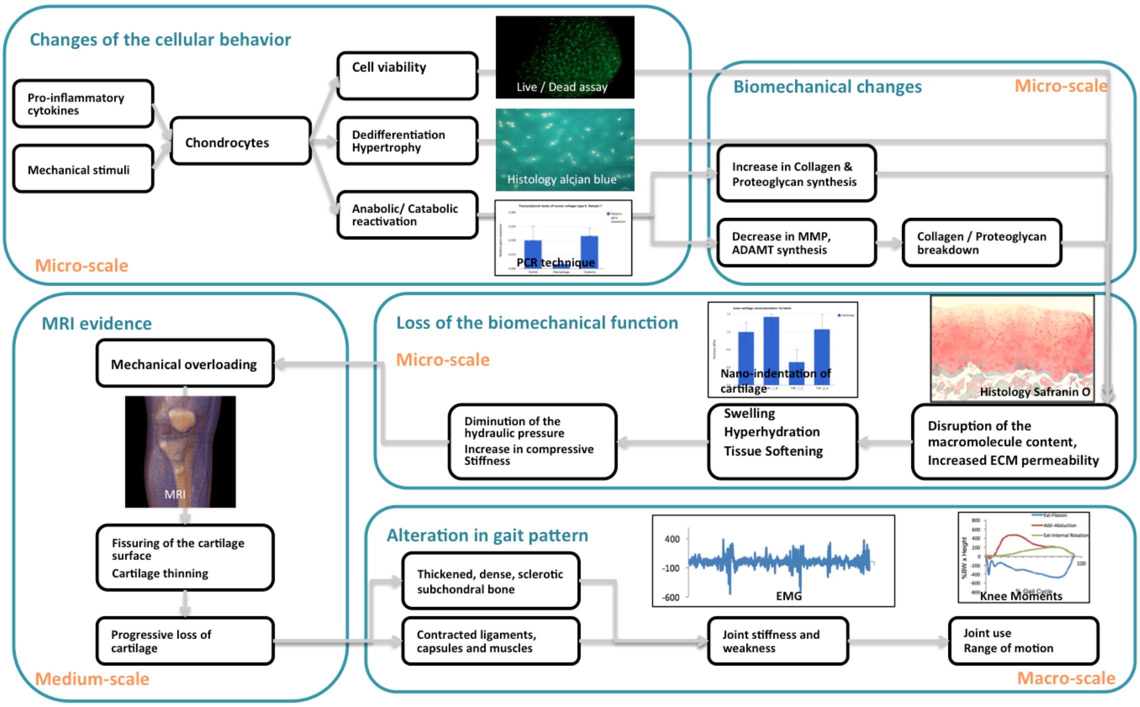


Figure 4.26: Degradation of articular cartilage during osteoarthritis (source [150]).

The articular cartilage degradation during osteoarthritis is graphically summarized in Fig. 4.26. Changes of the cellular behaviour (e.g. death of chondrocytes, dedifferentiation and hypertrophy or catabolic/anabolic reactivation) is a common feature of an osteoarthritic cartilage [141]. These evidences can be obtained through analysis of cross-sectional histology and cell viability assays [168]. The altered cellular behavior consequently causes the loss of the biomechanical function, due to the disruption of the macromolecular tissue network, which results in increased compressive stiffness and eventually in the softening of the cartilage, evidenced by variations in the mechanical properties, e.g. by using nano-indentation techniques. In more advanced phases the cartilage degradation can also be observed on MRI as thinning and progressive loss of cartilage at the organic scale. Finally, at the behavioral scale, this degenerative process reaches the gait pattern [38], causing weakness or overactivation of certain surrounded muscles, evidenced by electromyography (EMG). These facts lead to variations of joint stiffness and range of motion of the knee.

Traditional methodology of exploration

Initially, the biologist speculates with a hypothesis regarding the osteoarthritis and its cartilage degradation. An example could be the following [150]: "The cytokine induced cell death and shift in metabolic activity will result in the disruption of ECM integrity and inappropriate mechanical function of the cartilage." Such a hypothesis requires the investigation on several information sources, and their established relationships have to be considered. In the given example, the cell death has to be investigated on live/dead and histological assays, while the degeneration of cartilage can be seen on histology as well as on the MRI at the organic scale.

In order to analyze the validity of such a hypothesis, numerous acquisition sessions are performed (e.g. MRI of lower extremity, and micro-CT and cross-sectional histology of meniscus), producing a large amount of multi-scale and multimodal data.

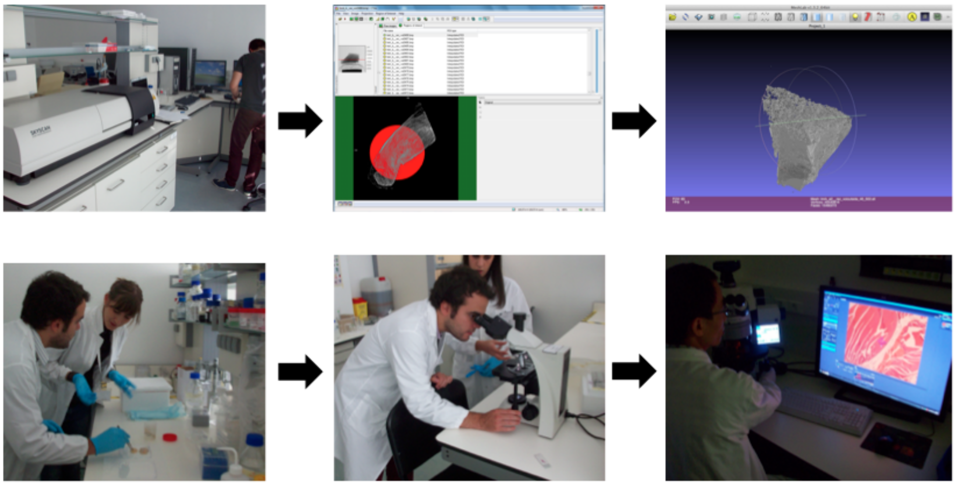


Figure 4.27: Examples of traditional methodology of exploration. At the top, acquisition of micro-CT of meniscus (scanner SkyScan [19]), obtaining of structural properties (with the software CTAn [3]) and visualization of 3D mesh model (Meshlab [11]). On the bottom, preparation of cartilage slices, and acquisition and visualization of histological images. Those both pipelines of different sources do not converge.

During the analysis of the acquired data, some data are processed (e.g. segmentation of MRI scans for 3D reconstruction of bones), allowing for obtaining several charaterization parameters (e.g. structural properties such as cartilage thickness from a 3D mesh modeling patient's meniscus). The analysis of the biologist are manually registered in a log book including the protocols, the steps of their optimization and also the results. This process of data collection is very time-consuming, and as a consequence of the heterogeneity of the data sets, which are often treated separately from each other, the results may be misinterpreted or treated without taking all the aspects into consideration (Fig. 4.27).

In order to interpret the data, the biologist first performs a statistical analysis and then evaluates if the acquired data supports the assumption. Only after the assessment of all data, the given hypothesis may either be supported by the data that satisfies the causality assumptions, or may be refuted.

The visualization systems used for such analyses are isolated and allow the exploration of features involving a concrete data type. However, the presentation of the complete collection of information sources to one single view is not possible. Moreover, the established relationships among different parameters obtained from the data sets are only in the log books or in biologist's mind, but not together with the data sets in one picture.

Proposed exploration

Addressing the lack of a global exploration in the traditional approach, the framework proposed in this chapter allows a direct and meaningful exploration of all related data sets of interest for the biologist during the analysis of hypotheses in osteoarthritis.

In the following, the process flow until the presentation of the data is summarized. Heteregeneous data are classified according the parameters referred in Sec. 4.2. This information is stored in the multi-scale ontology, which supports the visualization, as detailed in Sec. 4.4. The architecture makes feasible the extraction of information from the ontology as well as the distributed rendering, as indicated in Sec. 4.5. Finally, the visualization environment, presented in Sec. 4.3, allows the presentation of information sources from the entire range of scales and their known relationships.

First, *heteregeneous data are classified* according to the parameters referred in Sec. 4.2. Each DPF, denoted by large oval boxes in Fig. 4.26, such as "loss of biomechanical function", is evidenced by several SOEs, e.g. "swelling". Moreover each DPF is typically placed on a specific *spatiotemporal scale* (indicated with orange font). The arrows indicate how SOEs affect each other. Finally, some SOEs are associated with corresponding techniques, e.g. "nano-indentation of cartilage".

Second, all this information is stored in the *multi-scale ontology*, as detailed in Sec. 4.4. The information is categorized identically as in the example depicted in Fig. 4.10; Fig. 4.26 constitutes an evolution of the previous figure including a more complete number of factors involved in the articular cartilage degradation during osteoarthritis. Thus, the multi-scale biomedical knowledge consists of the features of the degradation process, their

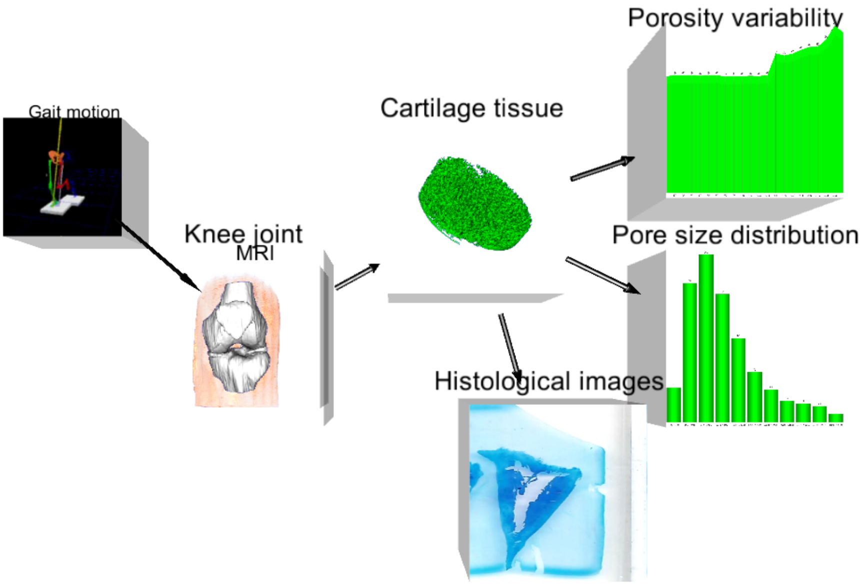


Figure 4.28: Example of multi-scale visualization environment for exploration of multi-scale data of knee joint.

relationships and the aforementioned information sources as evidence of the features, as depicted in Fig. 4.7.

Third, the *architecture of the exploratory system* makes feasible the extraction of information from the ontology and the composition of the visualization scene. Thus, features such as location of resources, visualization techniques and settings are sent to the distributed rendering scheme, which performs the rendering of the data sets (c.f. Sec. 4.5).

Finally, *the visualization environment* (c.f. Sec. 4.3) allows the presentation of the data sets from the entire range of scales as well as their known relationships needed to be explored (Figs. 4.28- 4.33). The 3D multilayered visualization environment presents the data sets as a network of spatially distributed and interconnected nodes. This allows the simultaneous access, proper visualization and natural exploration of heterogeneous data across domains of medical knowledge, facilitating the task of a specialist to explore hypotheses from a large perspective, as visual results from the performed analyses can be presented in one single environment. This kind of view also contributes to the formulation of new hypotheses, which would lead to perform new quantitative and statistical analyses.

In detail, the following figures represent examples of the multi-scale environment with multi-scale data of knee joint. Data coming from cellular, organic and behavior scales are placed on *focus* (knee joint, 3D reconstruction of micro-CT scan of cartilage of meniscus, graphs associated, and histological images of meniscus), *context* (MRI of knee) and *background* (gait motion analysis) layers.

Data sets from each spatiotemporal scale (i.e. micro, medium and macro) are encapsulated in nodes and positioned on one of these layers, which are distinguished by their z-order. As the user profile is biologist, micro-scale data are positioned on the *focus* layer, constituting the main scale of interest. Medium-scale data is place behind on the *context* layer, and macro-scale data in *background*, which is the last layer, least seen and less important, completing the general view across all the spatiotemporal ranges. The use of this representation alleviates the differences in the order of magnitude of data, and allows the direct extraction of information from the context. In addition, the rendering of data sets in independent nodes allows a consistent representation for heterogeneous data. The abstract scale is represented by arrows in the relations between nodes, indicating spatial origin of InfoVis sources, as well as the hierarchy of evidences which proof the different cartilage degradation process features represented by the available data sets.

The navigation on the environment is immersive, as the environment is shown in stereoscopic and full screen mode, in which data sets encapsulated in hollow cubes can be manipulated by performing actions on the nodes, e.g. motion, rotation (Fig. 4.33), zoom-in/out (see Sec. 4.9).

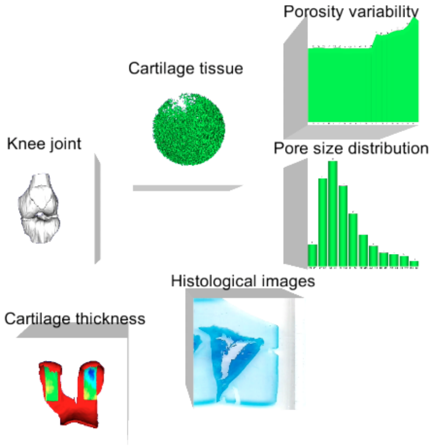


Figure 4.29: Multi-scale visualization environment for exploration of knee joint related data, including only the *focus* layer.

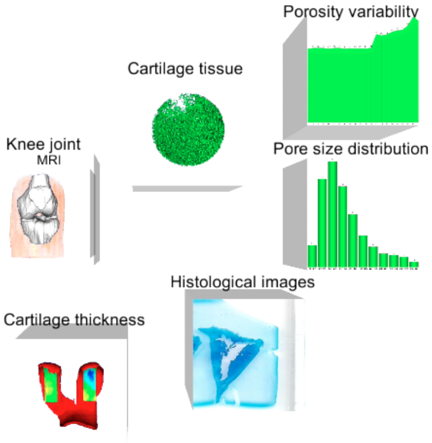


Figure 4.30: *Focus* and *context* layers.

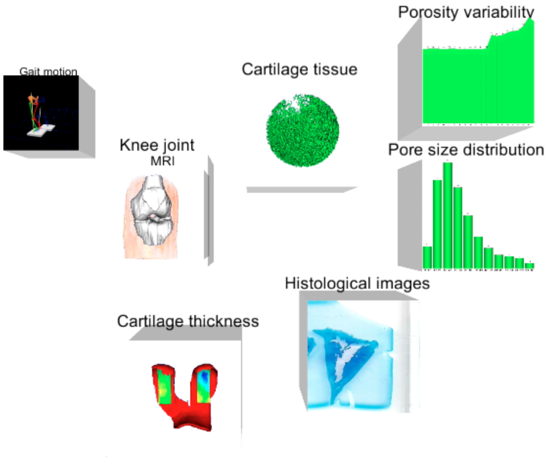


Figure 4.31: *Focus*, *context* and *background* layers.

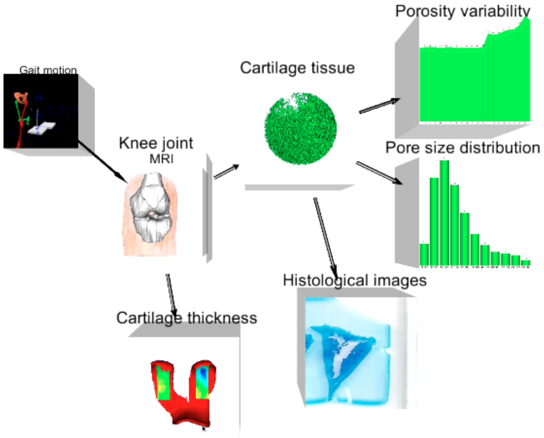


Figure 4.32: Arrows indicating SOEs, DPFs and origin of sources.

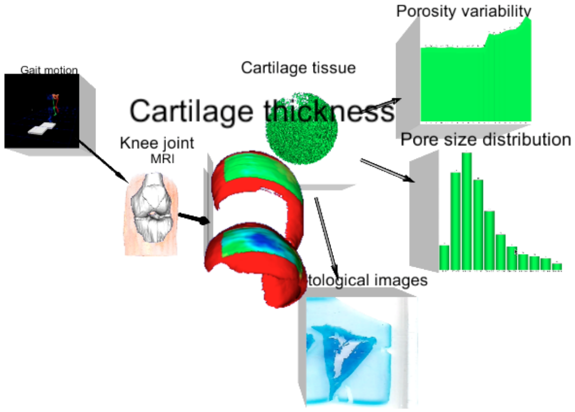


Figure 4.33: Exploration of the cartilage thickness.

4.7 EVALUATION

A controlled experiment was performed in order to obtain initial feedback from the potential users about the visual features proposed within the multi-scale visualization approach. This preliminary evaluation was performed during an initial phase of the development of the environment, which has been published in [192]. This section extends the description of the design of this evaluation and the obtained results.

Purpose

The aim of the experiment was to analyze if and to what extent the proposed visualization features for the multi-scale visualization environment are comfortable to the user with respect to some traditional visualization features, generally used for the exploration of multi-scale biomedical data sets (c.f. Sec. 3.2). The observed features are listed as below in Table 4.3:

Table 4.3: Exploration features under analysis.

Exploration features	**Traditional approach**	**Proposed approach**
E1. Representation of data sets	Tree list structure	Nodes displaying data sets
E2. Container shape of data set	Rectangle	Circle
E3. Transparency of container	Opaque	Semi-transparent
E4. Visualization style	Flat desktop	3D workspace
E5. Preservation of spatial dimensions among data sets	Yes (placeholders)	Not (non-linear depth)
E6. Display technique	3D Monoscopic	3D Stereoscopic
E7. Context preservation among SciVis and InfoVis views	None	Visual links
E8. Context information of data sets	Label description	Visual links

This preliminary analysis of the user comfort with the aforementioned features focuses on the exploration of multi-scale biomedical data sets. Therefore the participants were chosen among scientists which are familiar with the exploration of those biomedical data sets. Those scientists were asked to perform a sequence of tasks related to the exploration of multi-scale data in a controlled protocol, in which different visualization features appeared. The analysis of the users' preference led to point out the convenience and significance of the proposed visualization approaches.

Participant group

The participants were selected among members of the groups addressed in the design of the system. The test group comprised 13 graduates from the fields of: computer graphics (7 participants), biomechanical engineering (4 participants), physics (2 participants). The test group was composed of 9 men and 4 women aged 20 to 31 years (avg. 25.23yr std. 3.14).

The participants were tested for color vision deficiencies via an Ishihara test [110], and no disorders were found.

Setup

The visualization environment was performed on a computer MacBook Pro [10], including external keyboard and mouse. The visualization display was also external, concretely, a passive stereoscopic display Miracube Full HD (24 ″, ratio 16:10 [12]) with 3D glasses. The test was conducted under stable artificial light conditions (Fig. 4.34).

Protocol

Eight scenarios were designed to evaluate each pair of the features directly related to visualization (one extra is related to interaction, giving a total of 9 scenarios, see [192]), defined in Table 4.4. Each scenario was evaluated twice, firstly using a condition associated with the feature A, and then with the feature B, while other conditions remained unchanged during each scenario. All these 16 cases, were performed twice, by using two interaction techniques (mouse and Leap Motion [9]). In the case of the analysis of the visualization, this allows to increase the number of samples for the data analysis. All the participants performed the same set of 32 tasks in a random sequence different for each participant.

During each scenario participants were asked to perform tasks related to the exploration of multi-scale data of the knee joint. The tasks are summarized in the aforementioned Table 4.4. Every scenario was composed of a maximum of 8 nodes containing knee joint data sets from the behavior, organic and cellular scales which had different visualization properties (Fig. 4.35).

Prior to the presentation of the tasks, users were trained on two examples, in order to learn how to perform the experiment. After performing each task, participants gave a comfort score - an integer between 0 and 10 (0 indicating 'extremely uncomfortable'; 10 indicating 'extremely comfortable'). During all the duration of the experiment, users were observed. In addition, after

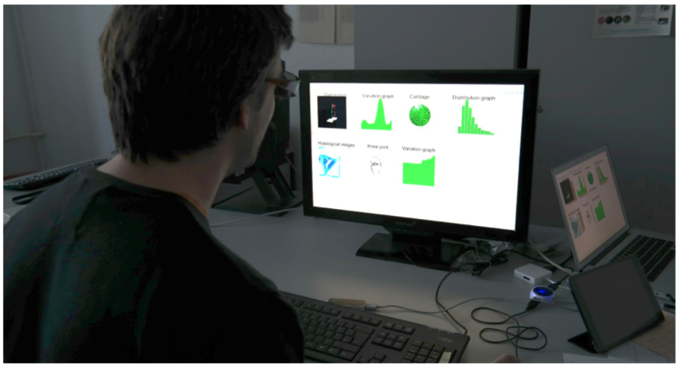


Figure 4.34: Setup presented to the user.

Table 4.4: Description of scenarios and evaluated visualization features (X indicates the pair of features under evaluation).

Cond.	Features		Scenarios							
	Feature A (trad.)	Feature B (prop.)	S1	S2	S3	S4	S5	S6	S7	S8
E1	File tree list	Data sets displayed in nodes	X	B	B	B	B	B	B	B
E2	Rectangle nodes	Circle nodes	A	X	A	A	B	B	A	B
E3	Opaque nodes	Semi-transparent	B	A	X	B	B	A	B	B
E4	Flat workspace	Multilayered workspace (max. 3 layers)	B	B	B	X	B	B	A	B
E5	Linear depth scale and placeholders	Non-linear depth scale	B	B	B	B	X	B	B	B
E6	3D Monoscopic	3D Stereoscopic	B	A	B	B	B	X	A	A
E7	Separated SciVis and InfoVis views	Linked views of SciVis and InfoVis	X	A	A	A	B	B	X	X
E8	Only description of each node	Visual (semantic) links between nodes	A	A	A	A	A	A	A	X

Task of the scenario

S1. Indicate the maximum value of the bar chart.

S2. Find zone in the cartilage.

S3. Find color of the MRI of the leg.

S4. Find the leg which belongs to the knee system.

S5. Find the color of the cartilage of meniscus.

S6. Specify number of vectors seen in the gait motion data set.

S7. Indicate the maximum value of variation during the gait motion.

S8. Find the data set which might be influenced by a problem on the knee system.

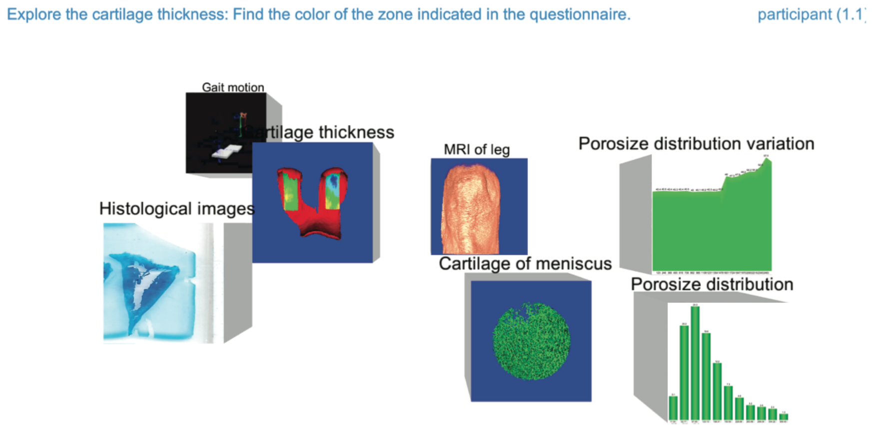
Data sets

- Gait motion analysis (*TemporalNode*).
- Two 3D-representations of knee joint (*3DNode* via DICOM and VTK workers).
- Two set of histological images from meniscus (*SetImageNode*).
- 3D reconstruction of cartilage of meniscus from micro-CT scans (*3DNode* via a VTK worker).
- Two graphs associated to pore size distribution and variation (*InfoVisNode*).

completing the experiment, users answered a written questionnaire in order to assess their comfort with concrete visualization properties (Table 4.5).

Data analysis and results

The scores obtained during the experiment of each user were processed in order to obtain trinary user preference values. The visualization preference was calculated by pairing cases with the same scenario and interaction method, and opposite condition under test. The following rule was used in



Explore the cartilage thickness: Find the color of the zone indicated in the questionnaire.

participant (1.1

Figure 4.35: Example of scenario presented to the user.

Table 4.5: Questions on written questionnaire (selection of preference and justification of answer).

Indicate preference between:
W1. File tree list / Nodes containing data sets.
W2. Cube / Sphere as shape of the node for exploration of SciVis data.
W3. Cube / Sphere as shape of the node for exploration of InfoVis data.
W4. Opacity / Transparency of nodes.
W5. Arrows / No arrows between nodes to understand the scene.

order to determine the preference value: if scores from the two cases have the same value then there is "no preference" else preference was chosen in favor of the case with the higher score. The distribution of preferences of all the participants based on the evaluated conditions is presented in Fig. 4.36.

From the *written questionnaire*, the collected data among the users showed preference for:

- W1. Nodes displaying data sets rather than a tree list structure (75%).
- W2. Cube as preferred node representation figure for InfoVis contents exploration (80%).
- W3. Cube as preferred node representation figure for SciVis contents exploration (70%).
- W4. Opaque nodes rather than transparent ones (64%).
- W5. Arrows between nodes rather than their absence to understand the scene (92%).

Those percentages were calculated from the option chosen (if any) by the participants which made the written questionnaire.

Regarding the last result, the observation of the users during the experiment revealed that the arrows were more useful for the users with no previous knowledge in the concrete scale which was focus of the task. The absence of arrows showed how their actions were based on spatial proximity or experience.

The written questionnaire also indicated the preference of cube as preferred node representation figure for the exploration of both SciVis and InfoVis, independently of the shape of the data sets (InfoVis graphs would fit *a priori* better in hollow cubes; SciVis volumetric renderings, in half-spheres).

The *distribution of preferences shown in Fig. 4.36* points out that the users preferred the proposed visualization for most of the conditions rather than conventional approaches. The preference is more visible in the following exploration features E1, E4, and E5 in which users found appealing the idea of:

- E1. Displaying all relevant data sets rather than a file tree list.
- E4. Multilayered workspace rather than flat workspace.
- E5. Non-linear depth scale rather than linear depth scale and placeholders.

The results also reveals that there is a susceptible lower preference for E6 (3D stereoscopic presentation of content). This might be attributed to the passive polarized stereoscopic technology display used during the experiment. Since this display has narrow vertical viewing angles, the users could have changed their body posture after initial calibration, causing visual discomfort and affecting the preference values.

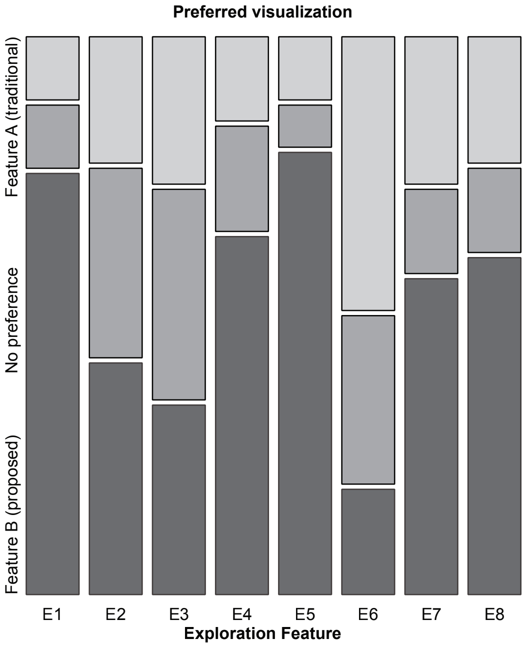


Figure 4.36: Distribution of user preference between the feature in the proposed approach (B) and in the traditional approach (A). Conditions are listed in Table 4.4.

4.8 DISCUSSION

The example of use described in Sec. 4.6 together with the preliminary evaluation of Sec. 4.7 points out the utility of the proposed approach for biomedical specialists confronted with massive amounts of multi-scale data on a daily basis. The multi-scale environment allows the simultaneous access and proper visualization of heterogeneous data across domains of medical knowledge, providing also semantic means to identify items during the exploration, e.g. to spatially observe the relationships among data sets, such as the propagation of the cartilage degradation evidenced in each data set, alleviating specialists' task of organization and understanding data.

This example of used discussed from the point of view of a biologist can be considered to be applicable for other specialists that are working on the exploration of multimodal or multi-scale biomedical data (c.f. Sec. 4.6). While the underlying architecture of the multi-scale environment makes feasible the distributed rendering, the incorporation of semantics allows for the indication of relationships among the data sets, and the integration of both InfoVis and SciVis views facilitates the representation of all the available and relevant data to the specialists.

Another example of use: exploration of dynamic images for functional evaluation and modeling of muscular activity

The multi-scale visualization environment has been also preliminary applied for the exploration of dynamic images for functional evaluation and modeling of muscular activity (Fig. 4.37). This case focuses on the analysis of muscular stimulation in rats by the radioactive PET tracer 11C-acetate [216], made by physicists. In short, a physiological electrical stimulation is delivered to a single muscle in one lower limb of the rat, where the contralateral muscle in the resting leg is used as a reference. The radioactive PET tracer 11C-acetate is injected intra-venous after stimulation, and uPET and uCT scans are acquired. The hypothesis to verify is the distinction between rest and exercised muscle by means of uPET and 11C-acetate.

Figure 4.37 illustrates the use of the multi-scale environment in this scenario. The scene is in this case composed of two layers: On the focus layer, data sets and intermediate analysis results of the stimulated leg of a rat are presented; on the background layer, information regarding the rest leg is shown. The presentation of the different multimodal information (uPET and CT scans including different volume of interests - VOI) are encapsulated in nodes (type *SetImageNode*, note that several nodes are empty due to the lack of information during the time of analysis of such a scenario). In those SciVis nodes representing images from uPET and CT scans, a half-sphere shape has been preferred as it fits with the kind of images obtained. The navigation through those nodes is synchronized, allowing to explore the same slide (spatial region) at different scan analyses instantaneously. On the other hand, InfoVis graphs are encompassed in nodes with appearence as hollow cubes. The arrows indicate the flow of the data processing, starting

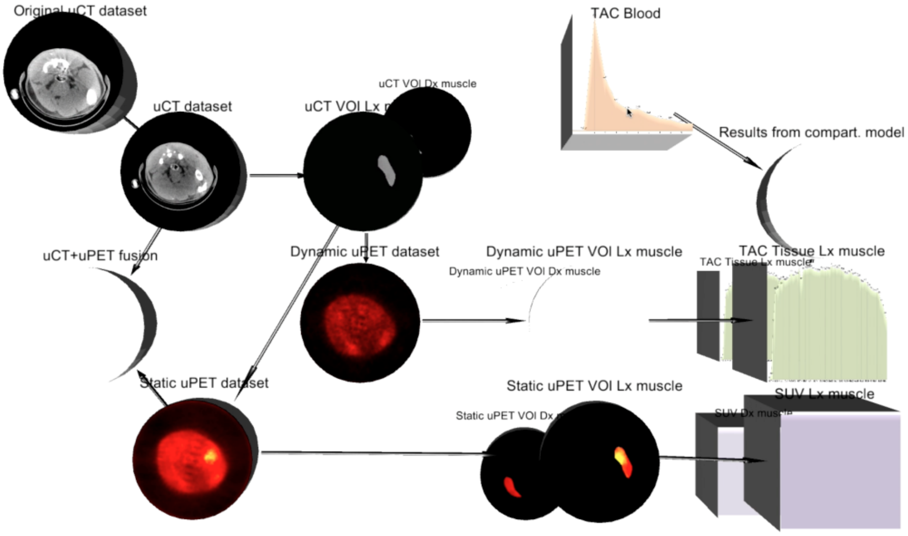


Figure 4.37: Exploration of dynamic images for functional evaluation and modeling of muscular activity [216] in the multi-scale visualization environment.

from original sources and finalizing with statistical data. The presentation of all the data sets in one single view with the aforementioned features can alleviate the exploration of heteregeneous data by the physicist in order to validate the hypothesis.

Moreover, the multi-scale environment remains scalable for the presentation of new subsets of the multi-scale biomedical information and new rendering workers. In any case, new rendering workers do not imply a complete new implementation from scratch. The reuse of existing advanced visualization software as rendering workers implies only minor development of a Remote Procedure Call (RPC) module on their side [52], allowing the obtaining of rendered images according to the view parameters through network. Thus, for extending the system in this regard, it suffices to create new rendering worker types and to include information about its use (c.f. Sec. 4.5). The system would automatize the process of selection of suitable visual properties for the exploration of new data.

4.9 INTERACTION

Interaction and visualization constitute both fundamental components establishing a connection between the user and the phenomenon under analysis running in a computer (c.f. Fig. 2.1). The process of knowledge discovery is intensified when the visualization incorporates a feedback loop based on interaction. The development of the interaction system which allows this feedback loop with the multi-scale visualization environment is not the subject of this thesis. Only for completeness and consistency, the multimodal interaction system developed is outlined. Extended details of its features can be found in the work titled "Multimodal interaction with an integrated visualization system for the analysis of multiscale biomedical data", authored by J. Rzepecki [191].

The described visualization (c.f. Sec. 4.3) uses a 3D multilayered environment for the presentation of nodes encompassing 3D content without a traditional GUI. In this environment data sets resemble a set of diverse tangible objects rather than a directory of computer files. Therefore, the proposed multi-scale visualization requires adaptation and extension of the interaction methods in order to satisfy a coupled strategy of visualization and interaction (c.f. Sec. 3.6). The basis of interaction was defined as a user sitting in front of a 3D stereographic display, which includes a set of interaction devices. The proposed approach employs a combination of 3D stereoscopic visualization and multimodal interaction [191, 192].

Regarding *stereoscopic visualization*, the system utilizes an immersive 3D multilayered environment, which allows the use of (passive and active) stereoscopic displays (Fig. 4.38) [192]. This feature has been implemented with the help of the stereoscopic rendering functionality included in Unity.

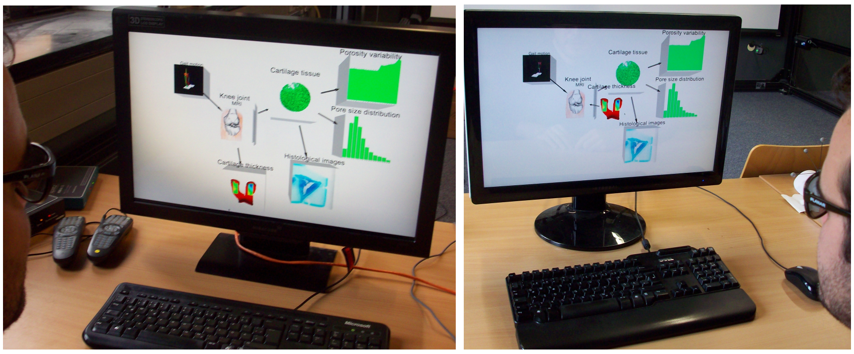


Figure 4.38: Stereographic visualization. Different alternatives: Miracube Full HD [12] and Hyundai W240SL [6].

The *multimodal interaction* approach proposes to replace the primary interaction from the traditional mouse input to hand gestures [191]. The representation of 3D content in the form of nodes with the absence of GUI has led to mimicking traditional interactions means with other strategies towards an intuitive and natural 3D interaction. Thus, actions can be performed by means of *hand gestures*, such as grasping and moving the hand in order to select and move contents of the nodes. In addition, *haptic interaction* allows the user to experience physical feedback of underlying structures from biomedical data. Finally, in order to prevent a lack of interaction tangibility or unavailability of other interaction systems, the use of *traditional interaction* is also allowed as an auxiliary interface. The set of devices which encompasses the interaction approach are depicted in Fig. 4.39.

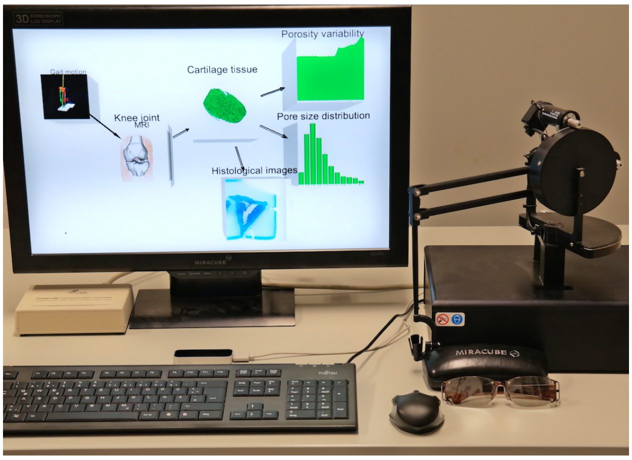


Figure 4.39: Interaction with the multi-scale environment (source [192]), including stereographic monitor (Miracube Full HD [12]) and multimodal interaction: hand gesture device (Leap Motion [9]), haptic interaction device (SensAble Phantom Premium [18]), and keyboard and mouse.

The following sections briefly describe the interfaces and subsequent scenarios:

Hand gesture interaction

Several hand gestures allow the manipulation of contents of the visualization environment [191, 192], including:

- *Grasping and moving* the hand will select a node and will move it in the environment (Fig. 4.40).
- *Two-hand stretching / compressing* nodes will initiate a zooming function for a detailed or more general observation of the content.
- *Pinching with two fingers* will change internal features of a concrete node, e.g. rotate a 3D model in a *3DNode* or change the speed of a temporal data set in a *TemporalNode*.
- *Waving hands horizontally* will clean the central part of the 3D workspace, by moving all nodes to the edges.

The Leap Motion device [9] has been chosen as device for hand gesture interaction. Leap Motion is a high-speed infrared depth camera that has a low-latency data processing and low price [236]. It is especially suited for hand tracking in a working space adjusted for a user sitting in front of the screen. All implemented gestures were designed and implemented according to this assumption.

Haptic interaction

Haptic interaction allows the user to examine concrete biomedical data with force feedback reactions. Haptic interaction provides feedback forces

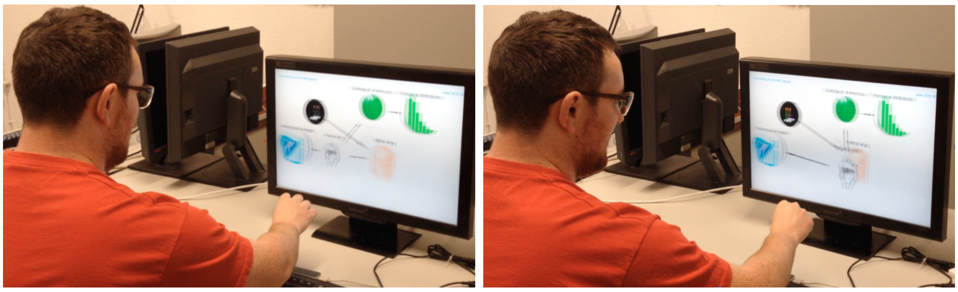


Figure 4.40: Example of grasping and moving a node by using hand gestures [191]. The user is moving the node corresponding to the 3D model of the knee joint.

and torques according to the collision response between the interaction tool in the virtual world and the object (c.f. Sec. 2.5.2.1). The focus of haptic interaction is volumetric data, since it is the most relevant data type to be felt, supplying different feedback forces depending on the properties of the data, e.g. fluid resistance when navigating through soft tissue (Fig. 4.41).

Regarding the implementation [191, 192], a SensAble Phantom Premium 1.5 [18] device has been used. The communication with the Phantom device is performed via a network using a H3D API-based server [17] working on a haptic interface machine. The need of an individual haptic interface machine is required due to the need of high rate control updates and high computational power. The interaction system synchronizes the position of the haptic device and the scene geometry with the haptic interface machine, performing haptic rendering of individual 3D data sets on the haptic machine. The use of another device is possible since the interaction system makes use of the framework H3D API, which supports other haptic devices and manufacturers as well.

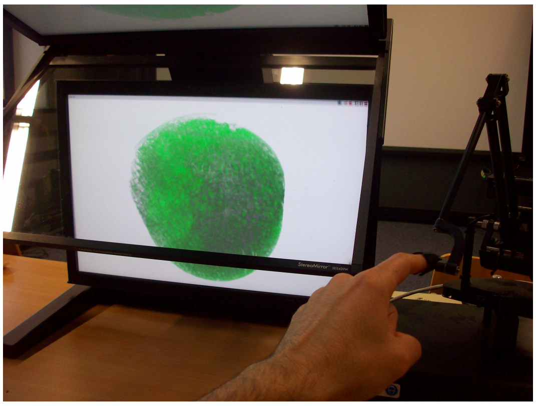


Figure 4.41: Example of haptic interaction with volumetric reconstruction of micro-CT scans of cartilage [82].

Traditional input

Although the multimodal interaction system design emphasizes supporting novel interaction scenarios, it still accepts basic input from mouse and keyboard.

The architecture of the interaction system ([191, 192]) follows the modular principle of the multi-scale environment system. Therefore, it is possible to decouple any of the interaction interfaces from the exploratory environment without loosing its major functionality. For instance, in the situation where none of the main input devices are available, the system provides an interaction method by means of keyboard and mouse input.

5

APPLICATION SCENARIO: HELICAL AXIS DATA VISUALIZATION AND ANALYSIS OF THE KNEE JOINT ARTICULATION

This chapter presents the application of the multi-scale visualization environment and its proposed methodology for the investigation of the knee joint articulation. The use of enhanced intra-scale visualizations specifically developed for the behavioral scale together with the multi-scale visualization environment allows an intuitive and flexible exploration of kinematical and other related data of the knee joint articulation.

5.1 INTRODUCTION

The analysis of human articulation requires comprehensive visualizations for the description of the motion in articulating joints. In this context, the helical axis is a kinematical concept describing the motion of the knee joint [218]. The translation of methods based on this concept to clinical practice has the potential to significantly contribute towards several tasks, such as the analysis of surgical techniques, implant types, and the evaluation of follow–up rehabilitation approaches. Despite the advantages and potentialities of the description based on helical axes, the existing processing methods and visualization techniques are insufficient for these tasks. Concretely, the methods of the **related work** (Sec. 5.2) are lacking in terms of robust analysis capabilities and intuitive visualization:

- A method which calculates stable, valid and smooth helical axes for the instantaneous description of the knee joint motion and subsequent analyses.
- An intuitive and comprehensive visualization of the previously calculated helical axes in terms of bone anatomy.
- An intuitive visualization for an overall comparison of helical axis data across several motion sequences.
- The incorporation of kinematical visualizations in a higher level of framework in order to extend their role on the study of the knee joint articulation, exploring related data sets and their known relationships distributed across multiple spatial scales (c.f. Sec. 2.3).

To those aims, a **methodology** for improving the current state of the art related to the analysis and visualization of helical axis data (see Table 5.1) is introduced in Sec. 5.3. In short, the **representation of motion sequences** of the knee joint is analyzed in a unifying mathematical method based on the **Lie group of rigid body motions and its Lie algebra** (Sec. 5.4). Based on this method, **intra-scale visualizations for accurately interpreting kinematical data** of flexion-extension motion have been developed (Sec. 5.5), concretely, the **anatomical visualization** (Sec. 5.5.1) and the **overall similarity visualization** (Sec. 5.5.2). The multi-scale visualization environment (described in detail in Chapter 4) allows the incorporation of these visualizations in a global framework for the **multi-scale exploration of knee joint data** (Sec. 5.6). In order to exemplarily demonstrate the utility of the proposed methods for the analysis of the knee joint articulation, Sec. 5.7 presents the **results** obtained from kinematical data of experimental sequences and related data sets of multi-scale nature (c.f. Chapter 4). Finally, the chapter concludes with a **discussion** on the results in Sec. 5.8.

Note: The application scenario was studied in a joint collaboration between the Laboratory for Biomechanics and Biomaterials of the Hannover Medical School (LBB-MHH) and the Welfenlab, in which the kinematic experimental set-up was coordinated by Sean Dean Lynch and Dr. med. Tilman Calließ, while Benjamin Fleischer and Dr. Alexander Vais were involved in the preprocessing of data.

Table 5.1: State of art of helical axis data visualization and analysis vs. the proposed approach.

Aspect	**State of art**	**Contribution**
Description of motion based on helical axes	Finite Helical Axis: Imprecise, sensitive to noise [218, 140]	**Method of IHA in terms of Lie algebra**: Valid and smooth helical axes (Sec. 5.4)
Anatomical visualization of helical axes	Lines through 2D sketch of knee [218]: Not intuitive	**3D and patient-specific anatomical visualization**: Intuitive presentation of helical axis data (Sec. 5.5.1)
Comparison of helical axis data	Helical axis parameters along gait pattern [49]: Difficult to analyze overall differences	**Overall similarity visualization based on proposed approach**: Stable and InfoVis analysis among motion sequences (Sec. 5.5.2)
Analysis of knee joint functional articulation and related musculoskeletal diseases	Analysis of behavioral scale do not suffice, not flexible exploration of multi-scale data [86, 164]	**Multi-scale visualization environment** including the previous intra-scale visualizations (Sec. 5.6)

5.2 BASIC PRINCIPLES AND RELATED WORK

In this section, basic principles regarding the description of motion based on the helical axis method as well as their current processing methods and visualization techniques towards the analysis of the knee joint articulation are presented, indicating their shortcomings (Table 5.2).

Table 5.2: Summary of properties regarding the state of art of helical axis data visualization and analysis.

Aspect	**Properties**
Description of motion based on helical axes	Finite Helical Axis: Imprecise, sensitive to noise [218, 140]
Anatomical visualization of helical axes	Lines through 2D sketch of knee [218]: Not intuitive
Comparison of helical axis data	Helical axis parameters along gait pattern [49]: Difficult to analyze overall differences
Analysis of knee joint functional articulation and related musculoskeletal diseases	Analysis of behavioral scale do not suffice, not flexible exploration of multi-scale data [86, 164]

5.2.1 *Description of motion based on helical axes*

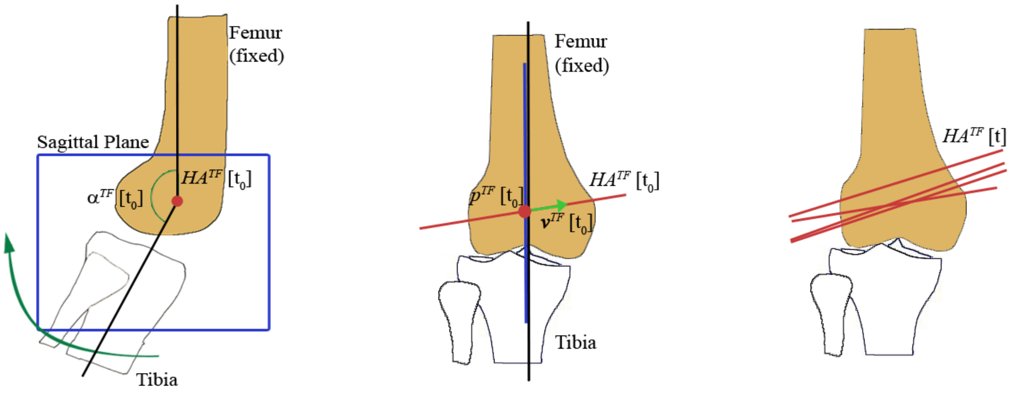
The description of joint motion in biomechanical engineering can be analyzed by several methods, such as Euler angles, Cardan angles or helical axes [184]. For hinge-like joints, such as talocrural and knee joints, the description of motion based on helical axes has been verified to be a valid tool [105]. Regarding the knee joint, its axis of rotation is commonly discussed in order to improve joint functionality and increase prosthesis longevity. The generally adopted method to define this axis depends on anatomical landmarks and is widely considered as a fixed axis to its referenced anatomical landmarks [75]. However, this practice has proven to have inter- and intra- individual discrepancies [224].

The description of motion based on a sequence of helical axes provides a more direct and specific representation of flexion-extension [218], removing repeatability errors [49, 218]. In contrast to the fixed axis of rotation, the description of a bone motion in three-dimensional space can be more faithfully captured in terms of a temporal sequence of helical axes $\mathrm{HA}[t]$ and angles of flexion $\alpha[t]$ with respect to a reference bone (Fig. 5.1) [148].

The helical axis concept is based on a classical result in kinematics due to Chasles [63], stating that any rigid body transformation can be considered being the result of a translation along an axis and a uniform rotation through an angle about the same axis (Fig. 5.2).

Euler or Cardan angles are widely used in biomechanics, providing a well-understood anatomical representation of joint angles [184]. However, the major disadvantage of such descriptions with respect to helical axes are the presence of undesirable non–linear properties and singularities known as "gimbal–lock" [90].

The description of motion in terms of helical axes can refer either to a finite rigid body transformation between two distinct positions or to an infinitesimal transformation, thereby characterizing the differential change along a curve of rigid body transformations. While the second is commonly known as the Instantaneous Helical Axis (IHA) [240], the first interpretation is appropriately denoted as Finite Helical Axis (FHA) [53], which provides a rough estimate of the IHA as the two positions approach each other.



(a) Sagittal view of a helical axis. (b) Frontal view of a helical axis. (c) Description of the motion based on helical axes.

Figure 5.1: Example of helical axes of tibia with respect to the femur (reference bone) $HA^{TF}[t]$, composed of instantaneous centers of rotation and direction vectors $HA^{TF}[t] = (p^{TF}[t], \vec{v}^{TF}[t])$, defined in three-dimensional space [151]. The angle $\alpha^{TF}[t]$ is defined between the axes attached to the femur and to the tibia, both of them being contained in the sagittal plane. $HA^{TF}[t]$ and $\alpha^{TF}[t]$ characterize the flexion-extension motion of the tibia with respect to the femur along the time t.

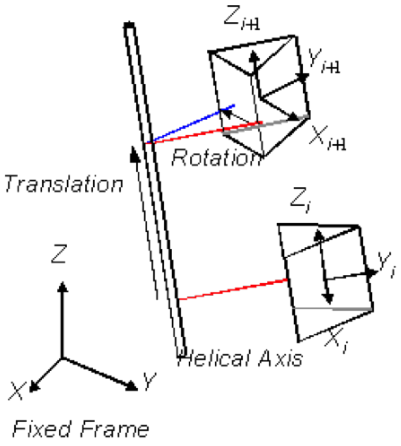


Figure 5.2: Representation of the description of a rigid body transformation based on helical axis (source [127]).

However, it is well known that the FHA is highly sensitive to noise in the two sample poses involved and its computation becomes numerically unstable for small differences [148, 241], while on the other hand using too large a difference yields only a bad approximation. This motivated Woltring et. al. [240] to favor the IHA over the FHA as obtained from a process involving the smoothing of the measured kinematical data. Nevertheless, recent biomechanical studies rely on the FHA [218, 140, 100], and its use is extended, which is easier to compute. Due to its lack of robust analysis capabilites, the translation of methods based on the helical axis concept to clinical practice has been limited.

5.2.2 *Visualization and comparison of helical axis data*

Conventional representations of helical axis data do not allow for an accurate analysis of the evolution of axes and their geometrical relationship to the bones involved. Besier et al. [49] represent their helical axis data with 2D graphical plots, i.e. alongside the conventionally captured gait curve. Bogert et al. [218] represent helical axes by lines passing through a 2D illustration of a joint model and use a numbering system to depict the temporal evolution of the axes (Figs. 5.3, 5.4). The representation by Bogert et al., while providing a coarse qualitative impression, is insufficient to assess the individual patient–specific anatomy [75, 219, 220].

The lack of a realistic visualization of the knee joint motion together with the representation of helical axes leads to difficulties for biomechanical engineers to fully understand the helical axis data and extract directly relevant information. For instance, the orientation of the helical axis configuration and the localization of the functional flexion axis in terms of anatomical bone motion can not be fully understood with 2D graphs (Fig. 5.3).

In addition, the analysis of similarity among several different motion sequences remains difficult. Plots of helical axis parameters (e.g. [49, 218, 243]) represent faithfully the temporal variation of a physical parameter. However, those do not directly support discerning overall differences between motion sequences. For instance, Fig. 5.4 contains only three motion sequences and the comparison of them is visually unclear.

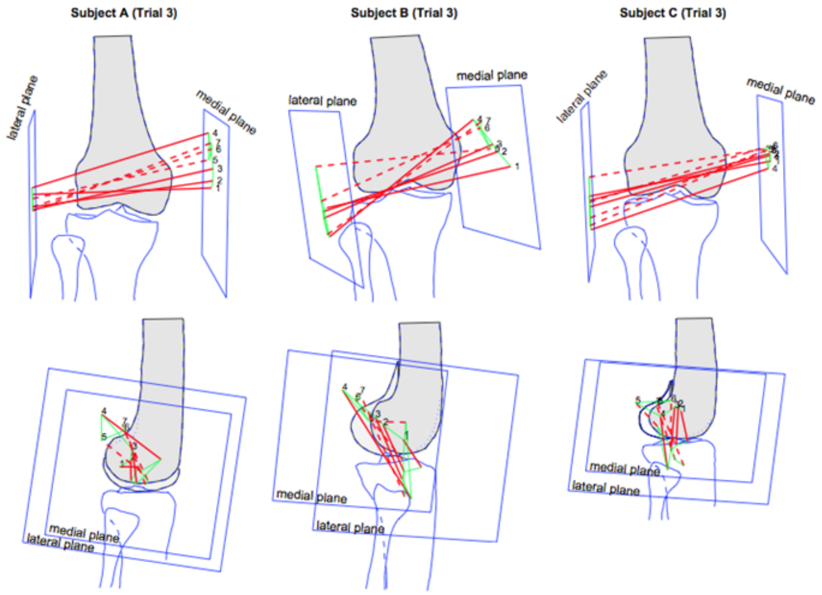


Figure 5.3: Representation of helical axes by means of a 2D illustration (source [218]).

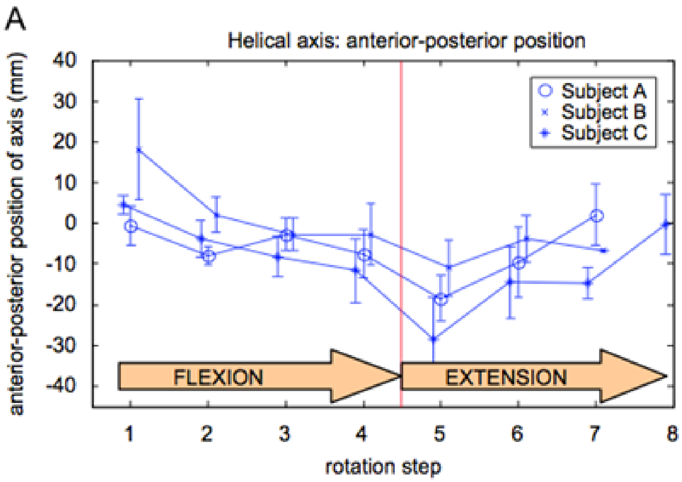


Figure 5.4: Type of plot required for the description of the orientation and position of the FHA during of the stance phase of running (source [218]).

5.2.3 *Helical axis data in the context of analysis of knee joint functional articulation*

In the context of a wider scenario of studying diseases of the knee joint, the interpretation of the helical axes contributes only partially to the description of the knee joint state. The study of diseases related to the knee joint requires data from multiple spatial scales and knowledge belonging to different medical domains (c.f. Sec. 2.3). The analysis of kinematical behavior and its relations with medical features found at other spatial scales, such as organic or cellular scale is required, e.g. the relation between degeneration of the articular cartilage (organic scale) and medial deviation of mechanical axes [117].

Osteoarthritis is an example of a pathology which simultaneously involves information relating diverse spatial scales (Fig. 5.5), as it has been described in Sec. 4.6. Osteoarthritis is a result of cartilage degradation [88], which starts with changes evidenced at cellular scale [107, 168], leading to alterations on mechanical properties at organic scale. Finally, those changes cause measurable variations of the range of motion of the knee at behavioral scale [38], which is the focus of this chapter.

The improvement of the visualization techniques able to encompass the complete spatial range of biomedical data sets has been highly requested for many authors, as it has been indicated in Sec. 2.3.3. Improvements in this direction would encourage the exploration of patient–specific data of multi-scale nature, and would lead to more feasible findings of relevant factors for the characterization of potential pathologies. However, specialists of each medical domain commonly use on a daily basis isolated systems for the exploration of features involving a multi-scale pathology. Those systems focus on features in a concrete domain and scale, preventing to analyze relations among features from different fields. In the last years, several proposals (e.g. [64, 108, 145]) have promoted a collaborative investigation of related diseases in the human body within an integrated approach. However, in terms of visualization, the integration of all information sources of the biomedical process under study and their known relationships clearly needs to improve [86, 152, 164] (c.f. Sec. 2.7).

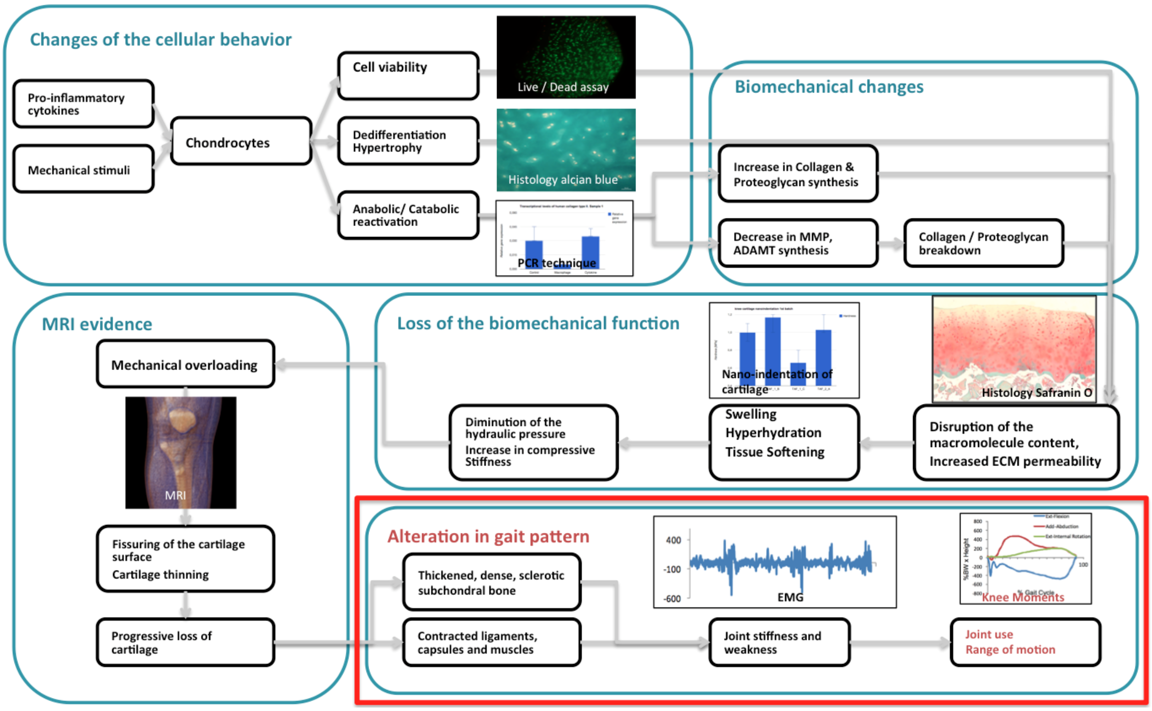


Figure 5.5: Degradation of articular cartilage during osteoarthritis (c.f. Fig. 4.26) and the relevance of the behavioral scale.

5.3 METHODOLOGY

In order to contribute to the aforementioned state of art, several methods have been developed for improving the visualization of helical axis data and the investigation of the knee joint articulation. The methods, summarized in Table 5.3, have been firstly published by the author in [151, 153]. In the following, this chapter expand upon those descriptions and results.

Table 5.3: Summary of proposed methods for helical axis data visualization and analysis (see the state of art in Table 5.2).

Aspect	**Proposed method**
Description of motion based on helical axes	Method of IHA in terms of Lie algebra (Sec. 5.4)
Visualization of helical axes	3D and patient-specific anatomical intra-scale visualization (Sec. 5.5.1)
Comparison of helical axis data	Overall similarity intra-scale visualization (Sec. 5.5.2)
Analysis of knee joint functional articulation and related musculoskeletal diseases	Multi-scale visualization environment including the previous intra-scale visualizations (Sec. 5.6)

First, the approach for the description of motion based on helical axes makes use of the Lie group SE(3) of rigid body motions and its Lie algebra $\mathfrak{se}(3)$ for a natural and smooth representation of motion sequences. This proposed method allows to obtain stable instantaneous helical axes from motion sequences. Those concepts, which have common applications in Robotics [158], have been applied in this work for the description of the knee joint, and are described in Sec. 5.4 including the necessary kinematics principles and the experimental kinematical data collection process.

Regarding the anatomical visualization of helical axis data, a specifically designed patient–specific three–dimensional visualization has been developed [151]. The visualization is based on the processed helical axis information and incorporates three–dimensional visualization from CT scans. This method allows for an intuitive interpretation of the axes and their geometrical relation with respect to the knee joint anatomy as described in Sec. 5.5.1.

The representation of motion sequences in terms of the Lie algebra $\mathfrak{se}(3)$ also allows for an efficient similarity comparison across several motion sequences. The subsequent visualization of similarities, which corresponds to an InfoVis method (c.f. Sec. 2.1.3.2), provides an overall comparison among sequences in order to differentiate cases, e.g. surgery techniques, presented in Sec. 5.5.2. Note that representing information regarding helical axes requires effectively the combination of scientific visualization and information visualization techniques, following the approach described in Sec. 3.3.

In the context of a wider scenario of analysis of diseases affecting the knee joint articulation, those two intra-scale visualizations are proposed in the framework of the multi-scale visualization environment. This environment, outlined in Sec. 5.6 (c.f. Chapter 4 for more details) increases the potential of those methods for the study of knee joint diseases, allowing the exploration with other related data sets distributed across multiple spatial scales.

5.4 INSTANTANEOUS HELICAL AXES IN TERMS OF THE LIE ALGEBRA $\mathfrak{se}(3)$

In this section, a smooth description of motion sequences of the knee joint in terms of infinitesimal helical axes is proposed, providing the basis for analysis and visualization (see Secs. 5.5,5.6) [153]. This method of description of motion exploits the unifying mathematical framework based on the Lie group of rigid body motions $SE(3)$ [158]. In this framework, the exponential map that relates the Lie group SE(3) with its associated Lie algebra $\mathfrak{se}(3)$ is used to parametrize the rigid body motions. Then, a polynomial fitting within the Lie algebra is performed to provide a smooth description of a given discrete knee motion sequence. The accuracy and stability in the obtained sequence is crucial for ensuring a stable derivative which is essential for computing the instantaneous helical axes (Fig. 5.6).

In the following, a short summary of the essential mathematical notions and kinematical background is described in Secs. 5.4.1,5.4.2, including definitions of the finite (Sec. 5.4.3) and instantaneous helical axis (Sec. 5.4.4). Next, the experimental data collection process used for obtaining the kinematic data is described in Sec. 5.4.5. Based on this background, the application of instantaneous helical axis for the description of flexion-extension motion of the knee joint in terms of the Lie algebra $\mathfrak{se}(3)$ is explained in Sec. 5.4.6.

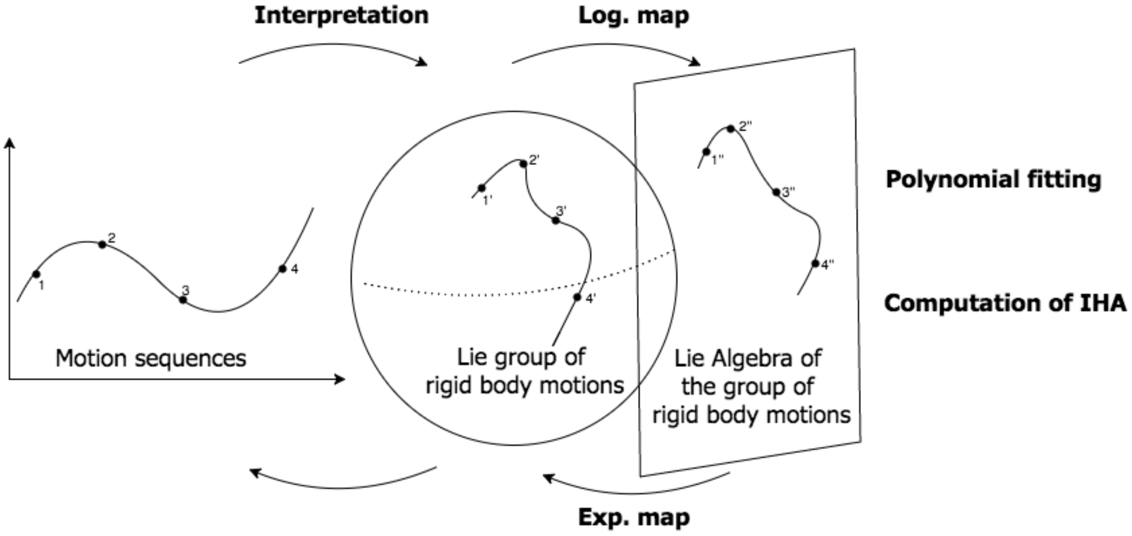


Figure 5.6: Schema of the proposed description of motion sequences based on IHA in terms of the Lie algebra $\mathfrak{se}(3)$: Motion sequences are represented as curves in the Lie group of rigid body motions. The associated Lie algebra is used to parametrize the rigid body motions, to perform the polynomial fitting of motion sequences and finally to compute instantaneous helical axes.

5.4.1 *Mathematical notions*

It is assumed that the reader is familiar with basic notions of algebra and differentiable manifolds c.f. [175, 131]. In addition, for the kinematical description in the following section, the notion of Lie groups is needed. Therefore, in the following a brief summary of the necessary definitions is given.

First of all, recall that group is an algeabric structure consisting of a set of elements G with an operation $\cdot$ that combines any two elements to form a third element, i.e. $\cdot : G \times G \to G$, $(a, b) \mapsto a \cdot b$. The operation is assumed to satisfy several natural properties, such as associativity, the existence of an identity element $1 \in G$ and the existence of an inverse operation $G \to, a \mapsto a^{-1}$ with $a \cdot a^{-1} = a^{-1} \cdot a = 1$.

A manifold is a topological space M satisfying additional requirements (i.e. being second countable and Hausdorff) in which each point has a neighborhood U that is homeomorphic to an open set $V \subseteq \mathbb{R}^n$. A set of such charts is called an atlas of M. Two charts $x : U_1 \to V_1$ and $y : U_2 \to V_2$ which overlap in $U = U_1 \cap U_2 \neq \emptyset$ induce the chart transition $y \circ x^{-1} : x(U) \to y(U)$. A manifold M is called differentiable if it is equipped with a maximal atlas such that all associated chart transitions are (infinitely) differentiable. Based on these concepts, several notions familiar from classical calculus, such as curves, tangent vectors, tangent spaces and the notion of differentiability of functions can be generalized. In particular, a map $f : M \to N$ between manifolds is called differentiable if its composition with any charts $x : U_1 \to V_1$ of M and $y : U_2 \to V_2$ of N is differentiable, i.e. if the map $y \circ f \circ x^{-1}$ (with apropriate restrictions of domains and codomains) is differentiable in the classical sense.

Based on the notion of group and differentiable manifold, a Lie group can be defined as a group G that additionally has the structure of a differentiable manifold, such that the group operation and the inverse operation are differentiable. For an extensive introduction to these topics, see [189].

5.4.2 *Kinematical background*

A rigid body transformation (also called an Euclidean transformation) in three-dimensional space can be described as a map $M : \mathbb{R}^3 \to \mathbb{R}^3, p \mapsto Rp + V$, where

- R describes the rotational component as an orthogonal transformation with unit determinant, i.e. $R \in SO(3) = \{A | A \in O(3) \text{ and } \det(A) = 1\}$.
- $V \in \mathbb{R}^3$ denotes the translational component.

The set of all possible rigid body transformations constitutes the Lie group SE(3), known as the special Euclidean group of 3-dimensional space. Using homogeneous coordinates, any rigid body transformation can be written in terms of a 4×4 matrix, thereby giving rise to the matrix representation

$$SE(3) := \left\{ \begin{pmatrix} R & V \\ 0 & 1 \end{pmatrix} \ : \ R \in SO(3),\ V \in \mathbb{R}^3 \right\} .$$

The tangents of curves of rigid body transformations passing through $\mathrm{id} \in SE(3)$ give rise to the tangent space $T_{\mathrm{id}}\, SE(3)$, known as the Lie algebra $\mathfrak{se}(3)$ with

$$\mathfrak{se}(3) := \left\{ \widehat{\xi} \ : \ \xi = (\omega, v) \in \mathbb{R}^3 \times \mathbb{R}^3 \right\},$$

$$\text{where } \widehat{(\omega, v)} := \begin{pmatrix} 0 & -\omega_z & \omega_y & v_x \\ \omega_z & 0 & -\omega_x & v_y \\ -\omega_y & \omega_x & 0 & v_z \\ 0 & 0 & 0 & 0 \end{pmatrix} .$$

The elements of $\mathfrak{se}(3)$ are called twists. In the following, by abuse of notation, the notational distinction between the pair of vectors ξ and the corresponding matrix $\widehat{\xi}$ will be omitted if no confusion can arise.

The exponential map $\exp : \mathfrak{se}(3) \to SE(3)$ given by $\exp(\xi) = e^{\xi} = \sum_{k=0}^{\infty} \frac{\xi^k}{k!}$ can be shown to be surjective and thereby allows any rigid body transformation to be described in terms of a twist.

Applying the Caley–Hamilton theorem, which states that ξ (viewed as a linear map on $\mathbb{R}^4$) yields zero upon formal substitution into its associated characteristic polynomial $P(\lambda) = \det(\xi - \lambda\,\mathrm{id})$, it can be shown that any analytical function of ξ, including e^{ξ}, evaluates to a third–order polynomial in ξ. The coefficients of the latter are determined by relating the eigenvalues of ξ to those of e^{ξ}. These considerations lead to the closed–form expression

$$e^{\xi} = \mathrm{id} + \xi + \frac{1 - \cos\theta}{\theta^2}\xi^2 + \frac{x - \sin\theta}{\theta^3}\xi^3 \;, \tag{5.1}$$

where θ is the norm of the ω component of $\xi = (\omega, \nu)$, i.e. $\theta = |\omega|$ [225]. Note that the coefficients have a removable singularity at $\theta = 0$ and are in fact analytic functions of θ, thus the above expression is actually well–defined and smooth for all twists ξ, including zero.

The twist representation has the advantage of not requiring redundant degrees of freedom, as it represents a rigid body transformation with the minimum amount of six parameters. Descriptions based on Euler or Cardan angles are similar in this regard, but they suffer undesirable non–linear properties and singularities known as "gimbal–lock" [90]. Other commonly used representations involving rotation matrices or quaternions lack the ability of easily approximating a sequence of rigid body transformations by a motion trajectory fully contained in the Lie group $SE(3)$ and require additional orthogonalization or normalization measures. Using the Lie algebra representation of rigid body motions and the exponential map as described above avoids these problems and provides an effective computational tool.

5.4.3 *Finite helical axis*

The equation (5.1) reduces to the Rodrigues rotation formula for twists of the form $\theta(\omega, 0)$ with unit vector ω. The Rodrigues formula describes a rotation of arc-length θ around ω [186]. A geometrical interpretation of the exponential map in the general case is obtained by relating it to Chasles' theorem [63], which states that every rigid body transformation that contains a rotational component can be expressed as a rotation of arc-length θ about an axis H followed by translation of $h\theta$ units along that axis (Fig. 5.7). This axis is called screw axis or *finite helical axis (FHA)*, while θ is the magnitude and h is the pitch of the screw. Indeed, the rigid body

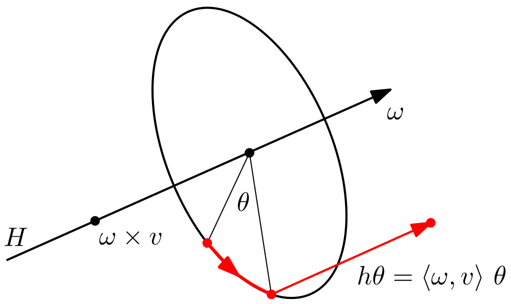


Figure 5.7: Description of a rigid body transformation in terms of a screw.

transformation $e^{\theta(\omega,\nu)}$ corresponding to the twist $\theta(\omega,\nu)$ where $|\omega| = 1$ is realized as a screw with

$$H = (\omega \times \nu) + \mathbb{R}\omega, \ h = \langle \omega, \nu \rangle \ . \tag{5.2}$$

5.4.4 *Instantaneous helical axis*

In this section, consider a fixed coordinate system A and a rigid body with an attached coordinate system B. It is assumed that B is moving relative to A such that both systems are related by $B = Ae^{\xi(t)}$ where $\xi : I \to \mathfrak{se}(3)$ is a one–parameter family of twists. A point p fixed to the moving body has constant coordinates p_B with respect to B, while its coordinates p_A with respect to A are $p_A = e^{\xi(t)} p_B$ and therefore depend on t. Taking the derivative with respect to t yields the velocity of p relative to the system A as

$$\frac{dp_A}{dt} = \frac{de^{\xi}}{dt} p_B = \frac{de^{\xi}}{dt} e^{-\xi} p_A .$$

The quantity $\frac{de^{\xi}}{dt} e^{-\xi}$ is a twist (i.e. it belongs to $\mathfrak{se}(3)$) and is called the instantaneous spatial velocity of the moving body. The associated screw axis (in the sense of equation (5.2)) constitutes the so–called *instantaneous helical axis (IHA)*. In order to compute $\frac{de^{\xi}}{dt} e^{-\xi}$ from ξ and its derivative $\frac{d\xi}{dt}$ one requires the differential of the exponential map $\exp : \mathfrak{se}(3) \to SE(3)$. To this end, the following relation is exploited, c.f. [189]:

$$\frac{de^{\xi}}{dt} e^{-\xi} = \frac{e^{\mathrm{ad}_{\xi}} - \mathrm{id}}{\mathrm{ad}_{\xi}} \, \frac{d\xi}{dt} \ . \tag{5.3}$$

Here ad denotes the action of $\mathfrak{se}(3)$ on $\mathfrak{se}(3)$ given by $\mathrm{ad}_{\xi}\, \zeta := [\xi, \zeta] := \xi\zeta - \zeta\xi$. The operator on the right–hand side of eq. (5.3) is defined in terms of its formal power series expansion and can, by a similar argument as the one leading to eq. (5.1), be evaluated in closed form using the Cayley–Hamilton theorem, yielding a fifth order polynomial in ad_{ξ}, namely

$$\begin{aligned} &\frac{e^{\mathrm{ad}_{\xi}} - \mathrm{id}}{\mathrm{ad}_{\xi}} = \\ &\mathrm{id} + \frac{1}{2}\,\mathrm{ad}_{\xi} + \frac{(4+c)\theta - 5s}{2\theta^3}\,\mathrm{ad}_{\xi}^2 + \frac{6c + s\theta + 2\theta^2 - 6}{2\theta^4}\,\mathrm{ad}_{\xi}^3 \\ &+ \frac{(2+c)\theta - 3s}{2\theta^5}\,\mathrm{ad}_{\xi}^4 + \frac{4c + s\theta + \theta^2 - 4}{2\theta^6}\,\mathrm{ad}_{\xi}^5 \end{aligned} \tag{5.4}$$

where $\xi = (\omega, \nu)$, $\theta = |\omega|$, $s = \sin\theta$, $c = \cos\theta$ [225]. As in the case of eq. (5.1) any ostensible singularity at $\theta = 0$ is removable, thus all coefficients constitute analytic functions of θ.

5.4.5 *Kinematic data collection*

The kinematic data collection is performed with the help of a specifically designed in vitro knee simulator (Fig. 5.8), following the experimental work described in Ostermeier et al. [169], and coordinated by LBB-MHH [153]. For each experiment, freshly frozen cadaver knee joints are prepared by removing skin and subcutaneous tissue, while keeping the articular capsule intact. The femur is fixed in position and the tibia is fixed to a lever arm that constrains the tibia to flexion–extension motion. The simulator applies loads to the quadriceps and hamstring tendons, forcing the knee specimen to complete an extension motion.

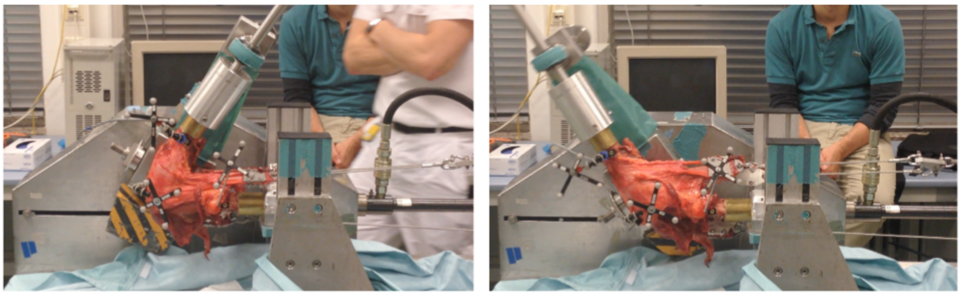


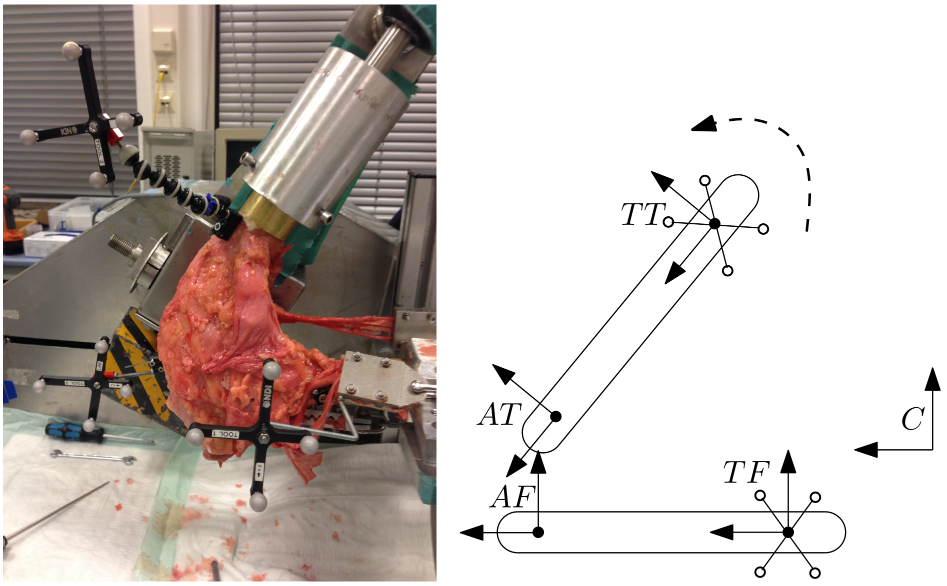
Figure 5.8: Kinematic experimental set–up, coordinated by LBB-MHH. The simulator applies loads to perform an extension motion of the knee joint, which have fixed passive reflective markers tools.

The tracking of bone motion is performed using a two camera Polaris Optical Tracking System [16], with passive reflective marker tools. Those are rigidly fixed to the femur, tibia and patella providing the tracking of rigid bone motion at an accuracy of 0.35mm at 10Hz. Moreover, a set of standardized physical anatomical landmarks L_E found on the bone's surfaces are also acquired in order to establish corresponding anatomical coordinate systems. The latter are defined according to the recommendations of the International Society of Biomechanics for reporting human joint motion of the lower body [242]. The acquisition of the landmarks is made manually by the surgeon touching specific points of the bones with a passive reflective marker pointer device (Fig. 5.12a).

The analysis in this work is focused on the relative motion of the tibia with respect to the femur. The patella-femur motion can be analyzed in a similar way. Referring to Fig. 5.9, AT, AF represent the anatomical coordinate systems for tibia and femur. Moreover, TT and TF denote the coordinate systems rigidly moving with the reflective marker tools attached to the tibia and femur. The tracking process yields for each time sample t the mappings $M^{C}_{TF}(t)$ and $M^{C}_{TT}(t)$ that transform the coordinates of a point relative to the marker systems TF and TT into the corresponding coordinates relative to the tracking coordinate system C. The computation of these transformations based on the tracked marker positions is performed by the methods presented in Spoor et al. [202]. Using the transformations M^{TF}_{AF} and M^{TT}_{AT} that map anatomical coordinates into marker tool coordinates (see Fig. 5.10), the relative motion between the femur and tibia is given by

$$M^{AF}_{AT}(t) = M^{TF}_{AF}(t)^{-1} M^{C}_{TF}(t)^{-1} M^{C}_{TT}(t) M^{TT}_{AT}(t). \tag{5.5}$$

The Cartesian basis vectors e_x, e_y, e_z of $\mathbb{R}^3$ are identified with the three axes of AF such that the sagittal plane is spanned by e_x and e_y.



(a) (b)

Figure 5.9: (a) Experimental set–up and (b) scheme of relevant coordinate systems.

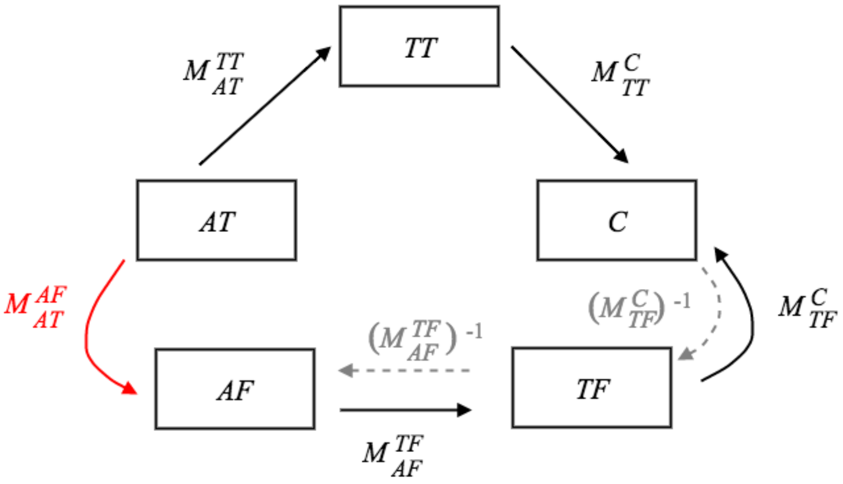


Figure 5.10: Scheme representing the obtaining of the relative motion between tibia and femur $M_{AT}^{AF}(t)$ (red color), by using the mappings given by the tracking process (black) and others which were computed (gray).

5.4.6 *Helical axes for the knee joint*

In the considered case of flexion-extension motion M_{AT}^{AF}, the time parameter t in eq. (5.5) can be replaced by a more convenient parameter, namely flexion angle α_z between the tibia and the femur. The latter is obtained by decomposing M_{AT}^{AF} as

$$M_{AT}^{AF} = \exp(0, r)\,\exp(\alpha_z e_z, 0)\,\exp(\alpha_y e_y, 0)\,\exp(\alpha_x e_x, 0).$$

As the flexion–extension motion is the main interest of this work, the parameter α_z is chosen as primary parameter.

In the following, in order to simplify the notation, α will be written instead of α_z and $M(\alpha)$ or simply M for the transformation M^{AF}_{AT}. The corresponding geometry is indicated schematically in Fig. 5.11.

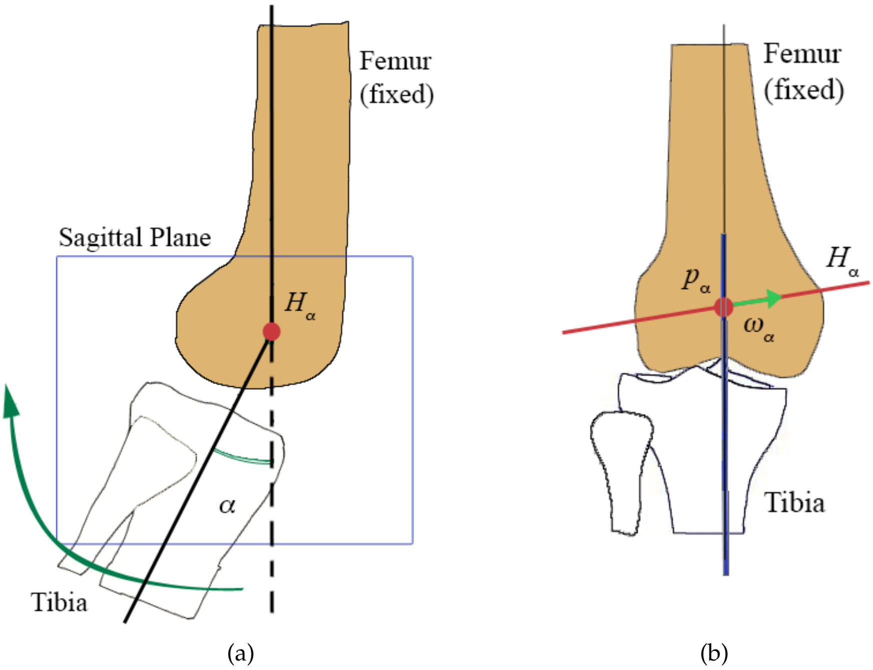


Figure 5.11: Geometrical configuration illustrating the flexion of the tibia with respect to the femur. The helical axis H_α is given by the point of rotation p_α and the unit vector ω_α for each angle α.

The tracking process outlined in the previous subsection gives rise to a sequence $M(\alpha_0), \ldots, M(\alpha_n)$ which, using $M = e^{\xi}$, is interpreted as a sequence $\xi(\alpha_0), \ldots, \xi(\alpha_n)$ of twists. Assuming an underlying smooth motion it is reasonable to apply a polynomial regression in order to obtain a smooth function expressed as

$$\xi(\alpha) = \left(\frac{2}{\alpha_n - \alpha_0}\right)^{\frac{1}{2}} \sum_{k=0}^{d} c_k L_k\left(\frac{2\alpha - \alpha_0 - \alpha_n}{\alpha_n - \alpha_0}\right) \tag{5.6}$$

where $c_0, \ldots, c_d \in \mathbb{R}^6$ are coefficient vectors and

$$L_k(x) = \left(k + \frac{1}{2}\right)^{\frac{1}{2}} \frac{1}{2^n n!} \frac{d^n}{dx^n}\left((x^2-1)^n\right) \quad k = 0, \ldots, d$$

are the normalized Legendre polynomials constituting a basis for the space of all polynomials of degree d, while the scaling factors in eq. (5.6) are included for later convenience. The Legendre polynomials are orthogonal with respect to the L^2 scalar product over $[-1, 1]$, i.e.

$$\int_{-1}^{1} L_i(y) L_j(y)\, dy = \delta_{ij}\,, \tag{5.7}$$

a fact that will be useful for analyzing the similarity of motion sequences (see Sec. 5.5.2).

Based on this description, and referring to equations (5.3) and (5.4), the twist

$$\zeta = \frac{dM}{d\alpha} M^{-1} = \frac{e^{\mathrm{ad}_\xi} - 1}{\mathrm{ad}_\xi} \frac{d\xi}{d\alpha} \tag{5.8}$$

and its associated screw (H, θ, h) are obtained, which yields the instantaneous helical axis H for each flexion angle α. The intersection of the helical axis with the sagittal plane yields the point

$$p = \omega \times v - \frac{(\omega \times v)_z}{\omega_z} \omega = \frac{e_z \times (v - wh)}{\omega_z},$$

which is known as the point of rotation (also indicated in Fig. 5.11). Visualizing its location and variation according to the flexion angle α contributes to an intuitive assessment of the position and orientation of the helical axis with respect to the geometry of the knee joint.

5.5 INTRA-SCALE VISUALIZATIONS FOR THE ANALYSIS OF HELICAL AXIS DATA

The computational approach for the representation of helical axis data and its approximation within the Lie algebra $\mathfrak{se}(3)$ presented in Sec. 5.4 provides the basis for the development of intra-scale visualizations which facilitate the joint motion representation and analysis. In this section, the following visualizations are presented:

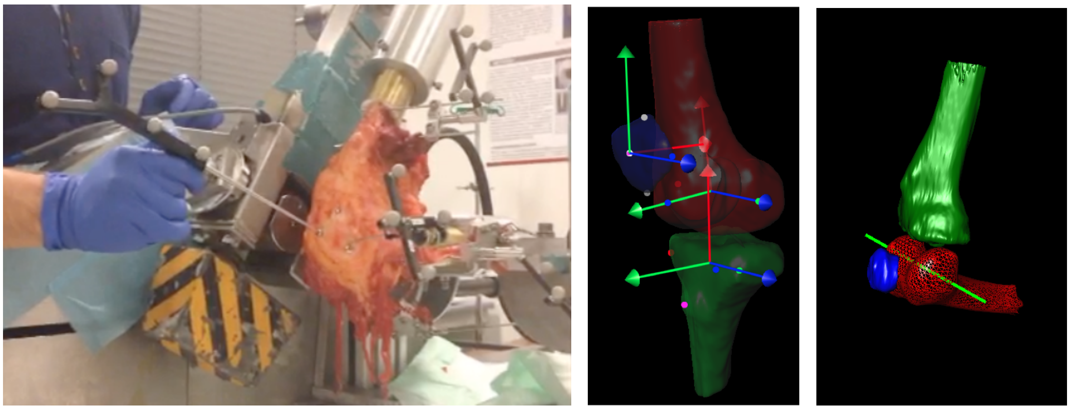
- Anatomical visualization of helical axis data: An intra-scale visualization which performs the three-dimensional motion of patient-specific bone segments as well as the representation of helical axes on the bone, described in Sec. 5.5.1.
- Overall similarity visualization for comparison of helical axis data: Based on the multi-dimensional scaling approach involving the previously determined polynomial approximation by means of Lie algebra, an intra-scale visualization based on a high–level comparison of motion sequences is proposed in Sec. 5.5.2.

5.5.1 *Anatomical visualization of helical axis data*

As indicated in Sec. 5.2.2, conventional representations of helical axis data have been insufficient for a complete anatomical understanding of the evolution of the helical axis data during the flexion–extension motion. Therefore, a viewer (or visualization) by means of an anatomical and three–dimensional representation has been developed in order to facilitate the observation of the helical axis data and the corresponding flexion-extension motion at the knee joint.

The data used for the proposed visualization has been obtained from the experimental set–up described in Sec. 5.4.5. Subsequently, those data are used in order to calculate helical axis data from biomechanical experiments applied to specific specimens, as described in Sec. 5.4.6. Additionally, CT scans from each specimen are acquired prior to the kinematic data collection.

Within the viewer, CT images of the considered specimen are accurately segmented, thereby obtaining a 3D segment-visualization of the femur, tibia and patella. Subsequently, a set of significant landmarks L_V is specified by biomechanical engineers within the viewer (Fig. 5.12b). These landmarks correspond to the physical landmarks L_E on the bone's surfaces acquired in the data collection process (Fig. 5.12a, c.f. Sec. 5.4.5). These landmarks can be specified using manual or automated approaches, also on MRI images [167] (Fig. 5.14). Afterwards, a matching between L_E and L_V is used to establish the mapping between the experimental tracking set–up T_E and the reference frame T_V used within in the viewer. Thus, the kinematical data can be reinterpreted within the viewer reference system. Then, the visualization performs the three–dimensional motion of the patient–specific bone segments obtained from CT scans incorporating the representation of the calculated sequence of helical axes (Fig. 5.12c).



(a) Experimental set-up (b) Definition of T_V (c) Representation of knee joint motion

Figure 5.12: (a) Experimental set-up with the tracking coordinate system T_E. (b) Landmarks on the bone's surfaces L_V defined in the viewer in order to obtain the coordinate system T_V. (c) 3D Representation of the knee joint flexion and helical axis of the tibia with respect to the femur $HA_V^{TF}[t]$.

The implemented visualization has the following functionalities:

- The 3D view shows the three–dimensional spatial configuration of the instantaneous helical axis H_α given by the point of rotation p_α and the unit vector ω_α (see Fig. 5.11), reproducing the relative motion of the tibia with respect to the femur according to the flexion angle α (Fig. 5.13). The visualization is able to represent the smooth temporal evolution of the IHA as computed previously (c.f. Sec. 5.4) but also FHA calculations [151].

The visualization incorporates several features (see also Figs. 5.19, 5.20), e.g. the analysis of the trajectory of the point of rotation p_α, which is shown as a curve on the sagittal plane. Similarly, the visualization allows analogously for an inspection of curves obtained by intersecting the helical axes with individual bone segments or other specific planes of interest.

- The 2D sub-panel view enables the quantitative inspection of related data concerning, e.g. the translations of the centers of rotation (i.e. indicating anterior and posterior shifts). Both 2D and 3D views are synchronized in time, allowing an interactive inspection of the kinematics in terms of the helical axis for any chosen flexion angle.

The visualization was implemented in Java programming language using the Java3D API [8]. The viewer constitutes a plugin for the open platform for 3D–visualization and 3D segmentation of medical volume data YaDiV [81]. Therefore, the viewer can take advantage of YaDiV features regarding segmentation, stereographic volume visualization [82] and haptic interaction [228].

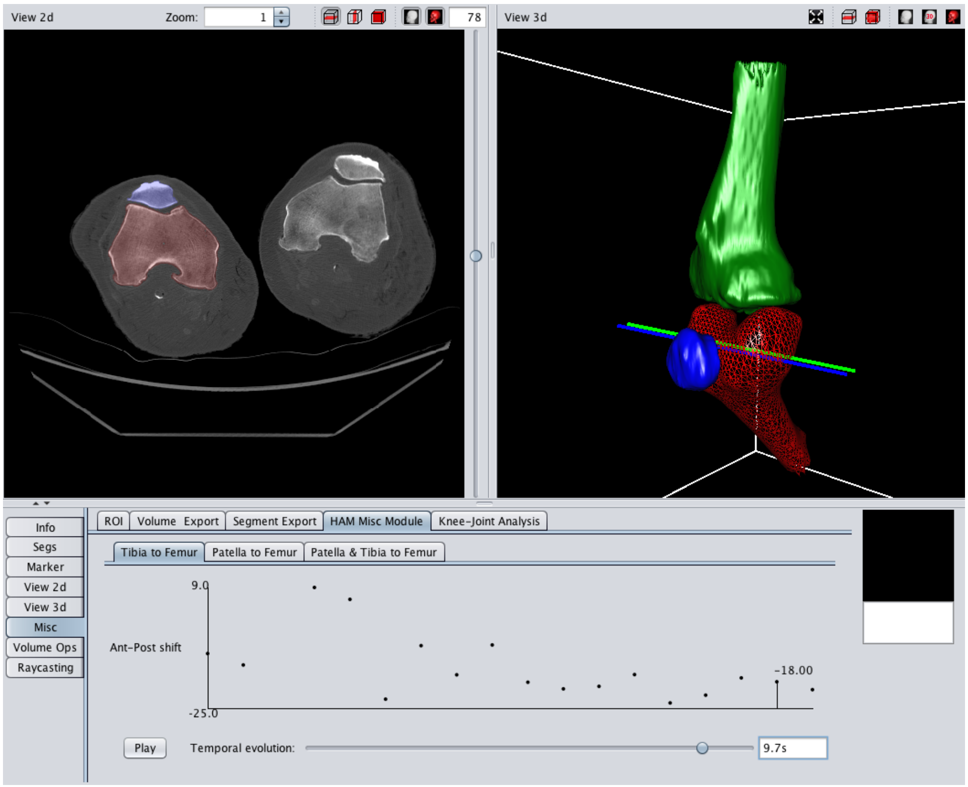
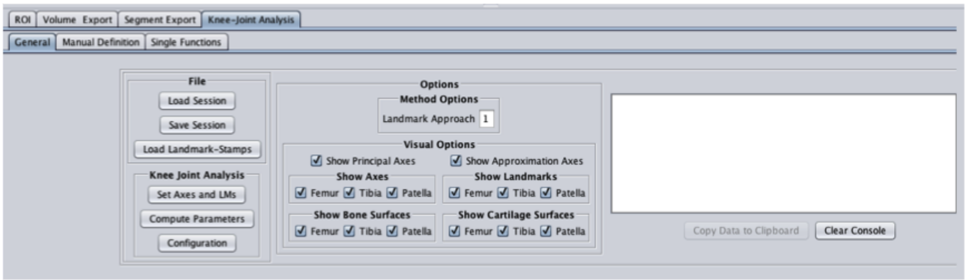


Figure 5.13: Visualization of a healthy knee joint completing flexion-extension motion from experimental data, including the helical axes $HA_V^{TF}[t]$ (green) and $HA_V^{PF}[t]$ (blue).



Landmark Approach 1

☑ Show Principal Axes ☑ Show Approximation Axes

Show Axes: ☑ Femur ☑ Tibia ☑ Patella

Show Landmarks: ☑ Femur ☑ Tibia ☑ Patella

Show Bone Surfaces: ☑ Femur ☑ Tibia ☑ Patella

Show Cartilage Surfaces: ☑ Femur ☑ Tibia ☑ Patella

Figure 5.14: Another example of YaDiV plugin. Plugin for the creation of knee coordinate systems [167].

5.5.2 *Overall similarity visualization for comparison of helical axis data*

The lack of robust capabilities in the analysis of helical axes which previous works offered has limited the possibilities of analysis of motion sequences (c.f. Sec. 5.2.2). Previous works were insufficient to intuitively discern the overall similarity between the motion sequences corresponding to different cases and states.

For the comparison of motion sequences, it is useful to have a notion of length on SE(3). A natural notion of length on Lie groups is generally provided by a so–called bi–invariant Riemannian metric which can be induced by defining a positive definite inner product on the corresponding Lie algebra. This approach works for the group of rotations SO(3), but the Lie algebra $\mathfrak{se}(3)$ of SE(3) is not naturally equipped with a positive definite inner product and no such prescription induces a bi–invariant Riemannian metric on SE(3). Nevertheless, a fixed inner product can be extended to a right- (or left-) invariant metric, which still provides a useful means of comparing rigid body motions. By assuming the Lie algebra $\mathfrak{se}(3)$ to be equipped with the Euclidean inner product, it is possible to identify $\mathfrak{se}(3) \simeq \mathbb{R}^6$ introduced in Sec. 5.4.2 [47, 158]. This induces a norm $|\cdot|$ on $\mathfrak{se}(3)$ which is sufficient for the purpose of this work.

Thus, a measure of the similarity between two sequences of motion $\xi, \widetilde{\xi} : [\alpha_0, \alpha_n] \to \mathfrak{se}(3)$ is given by

$$d(\xi, \widetilde{\xi})^2 = \int_{\alpha_0}^{\alpha_n} |\xi(\alpha) - \widetilde{\xi}(\alpha)|^2 \, d\alpha. \tag{5.9}$$

If $\xi(\alpha)$ and $\widetilde{\xi}(\alpha)$ are represented according to eq. (5.6) by corresponding coefficient vectors $c, \widetilde{c} \in (\mathbb{R}^6)^{d+1}$, then the last equation reduces to

$$d(\xi, \widetilde{\xi})^2 = \sum_{k=0}^{d} |c_k - \widetilde{c_k}|^2. \tag{5.10}$$

This follows from the orthogonality of the Legendre polynomials exhibited in eq. (5.7).

A collection of motion sequences can be compared based on this measure of similarity by employing classical multidimensional scaling approaches [55], reducing the dimensionality of the space from $(\mathbb{R}^6)^{d+1}$ to two dimensions [153]. For the transformation of those data into a spatial presentation being graphically intuitively accessible (i.e. InfoVis, c.f. Sec. 2.1.3.2), a classical MDS approach is employed [68] (Fig. 5.15, note that the measurement is dimensionless) which was also used in Reuter et al. [181] with a similar aim.

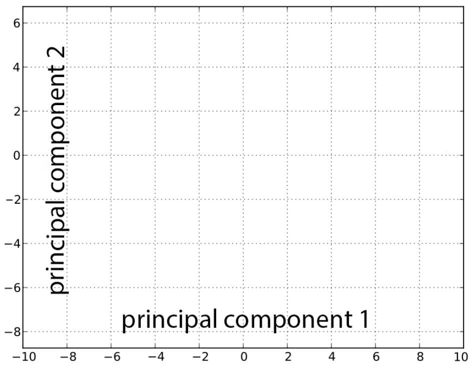


Figure 5.15: Scheme of the proposed overall similarity visualization (see Fig. 5.21 for details).

5.6 MULTI–SCALE EXPLORATION OF THE KNEE JOINT DATA

As described in Sec. 2.3.2, a complete visualization of multi-scale data such as those obtained from the knee joint articulation needs a visualization that satisfies the multimodal and multi-scale requirements. First, it requires data acquired from different acquisition modalities. In this application scenario, for now, CT images and kinematic data are employed in order to analyze the knee joint flexion motion. Moreover, finding the relevant factors for the characterization of potential musculoskeletal diseases requires data and knowledge from multiple spatial scales and other different medical specialties. For instance, for the study of the correlation between degeneration of the articular cartilage and medial deviation of mechanical axes, e.g. [117], the use of data coming from different fields such as biomechanical and tissue engineering becomes important.

The intra-scale visualizations described in this chapter (c.f. Sec. 5.5) have dealt with the multi-modal requirement, and have been focused only on the behavioral scale. Both the anatomical and similarity visualizations of helical axis data constitute enhanced intra-scale visualizations, as proposed in the methodology of this work (c.f. Sec. 3.5). In the following, it is proposed to extend the role of such visualizations to a multi–scale scenario, where those methods can be used together with other related data sets distributed accross multiple spatial scales for a global investigation of knee joint data. To this aim, the aforementioned intra-scale visualizations are proposed to be integrated in the multi-scale visualization environment (Fig. 5.16), as described in more detail in Chapter 4.

The multi-scale visualization environment effectively supports the exploration of biomedical knowledge coming from different spatial scales and the known relationships between them. The system addresses portability and scalability requirements, being able to deal effectively with the visualization of massive data sets. Its flexible object oriented structure allows previously developed viewers to be re–used and easily extended as rendering workers within the exploratory environment (c.f. Sec. 4.5).

The environment makes use of a multilayered visualization (c.f. Sec. 3.2), employing a flexible combination of SciVis and InfoVis views (c.f. Sec. 3.3). Data sets are distributed over several layers, distinguished by the depth, the nearest being the most important for the user. SciVis views, such as the three–dimensional visualization of helical axes, and InfoVis ones, such as the view of similarity among helical axis sequences, are displayed independently and consistently in different nodes. These nodes are connected through visual links, representing semantic relations, which are obtained with information extracted from the multi-scale ontology. This ontology encompasses the multi-scale biomedical knowledge and the information for obtaining all necessary visualization parameters (c.f. Sec. 3.4).

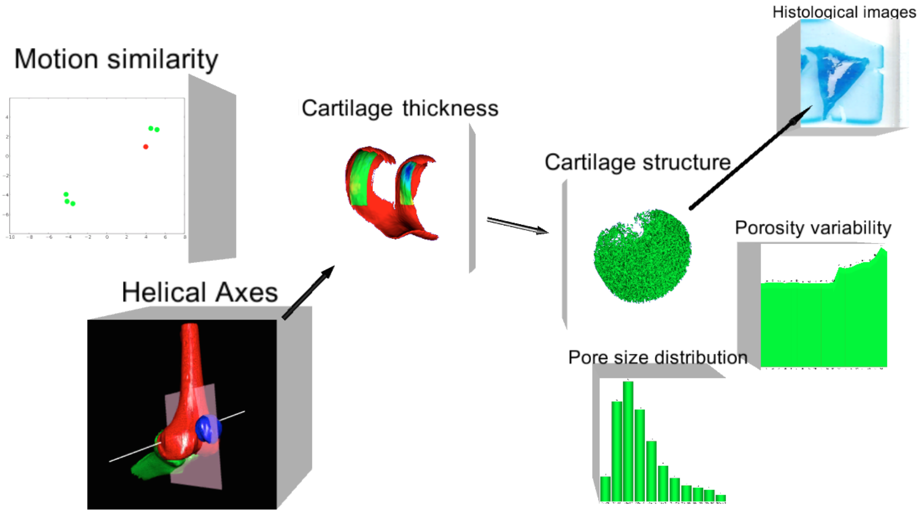


Figure 5.16: Multi–scale visualization environment for exploration of knee joint related data and the intra-scale visualizations for the analysis of helical axis data.

5.7 RESULTS

This section presents the results obtained in the application scenario by using kinematical data from experimental sequences as well as knee joint related data of multi-scale nature, exemplarily demonstrating the utility of the proposed visualization techniques.

Regarding the kinematical data, the techniques have processed experimental data gathered in the data collection, as described in Sec. 5.4.5. The performed data collection has provided several motion sequences, being each sequence the result of a tracking measurement. The collection has included specimens of left and right legs prior to and after surgery of total knee replacement. For the surgery, two different techniques have been applied: measured resection and patella in place gap balancing [71]. Repeated measurements have been performed on each individual case to obtain a representative amount of kinematical data. Regarding the knee joint related data of multi-scale nature, data sets described in Table A.1 have been employed, as previously used in Chapter 4.

The following subsections demonstrate the description of the IHA in terms of Lie algebra, the anatomical and similarity intra-scale visualizations of helical axis data as well as the visualization of helical axes data in a multi-scale scenario.

Instantaneous helical axes in terms of Lie algebra

In the following, motion sequences are discussed in the Lie group of rigid body motions. Its associated Lie algebra is used to i) parametrize the rigid body motions, ii) perform the polynomial fitting of motion sequences and iii) compute subsequently instantaneous helical axes.

Initially, the processing methodology is exemplified focusing first on an individual motion sequence, coming from a left leg of a healthy specimen. Figure 5.17 illustrates the use of Lie algebra as a space to describe rigid body motions. Concretely, it depicts individual samples representing the rigid body motions relating the anatomical femur coordinate system and the anatomical tibia coordinate system in terms of twists, as discussed in Sec. 5.4.6. The two plots show the individual components $\omega_x, \omega_y, \omega_z$ and ν_x, ν_y, ν_z of twists $\xi = (\omega, \nu)$ parametrized by the flexion angle α. The range encompasses from $\alpha_0 = 5°$ to $\alpha_n = 115°$.

The measured samples are smoothly approximated by a low order polynomial $\xi(\alpha)$, as discussed in Sec. 5.4.6. In the case of the obtained motion sequences, a third–order approximation suffices for a high degree of accuracy while avoiding oscillatory behavior. In addition, the polynomial fitting effectively allows to deal with the non–uniform spacing and potentially different numbers of data samples present in the motion sequences.

The lack of oscillations is extremely important for ensuring a stable derivative which is essential for computing the instantaneous helical axis using eq. (5.8). Figure 5.18 compares the individual components of the helical axes $\omega_x, \omega_y, \omega_z$ by using the proposed approach and the approach

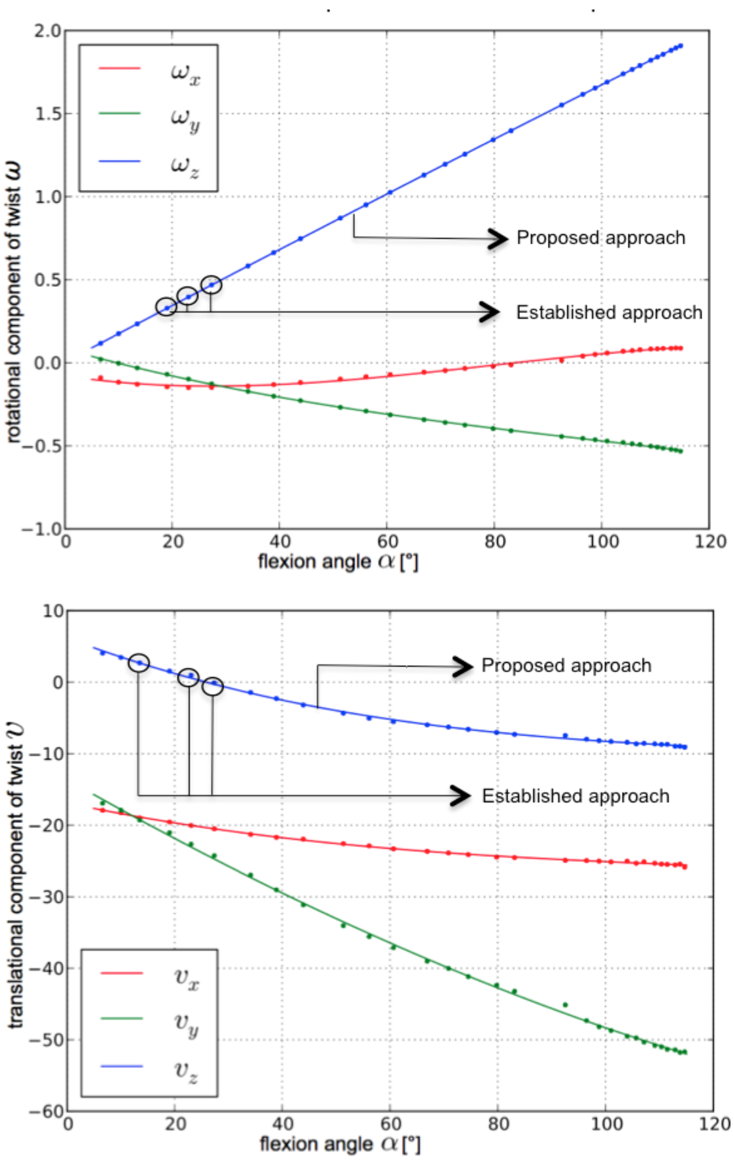


Figure 5.17: Representation of a sampled motion sequence within the Lie algebra $\mathfrak{se}(3)$ with a third order polynomial approximation. The points indicate the individual samples representing rigid body motion from the established approach. The polynomial fitting within the Lie algebra performed in the proposed approach allows the obtaining of valid and smooth helical axes for further steps on visualization.

based on van den Bogert et al. [218], with some adaptations of the algorithm presented in Spoor et al. [202] and accuracy improvements proposed in Metzger et. al [148]. Despite of those adaptations, the established approach are still sensitive to noise. The proposed approach provides a smooth and valid sequence of helical axes, as it assures the sequence to be in the Lie group of rigid body motions.

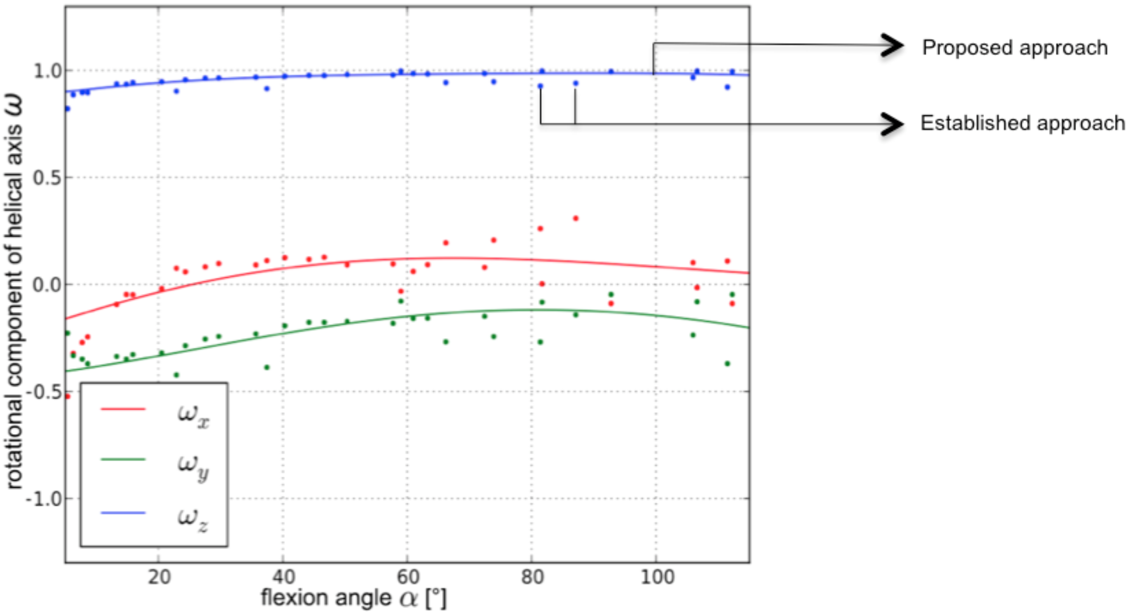


Figure 5.18: Instantaneous helical axes obtained with the proposed method (continuous curves) and based on van den Bogert et al. [218] (samples). The established approach obtains finite helical axes, which are sensitive to noise. The proposed method obtains smooth and valid helical axes.

Anatomical visualization of helical axis data

Following up the intermediate results indicated in previous figures, results of the corresponding anatomical visualization of the motion sequence are shown in Figs. 5.19, 5.20.

In Fig. 5.19, the panel on the right side provides a three–dimensional view of the fully segmented knee joint including a depiction of the helical axis in terms of the point of rotation p_α and the direction vector ω_α, for a chosen

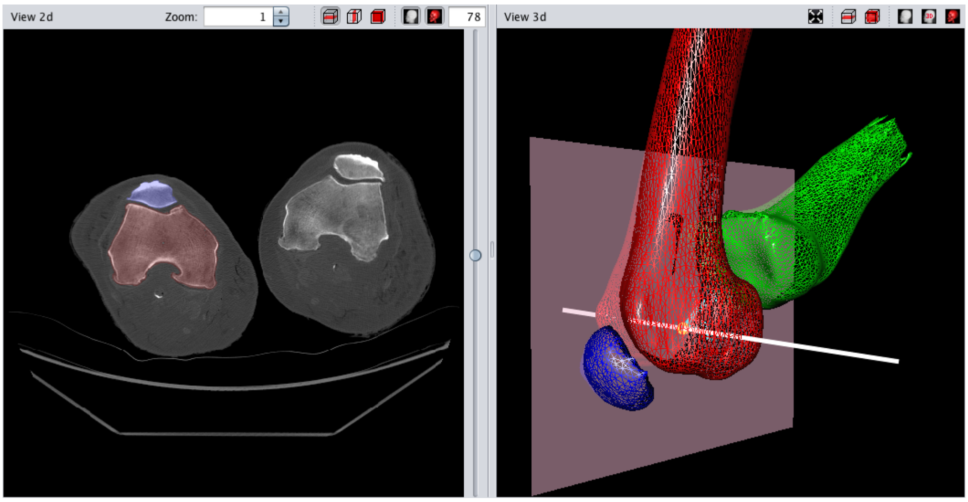


Figure 5.19: Anatomical visualization of helical axis data.

flexion angle α. The motion of the knee joint can be studied interactively by smoothly varying α within the available bounds and selecting individual positions or ranges for inspection using the available tools (e.g. showing the trajectory of p_α on the sagittal plane). The left panel presents a transversal two–dimensional cross section of the knee joint assisting the user to take advantage of the several segmentation tools also available in the extension of YaDiV [82].

Figure 5.20 shows the trajectory of p_α on the sagittal plane within the developed viewer as obtained by (a) using the proposed method and (b) the approach described in van den Bogert et al. [218], demonstrating again the smoothness of the results with the proposed approach.

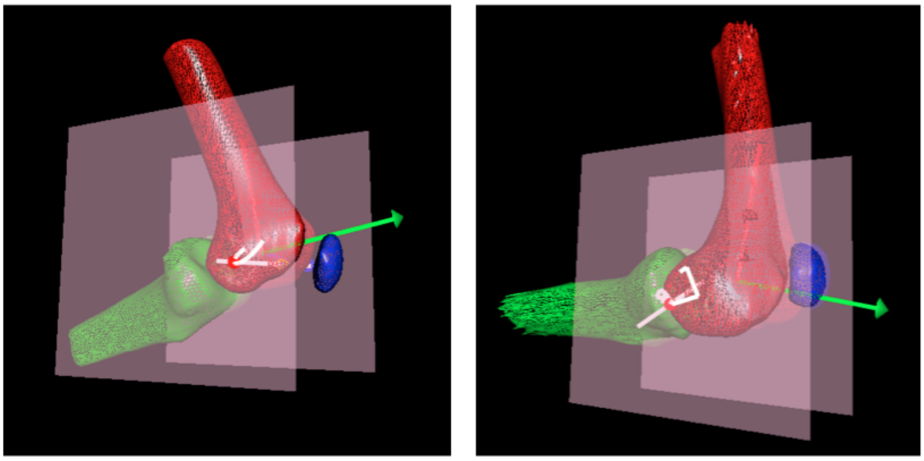


Figure 5.20: Anatomical visualization of the helical axis data, (a) with the proposed method and (b) based on van den Bogert et al. [218].

Overall similarity visualization for comparison of helical axis data

Apart from the analysis and visualization of an individual sequence, another intra-scale visualization allows for comparing several motion sequences chosen by the user within the exploratory environment. An example is depicted in Fig. 5.21, where three sequences from a subject after a patella in place gap balancing (denoted by P) surgery are compared with sequences corresponding to the pre–operative native state (denoted by N).

Figure 5.21 shows a qualitative measurement of similarity, proposed in Sec. 5.5.2, based on the eq. (5.9) and the PCA approach (note that this measurement is dimensionless). Each point represents a twist trajectory, as shown in the Fig. 5.17. Therefore, the proposed approach is adequate as a visual aid for discriminating between overall sequences. In addition, the resultant clustering confirms the stability of the results with the proposed methodology. The Euclidean distance between centroids of the cluster comparing pre- and postoperative sequences over the same knee constitutes a method for comparing motion sequences.

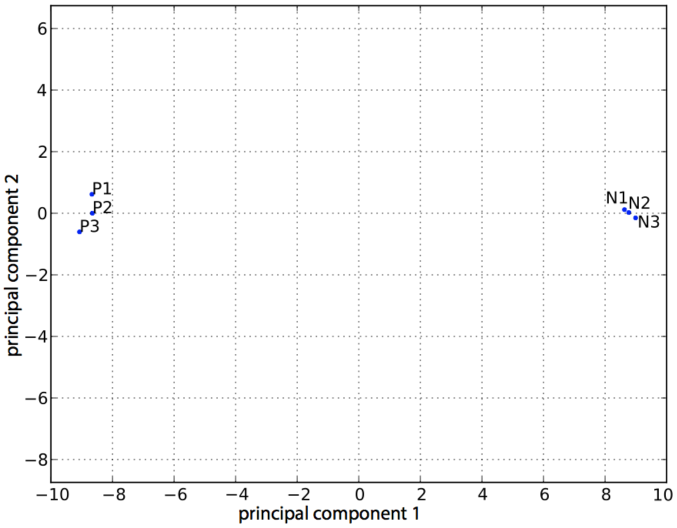


Figure 5.21: Overall similarity visualization for comparison of helical axis data on a subject with motion sequences in a pre– (denoted by N) and post–operative state (P).

Multi–scale exploration of the knee joint data

Finally, the developed intra-scale visualizations for kinematical analysis can be incorporated into the multi-scale visualization environment (c.f. Sec. 5.6 and Chapter 4 in detail), which constitutes a higher level framework for the study of knee joint data. A larger framework of information available to a range of specialists with more accurate and detailed analysis presents the ability to observe variances of the knee state and causal output. In particular, the analysis of musculoskeletal diseases, such as osteoarthritis, requires the kinematic behavior to be explored together with data sets from the organic and cellular scales (c.f. Sec. 5.2.3).

Figure 5.22 exemplarily depicts the exploration of patient–specific knee joint related data with the help of the multi–scale visualization environment. Intra-scale visualizations of helical axis data (behavioral scale) are explored together with other related data sets for a complete analysis of knee joint diseases with a multi–scale nature. In the example, it incorporates views of the cartilage (organ scale), including a femoral cartilage thickness map and a 3D reconstruction of a micro–CT scan from a cartilage sample, with some structural characteristics represented by an InfoVis visualization placed in the neighborhood of the latter, and histological images of cross sections (cellular scale).

The proposed environment (c.f. Sec. 4.3) can combine the visualizations provided by different rendering worker entities (c.f. Sec. 4.5), allowing for a global overview and interpretation of all the involved data sets, spatially emphasizing the relationships among them. For instance, the arrow between the nodes containing the thickness and the cartilage structure in Fig. 5.22 could imply that there is a potential disease feature which relates both of them, in this specific example indicating that a progressive loss of cartilage can be foreseen in structural properties of cartilage samples. Such domain

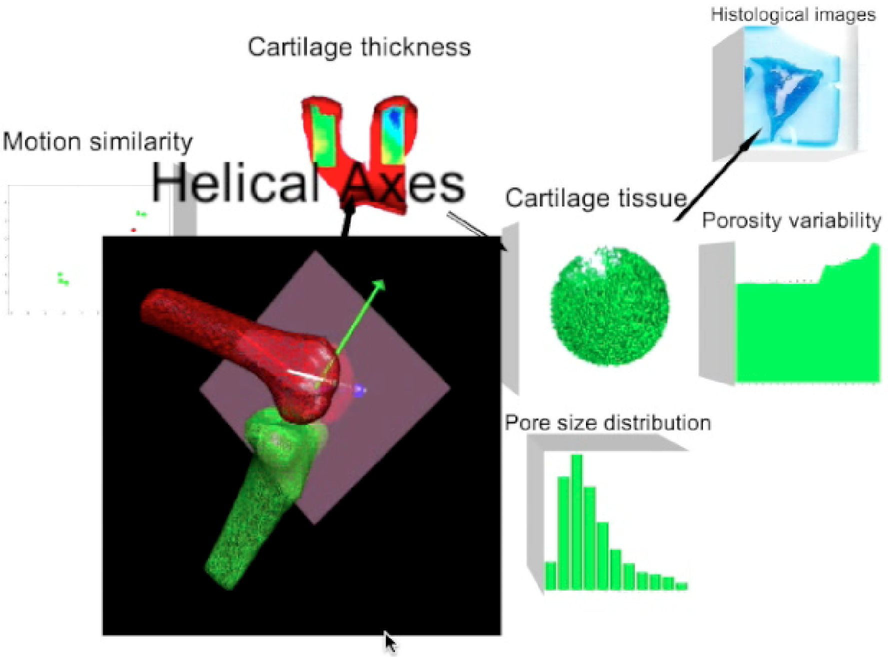


Figure 5.22: Proposal of exploration of patient–specific knee joint related data with the help of the multi–scale visualization environment including the intra-scale visualizations for the analysis of helical axis data. In the image, the user is exploring the anatomical visualization of helical axes in the focus layer.

knowledge is provided by medical experts and can be encoded in the multi-scale ontology (c.f. Sec. 4.4) [13]. Therefore, the proposed presentation also allows the knowledge of kinematical analysis based on helical axes to be shared in the context of multidisciplinary work involving other experts.

5.8 DISCUSSION

This chapter presents a set of visualization methods for inspecting knee joint articulation data (Table 5.4). The initial description of helical axes based on concepts of Lie group leads to accurate and intuitive intra-scale visualizations for the analysis of kinematical data. Together with the multi-scale visualization environment, they allow a flexible exploration of the discussed data sets and of related data, thereby supporting the clinical workflow during the analysis of the knee joint articulation.

The *description of the knee joint motion* based on helical axes presented in this work (c.f. Sec. 5.4) considers both the FHA describing a rigid body transformation relating two different configurations of the knee joint as well as the IHA of a smooth rigid body motion. Both descriptions based on helical axes are naturally discussed in the context of the Lie group $SE(3)$ of rigid body motions and its associated Lie algebra $\mathfrak{se}(3)$, which generalizes the description of rigid body motions made with Euler or Cardan angles in 3D. Approximating a sequence of rigid body transformations by

Table 5.4: Summary of properties of the proposed approach for helical axis data visualization and analysis.

Aspect	**Proposed approach**
Description of motion based on helical axes	Method of IHA in terms of Lie algebra: Valid and smooth helical axes
Visualization of helical axes	3D and patient-specific anatomical intra-scale visualization: Intuitive presentation of helical axis data
Comparison of helical axis data	Overall similarity visualization: Stable and InfoVis analysis among motion sequences
Analysis of knee joint functional articulation and related musculoskeletal diseases	Multi-scale visualization environment including the previous intra-scale visualizations

a smooth trajectory is conveniently done within $\mathfrak{se}(3)$ and then mapped onto the Lie group $SE(3)$ by the exponential map. This proposed method ensures the obtaining of only valid rigid body transformations without requiring artificial normalization or orthogonalization procedures, avoiding common singularities associated with Euler or Cardan angles. By analytically differentiating the smooth trajectories, this method effectively allows the calculation of *smooth and valid helical axes*. Figures 5.17, 5.18 show that this proposed method allows for obtaining stable, valid and smooth helical axes, allowing for the development of intra-scale visualizations methods with practical impact.

The *visualization of helical axes* by means of a *3D and patient-specific anatomical visualization* allows for an inspection that relates the processed kinematical data to the individual patient–specific anatomy, as presented in Sec. 5.5.1. The realistic visualization of bone motion incorporating helical axis data provides with respect to previous works (e.g. Fig. 5.3) an understandable and precise representation of the knee joint functional articulation. The proposed description enables a smooth interactive visualization of knee joint kinematics with several tools to interpret spatially the orientation, position and the temporal trajectory of the helical axes with respect to the knee joint anatomy. In clinical practice, the visualization (e.g. Fig. 5.19) can facilitate to distinguish variances of surgery and prosthetic wear. The development of aseptic loosening can also be easily visualized and better determine a stage of revision surgery.

The *comparison of helical axis data* also benefits from the aforementioned motion trajectory description, which naturally allows for a comparison among several motion sequences by means of the *overall similarity visualization*, as described in Sec. 5.5.2. A helpful overview for the study of similarities among a collection of experimental data improves previous visualizations focused on temporal variation of physical parameters, which have the disadvantage of being visually unclear when comparing a substantially large collection of data (e.g. Fig. 5.4). The proposed similarity visualization (Fig. 5.21) is potentially useful for epidemiological analysis of surgical techniques, best fit implant type, alignment type, as well as follow–up analysis.

Regarding the *analysis of knee joint articulation data*, the aforementioned intra-scale visualizations are proposed to be encompassed in the *multi-scale visualization environment* (c.f. Sec. 5.6). This allows sources of information with heterogeneous visual properties (e.g. InfoVis and SciVis) found across different spatial scales as well as their known relationships to be explored interactively as a whole. In the context of the study of musculoskeletal diseases, this environment contributes to the support of the visualization of causality across evidences existing within multi-scale biomedical data. Therefore, the multi-scale visualization environment (Fig. 5.16) potentially enables a complete exploration of the knee joint data (possibly in multiple states, e.g. comparing pre– and post–operative states) incorporating the developed intra-scale visualizations as well as views from other related non-kinematical data sets.

6

CONCLUSIONS AND FUTURE WORK

This work presents several processing methods in order to improve the visualization of multi-scale biomedical data, exemplified with knee joint articulation data as application scenario. The designed multi-scale visualization environment allows for the presentation of a complete set of multi-scale data with different visualization properties in a single view [150, 192]. In addition, the designed environment incorporates semantics for the enrichment of the multi-scale visualization [35], allowing scientists to amplify the cognition about the multi-scale data present in the visualization scene. In this context, the enhanced intra-scale visualizations are applicable to enrich the presentation and analysis of data within the considered scale. In this work, very relevant methods have been developed for the analysis of knee joint kinematics at the behavioral scale [151, 153].

The major contributions of this thesis can be summarized in the following aspects:

- **Design and development of a multi-scale visualization environment for multi-scale medical data analysis:** Integrated visualizations have been demanded by the biomedical community for a simultaneous presentation and exploration of data across multiples scales. However, recent works have not facilitated those tasks, and the community still make use of traditional isolated visualization systems, which allow only the exploration of features involving a concrete data type. In this work, the developed multi-scale visualization based on a 3D multilayered environment, visual links and a combination of SciVis and InfoVis techniques allows a consistent presentation and navigation of heterogeneous biomedical data. The approach of this environment encompasses data from different spatiotemporal ranges and levels of abstraction, and potentially supports the various medical domains involved in the analysis of the data.

- **Support of multi-scale visualization based on knowledge formalization:** The difficulty of exploring heterogeneous data sets increases if ways to understand the meaning of such data sets and their relations are not provided. In this work, the semantic organization provided by ontology is used in the multi-scale environment for extracting visual parameters and semantic information useful for the creation, customization and enrichment of the visualization scene. This approach allows for a meaningful presentation and navigation across the data sets of multi-scale nature.

- **Analysis and visualization of kinematical data of the knee joint articulation:** The computational methodology approach for the description of motion based on helical axes makes use of the Lie group

> of rigid body motions and its Lie algebra for a natural representation of motion sequences. This approach allows for obtaining stable, valid and smooth helical axes from in-vitro kinematical measurements. The developed intra-scale anatomical and similarity visualizations, based on this computational methodology, improve the clinical workflow during the analysis of surgical techniques and implant types, as well as the evaluation of follow-up rehabilitation approaches.

The limited attention given to the potential users of visualization analyzing their demands and their underlying fields has been criticized in the literature [137, 221, 152]. In this work, visualization processing methods have been developed during an interplay of working with and for different experts in biomedicine, e.g. biologists, biomechanical engineers. This interaction framework, based on the analysis of scientists' needs and their underlying fields, has been essential in order that such visualization processing methods contribute to the improvement of the insight into biomedical phenomena and their medical applications.

In the following, the aforementioned aspects are detailed.

Design and development of a multi-scale visualization environment for multi-scale medical data analysis.

The interplay of domains of science across spatial scales is beneficial for a more complete analysis of biological phenomena. Resulting from a multidisciplinary conception among scientists and visualization researchers, the observation and quantification of natural processes occurring at multiple scales require a multi-scale framework. However, works until now (c.f. Chapter 2) have shown that no efforts have been made in terms of visualization in order to aid scientists in the multi-scale biomedical exploration. There had been a lack of visualization strategies able to deal with the complete range of biological data obtained with the large number of diverse acquisition modalities, as in recent works small scale data do not have visibility in large scale views. In addition, current multimodal frameworks had been insufficient for completely understanding biomedical phenomena, as they do not provide semantic means to visually understand internal relations between data sets. Integrated visualization environments desired by the biomedical community would allow a simultaneous presentation of and navigation across data from multiple spatial scales and modalities including visual links (Fig. 2.20).

The proposed exploratory environment (c.f. Chapter 4) supports effectively the analysis of multi-scale biomedical data which encompass diverse spatiotemporal ranges and levels of abstraction, such as osteoarthritis (c.f. Sec. 4.6, Fig. 4.26) [150, 192]. The proposed visualization (c.f. Sec. 4.3) allows for the presentation of a complete set of multi-scale data sets as individual nodes in a single view, visually indicating semantic connections between the nodes in order to understand relations of the contained data sets, e.g. the propagation of the cartilage degradation evidenced in each data set. In this context, the established differentiation between SciVis and InfoVis techniques was overcame in order to maximize the visualization capabilities for the exploration of biomedical data sets and their relations. Its architecture (c.f. Sec. 4.5) makes feasible the presentation of large data sets in a single view. This approach potentially facilitates the work of a multidisciplinary group of specialists collaboratelly working on the analysis of pathologies that involves multi-scale data, as they could still use their habitual visualizations in a wider and richer scenario. The environment allows an intuitive and fast observation of the relevant data sets, as well as a spatial observation of relationships among them.

Support of visualization based on knowledge formalization

A meaningful representation of data sets in a multi-scale scenario is required due to the difficulty of exploring heterogeneous and multidisciplinary data. First, the heterogeneity of data (regarding the spatial scale they belong to, the discipline which studies them, and the visualization techniques employed to represent them) requires semantic organization to understand the meaning of such data sets and their relations. Second, the need of semantic means gains even more importance in a multidisciplinary scenario, as scientists have depth expertise in one concrete specialty, but they lack the big picture.

The multi-scale visualization environment proposes the semantic organization provided by an application ontology in order to extract visual parameters and semantic information useful for the creation, customization and enrichment of the visualization scene (c.f. Sec. 4.4) [35]. As example of application, it makes use of knowledge of the involved domains stored by means of the application ontology namely the multi-scale ontology [13]. The visualization is supported through ontology by providing semantic means to carry out several tasks for the presentation of data within the exploratory system for the user, such as customization of the visualization scene and extraction of semantic links among multi-scale data sets. The combination of the multi-scale ontology with the multi-scale visualization environment provides a cognitively rich and realistic presentation and exploration of the data sets, integrating visualization at the conceptual level with visualization of patient data [150]. This combination also overcomes the traditional ontology visualization tools, based on only InfoVis techniques without realistic representations, which would hinder the use of formalized semantic description.

Analysis and visualization of kinematical data of the knee joint articulation

A very relevant contribution has been performed at the behavioral scale of the study of human joint articulation. Enhanced intra-scale visualizations have been developed for accurately characterizing and interpreting kinematical data of flexion-extension motion of the knee joint in terms of helical axes.

The methods based on the helical axis concept have the potential to significantly contribute in clinical practice, e.g. the analysis of surgical techniques and implant types as well as the evaluation of follow-up rehabilitation approaches. However, tools found in the literature were insufficient for these applications as they were lacking in terms of robust analysis capabilities and intuitive visualization.

In this work it has been described how the use of the Lie group of rigid body motions, particularly its Lie algebra and the exponential map relating those supply a smooth description of a given discrete knee motion sequence, obtaining computationally stable and valid instantaneous helical axes. This computational methodology leads to a set of intra-scale visualizations with practical impact. First, the designed patient-specific three-dimensional visualization of the instantaneous helical axes provides an intuitive interpretation of the axes and their geometrical relation with respect to the knee joint anatomy. Second, the similarity visualization compares across several motion sequences allows to efficiently differentiate among several cases and states of knee joint in the course of medical analysis and surgery. The aforementioned visualizations are proposed in the framework of the multi-scale environment, allowing also for a global analysis of knee joint related data, including data sets acquired from different modalities and spatial scales [153].

This set of visualization methods improves the clinical workflow for the analysis of the knee joint articulation (c.f. Chapter 5). First, the anatomical visualization provides to the clinicians a more direct and specific representation to observe the true motion of the bones with respect to a graph indicating the flexion-extension axes [151]. This method facilitates to distinguish variances of surgery, prosthetic wear and states. For instance, the development and resultance of aseptic loosening can be easily visualized and better determine a stage for revision surgery. Second, the similarity visualization improves previous visualizations focused on temporal variation of physical parameters, which were visually unclear when comparing a considerable large data collection. This method is useful for epidemiological analysis of surgical techniques, best fit implant type, alignment type, as well as follow–up analysis. Finally, the multi-scale visualization environment is proposed as a framework in order to support the aforementioned tasks for a global exploration of the knee joint related data (possibly in multiple states, e.g. comparing pre– and post–operative states) incorporating the developed kinematical methods and other related non-kinematical data sets.

Design and development of scientist-centered visualizations

All the developed visualization methods have been performed following a design based on a scientist-centered approach. Sometimes it is forgotten that the user is the indispensable main actor of the visualization process and "responsible" for getting insight from the phenomena under analysis, in the same way as the user sometimes underestimates the importance of aspects such as software architecture required in order to obtain a visualization.

At the beginning of a collaboration for designing a visualization tool, a bridge of expectations between the scientist (future visualization user) and the visualization researcher (creator of the visualization) is usually formed. This fact is due to the lack of an alliance between visualization researchers and the fields of application of visualization, which has been required in the literature [137, 221] as well as during recent visualization conferences.

In this work, the designed visualization methods have been developed in the context of a methodology (c.f. Chapter 3) which analyzes scientists' needs and their underlying fields, including different aspects, such as: initial specification of data, objective, context of application, common understandable representation and continuous evaluation. Different experts in biomedicine – biomechanical engineers, radiologists, biologists under the MultiScaleHuman Project [15] – have collaborated in order to reciprocally be helped: to facilitate them to amplify their cognition about physiological human articulation. Only after this kind of sinergies can visualization improve through the means of new and novel methods the biomedical data exploration and their further interpretation by biomedical experts.

FUTURE WORK

There are several ways of applying and expanding the visualization methods proposed in this work. Some of the more promising possibilities are:

Applicability of the exploratory environment in other fields and scales

The application scenario (c.f. Chapter 5) described in this work for the analysis of knee joint articulation can be considered to be applicable for any other scientific field where specialists are working on the exploration of multimodal or multi-scale biomedical data. One example is the exploration of dynamic images for functional evaluation and modeling of muscular activity [216] (c.f. Sec. 4.8).

Following up with the application scenario, similar investigations as the ones performed in this work at the behavioral scale can be performed at other scales, contributing with new enhanced intra-scale visualizations for improving the understanding of data attached to those concrete scale. All intra-scale visualizations and new improvements can be encompassed in the multi-scale visualization environment. The scalability of its software architecture allows that every new visualization can be represented in a node, including new information for the multi-scale ontology. Together with experts in the field, the knowledge is augmented with their findings, discussing their conclusions and continuing the discovery by using the visualization environment. In this context, the next step could be the development of a rendering worker which includes all the features of YaDiV.

Adaptiveness of the multi-scale visualization environment

In this work, semantics is incorporated in a multi-scale visualization environment to provide visual means to identify relevant items for a didactical presentation to the user. The introduction of semantics in this context opens new roads for further integration between visualization and knowledge formalization.

An interesting example is a further support of collaborative diagnosis, introduced in [150]. Consider a scenario where different medical specialists could work together in the same environment, share experiences with each other and formulate conjectures, e.g. involving the exploration of past studies. This scenario requires a dynamic use of the visualization and semantics, where both are adapted during the workflow of the specialists. Thus, the visualization composition should be dynamically performed according to the knowledge, which should vary according to the inclusion of the formulated conjectures. In this case, the user interface should be extended in order to receive and process such hypotheses. Initial ideas in this direction are the integration of scoring techniques on the knowledge base level, influence positioning of nodes based on user interests, as well as the incorporation of a voice recognition system.

The integration of customized visualizations with semantics can also improve the medical support based on artificial intelligence and the experts' workflow for interpreting medical data. Currently, systems as PACS (Picture Archiving and Communication System) or RIS (Radiology Information System) allow only to centralize data, where experts from different specialties can obtain medical information from a centralized repository. Idealistically, the integration of systems as PACS within the proposed methodology would provide experts not only organized data, but also related knowledge among these data (metadata) as well as a global visualization framework and a customized set of visualization tools according to the scientist's field and interests for supporting knowledge discovery.

Improvements on the visualization and analysis of the knee joint articulation at the behavioral scale

The performed intra-scale visualizations described in the application scenario have also several interesting future steps to investigate.

Regarding the anatomical visualization (c.f. Sec. 5.5.1), establishing an automated mapping between the anatomical landmarks detected in the visualization tool and in the experiments is desirable, as it is currently based on the expertise of surgeons and biomechanical engineers. An alternative is the combination of automatic landmark detection with 3D printing technologies in order to produce patient–specific bone templates for a guided determination of the landmarks prior to the data collection. This improvement would facilitate the translation of this visualization method to the clinical practice in surgical operations, as the optical tracking technique employed in the data collection is also used during total knee replacement surgeries. Thus, surgeons could potentially make use of this tool to evaluate during operations the behavior of the helical axes. Regarding the similarity visualization (c.f. Sec. 5.5.2), extended kinematical studies yielding a large collection of motion sequences could lead to better models of healthy vs. pathological knee joint functionality.

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A

TABLE OF DATA SETS

Table A.1 lists the data sets used in the proposed multi-scale visualization environment, including the following features: visualization properties, technique, degradation process feature, source of evidence, user profile and spatial scale (c.f. Chapter 4). Note that those data sets do not correspond to the same patient, therefore they might be affected with different grades or states of diseases. However, in terms of visualization, they serve for illustration purposes when describing the multi-scale visualization environment.

Table A.1: Multi-scale data sets

Data set	Description	Visualization properties	Technique	Degradation process feature	Source of Evidence	User profile	Spatial scale
Histology-AlcianBlue	Articular cartilage slices by using Alcian blue for the staining method	Set of images	Alcian blue histology	Cellular change	Cell dedifferentiation, hypertrophy	Molecular biologist, Tissue engineer	Micro
Histology-SafraninO	Articular cartilage slices by using Safranin O for the staining method	Set of images	Safranin O histology	Loss of biomechanical funcion	Disruption of the macromolecule content	Molecular biologist, Tissue engineer	Micro
Cartilage-Structure	3D reconstruction of volume of interest (VOI) from micro-CT scans of cartilage	Volume	Micro-CT	Loss of biomechanical function	Swelling, Hyperhydration, Tissue softening	Molecular biologist, Tissue engineer	Micro
Porosity-Variability	Variation of the fraction of the volume of voids over the total volume along the different layers of the VOI of cartilage	Bar chart	Micro-CT	Loss of biomechanical function	Swelling, Hyperhydration, Tissue softening	Molecular biologist, Tissue engineer	Micro
PoreSize-Distribution	Measure of the range of pores in the VOI of cartilage	Bar chart	Micro-CT	Loss of biomechanical function	Swelling, Hyperhydration, Tissue softening	Molecular biologist, Tissue engineer	Micro
Nanoindentation-Cartilage	Mechanical properties of cartilage by using the nanoindentation technique	Bar chart	Nanoindentation	Loss of biomechanical function	Swelling, Hyperhydration, Tissue softening	Molecular biologist, Tissue engineer	Micro
Cell Viability-Rate	Proportion of damaged cells in the cartilage sample obtained from Live/Dead assays	Pie chart	Live/Dead cell analysis	Cellular change	Cell viability	Molecular biologist, Tissue engineer	Micro
LiveDead-Assay	Images from Live/Dead assays illustrating the cell viability	Raster images	Live/Dead cell analysis	Cellular change	Cell viability	Molecular biologist, Tissue engineer	Micro
PCR	Graph for the analysis of disease development in osteoarthritis research by means of PCR (Polymerase chain reaction) analysis on cartilage	Bar chart	PCR analysis	Cellular change	Anabolic/ Catabolic reactivation	Molecular biologist, Tissue engineer	Micro
Cartilage-Thickness	Femoral cartilage thickness by means of colormaps on the volumetric visualization	Manifold surface mesh with colormap	MRI	MRI evidence	Cartilage thinning, fissure	Radiologist	Medium
MRI	Volumetric visualization of knee joint from MRI scans	Volume	MRI	MRI evidence	Cartilage thinning, fissure	Radiologist	Medium
Knee-Angles	Angles of the knee joint during gait pattern analysis	Line chart	Gait analysis	Alteration in gait pattern	Joint use range of motion	Biomechanical engineer	Macro
Knee-Moments	Moments of the knee joint during gait pattern analysis	Line chart	Gait analysis	Alteration in gait pattern	Joint use range of motion	Biomechanical engineer	Macro
EMG	Electromyography of knee joint related muscles during gait pattern analysis	Line chart	EMG	Alteration in gait pattern	Joint stiffness	Biomechanical engineer	Macro
Helical-Axes	Volumetric visualization of knee joint motion combining kinematical data processed after in vitro studies (c.f. Sec. 5.4.5) and their corresponding CT scans	Video	In vitro knee simulator	Alteration in gait pattern	Joint use range of motion	Biomechanical engineer	Macro
Motion-Similarity	Similarity of knee joint motion sequences after processing the data from in vitro studies (c.f. Sec. 5.4.5)	Scatter plot	In vitro knee simulator	Alteration in gait pattern	Joint use range of motion	Biomechanical engineer	Macro
Gait-Motion	Motion capture video obtained from a 3D optical motion capture system	Video	Gait analysis	Alteration in gait pattern	Joint use range of motion	Biomechanical engineer	Macro

B

CONTRIBUTIONS OF THE AUTHOR OF THE THESIS WITHIN JOINT PUBLICATIONS

The author of this thesis has been co-author of the following publications, listed in chronological order. This annex is intended to summarize the contributions of the author in those scientific works.

- Millán Vaquero R., Rzepecki J., Friese K.-I., Wolter F.-E. Visualization and User Interaction Methods for Multiscale Biomedical Data. In: 3D Multiscale Physiological Human. pp. 107-133. Springer. 2014 [152].

  This work describes visualization and interaction approaches for the exploration of multi-scale biomedical data. The increasing amounts of data at different scales has the potential to explore complex phenomena in human physiology which spread amongst multiple scales, therefore requiring an analysis of current multi-scale visualization and interaction methods. In this publication, the author of this thesis focuses on the visualization part. The author discusses the current complexity of representing biomedical data, and describes current techniques and proposes alternatives for multi-scale visualization.

- Agibetov, A., Millán Vaquero R., Friese, K.-I., Patanè, G., Spagnuolo, M., Wolter, F.-E. Integrated Visualization and Analysis of a Multiscale Biomedical Knowledge Space. In EuroVis Workshop on Visual Analytics pp. 25-29. The Eurographics Association. 2014 [35].

  This work proposes a visualization prototype to integrate a multiscale biomedical data set into the same view, taking advantage of the biomedical knowledge about the data and their connections formalized in an ontology. In this publication, the author of this thesis focuses on the design of a specific integrated multi-scale visualization approach. The author identifies properties for the classification of multi-scale biomedical data, to be encoded into the ontology. This information allows for obtaining visual parameters and semantic means to configure by the author the visualization environment, as exemplified within a scenario dealing with the exploration of musculoskeletal diseases.

- Rzepecki J., Millán Vaquero R., Vais A., Friese K.-I., Wolter F.-E. Multimodal Approach for Natural Biomedical Multi-scale Exploration. In Advances in Visual Computing: 10th International Symposium on Visual Computing. pp. 620-631. Springer. 2014. [192].

  This paper presents an approach for the exploration of multi-scale biomedical data, combining the proposed visualization with hand and haptic interaction. In this publication, the author of this thesis focuses on the concrete realization of the visualization environment, based on a multilayered workspace and a flexible combination of scientific and information visualization, including an evaluation yielding a preliminary analysis of the introduced features.

- Millán Vaquero R., Agibetov A., Rzepecki J., Ondrésik M., Vais A. Oliveira, J.M., Patanè G., Friese K.-I., Reis R.L., Spagnuolo M., Wolter F.-E. A semantically adaptable integrated visualization and natural exploration of multi-scale biomedical data, 12th International Conference BioMedical Visualization MediVis 2015. pp. 543-552. IEEE. 2015 [150].

  This paper is a summary of the common efforts from visualization, interaction and knowledge formalization in order to improve the exploration of multi-scale biomedical data. In this publication, the author of this thesis focuses on the visualization part, analyzing the use of the visualization environment within an application scenario of a biologist investigating a pathology that requires the analysis of knee joint data from multiples scales. In particular the author compares the traditional way of visualizing data related to the degradation of articular cartilage during osteoarthritis with the one deduced from the proposed methodology.

- Millán Vaquero R., Lynch S., Fleischer B., Rzepecki J., Friese K.-I., Hurschler C., Wolter F.-E. Enhanced visualization of knee joint functional articulation based on helical axis method. Proceedings Bildverarbeitung für die Medizin 2015. pp. 449-454. IEEE. 2015 [151].

  This work focuses on the visualization of knee joint data at behavioral scale, concretely on the visualization of knee joint motion described in terms of helical axes. In this publication, the author of this thesis provides an enhanced intra-scale visualization for a realistic motion representation of the knee joint functional articulation. Basing on finite helical axis data obtained from biomechanical experiments, the visualization has been developed in order to especially facilitate the location of functional flexion axes in terms of anatomical bone motion.

- Millán Vaquero R., Vais A., Lynch S., Rzepecki J., Friese K.-I., Hurschler C., Wolter F.-E. Helical axis data visualization and analysis of the knee joint articulation. Journal of Biomechanical Engineering. ASME. DOI:10.1115/1.4034005. 2016 [153].

  Following up on the previous publication, this paper provides an extended analysis of helical axis data and several visualization methods for investigating the knee joint articulation. In this publication, the author of this thesis starts with the analysis of kinematical data of flexion-extension motion of the knee joint provided from biomechanical engineers. Processing methods relying on Lie group theory lead to a smooth description of motion sequences, which allow the calculation of instantaneous helical axes for a more accurate data evaluation. The described visualization methods, which include intra-scale visualizations and the multi-scale environment, are proposed to

support the analysis of motion sequences of knee joint articulations and their related data.

C

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