

From individual to population: Challenges in Medical Visualization

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1 Introduction

Since the advent of magnetic resonance imaging (MRI) and computed tomography (CT) scanners around the early seventies, and the consequent ubiquitousness of medical volume data, Medical Visualization has undergone significant development and is now a vibrant branch of Visualization. It finds application in diagnosis, for example virtual colonoscopy, treatment, for example surgical planning and guidance, and medical research, for example visualization of diffusion tensor imaging data.

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Although the field of medical visualization only established itself with this name in the late eighties [53], we shall see in the next section that already in the seventies there were published examples of computer-generated images, based on medical data and used for medical applications.

During the past decades, medical image acquisition technology has undergone continuous and rapid development. It is now possible to acquire much more and much more complex data than ever before. For example, in High Angular Resolution Diffusion Imaging (HARDI), fourty or more diffusion-weighted volumes are acquired in order to calculate and visualize water diffusion and indirectly structural neural connections in the brain [66]. In fMRI-based full brain connectivity, time-based correlation of neural activity is indirectly measured between all pairs of voxels in the brain, thus giving insight into the functional neural network [22]. Moreover, the questions that users attempt to answer using medical visualization have also become significantly more complex.

In this paper, we first give a high-level overview of medical visualization development over the past 30 years, focusing on key developments and the *trends* that they represent. During this discussion, we will refer to a number of key papers that we have also arranged on the medical visualization research timeline shown in figure 1.

Based on the overview and our observations of the field, we then identify and discuss the medical visualization research challenges that we foresee for the coming decade.

2 Thirty-year Overview of Medical Visualization

Already in 1978, Sunguroff and Greenberg published their work on the visualization of 3D surfaces from CT data for diagnosis, as well as a visual radio-therapy planning system, also based on CT data [60]. Five years later, Vannier *et al.* published their results developing and evaluating on more than 200 patients a system for the computer-based pre-operative planning of craniofacial surgery [67]. Their system was based on the extraction and visualization of 3D hard and soft tissue surfaces from CT data. Through the integration of an industrial CAD application, it was also possible to perform detailed 3D measurements on the extracted surfaces.

2.1 Practical and multi-modal volume visualization

In 1986, Hohne and Bernstein proposed using the gray-level gradient to perform shading of surfaces rendered from 3D CT data [24]. In 1987, Lorensen and Cline published the now famous Marching Cubes isosurface extraction algorithm, which enabled the fast and practical extraction of 3D isosurfaces from real-world medical data. In the year thereafter, Levoy introduced the idea of volume raycasting in

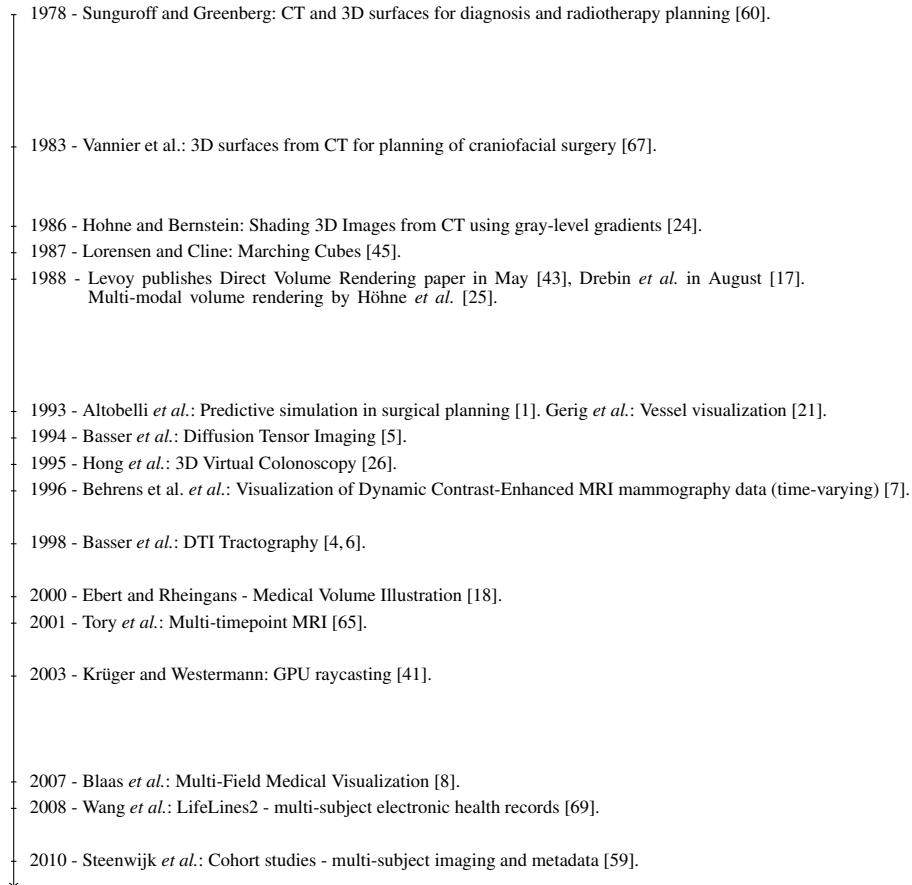


Fig. 1 Timeline with a subset of medical visualization papers showing the progression from scalar volume datasets through time-dependent data to multi-field and finally multi-subject datasets. This timeline is by no means complete, instead attempting to show a representative sample of papers that represent various trends in the development of the field.

May [43], and Drebin *et al.* in August [17]. Although medical volume visualization was possible before these publications, as witnessed by a number of publications, previous techniques were either not as fast or yielded less convincing results. With the introduction of Marching Cubes and volume raycasting, volume visualization became a core business of visualization and medical visualization for the years to come.

Up to this point, research had focused on uni-modality data, primarily CT. However, already in 1988 the first multi-modal volume rendering paper was published by Höhne *et al.*, in which they demonstrated the registration and combined visualization of CT and MRI.

2.2 Therapy planning, predictive simulation, and diagnosis

Therapy planning was one of the first real applications of medical visualization and remains important to this day. In 1993, Altobelli *et al.* published their work on using CT data to visualize the possible outcome of complicated craniofacial surgery [1]. By manually repositioning soft tissue fragments based on the bony surfaces under them, in certain cases taking into account bone-skin motion ratios from literature, it was possible to visualize the possible outcome of a craniofacial procedure, also in terms of how the patient's skin surface geometry would change. Although still rudimentary, this could be considered one of the earliest cases of *predictive or outcome simulation* integrated with visualization for surgical planning. The idea of predictive simulation, or predictive medicine, was further explored by Taylor *et al.* for cardiovascular surgery [62].

With the introduction of virtual colonoscopy in 1995 [26], medical visualization also gained diagnosis as an important medical application, namely screening for colon cancer. This work was also the basis for many other virtual endoscopy systems, e.g., virtual bronchoscopy and virtual angioscopy. A careful integration of image analysis (segmentation, skeletonization), with efficient rendering (occlusion culling) and interaction (camera control based on predefined paths) are major ingredients of such systems [3].

2.3 Multi-field data

Diffusion Tensor Imaging, or DTI, is an MRI-based acquisition modality, introduced in 1994 by Basser *et al.*, that yields 3×3 symmetric diffusion tensors as its native measurement quantity [5]. The tensors represent the local diffusion of water molecules, and hence indirectly the presence and orientation of fibrous structures, such as neural fiber bundles or muscle fibers. Already in this first paper, the authors employed 3D glyphs to visualize the eigensystems represented by the tensors, see figure 2.

Basser and his colleagues were also some of the first to extract and visualize fiber-tract trajectories from DTI data of the brain [4, 6], thus linking together the point diffusion measurements to get an impression of the global connective structures in the brain. With DTI it was encouraging to see that the first visualization efforts were initiated by the scientists developing this new scanning modality themselves. Early work by the visualization community includes tensor lines for tractography [72] and direct volume rendering of DTI data [34, 35].

Importantly, DTI serves as one of the first examples of natively multi-field medical data, that is medical data with multiple parameters defined over the same spatio-temporal domain. The advent of DTI initiated a whole body of medical visualization research dedicated to the question of how best to visually represent and interact with diffusion tensor data in particular and multi-field medical data in general. The 2007

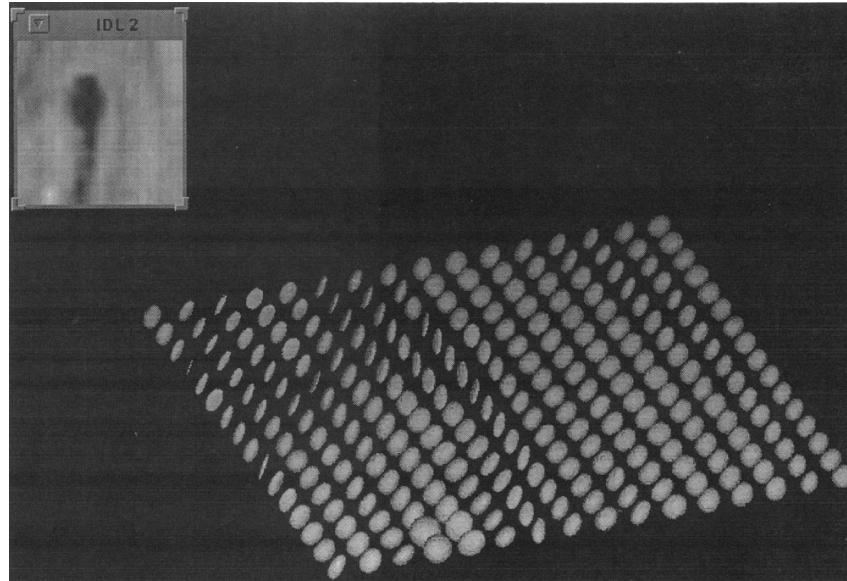


Fig. 2 Effective diffusion ellipsoid glyphs from 2D region of interest of DTI dataset of cat brain. Image taken from [5].

paper by Blaas *et al.* presented a visual analysis-inspired solution to this problem based on linked physical and feature space views.

2.4 Time-varying Data

Time-varying medical volume data visualization made its entrance in 1996 with work by Behrens *et al.* on supporting the examination of Dynamic Contrast-Enhanced MRI mammography data with the display of parameter maps, the selection of regions of interest (ROIs), the calculation of time-intensity curves (TICs), and the quantitative analysis of these curves [7]. In 2001, Tory *et al.* presented methods for visualizing multi-timepoint (1 month interval) MRI data of a multiple sclerosis (MS) patient, where the goal was to study the evolution of brain white matter lesions over time [65]. Methods used included glyphs, multiple isosurfaces, direct volume rendering and animation.

Coto *et al.* applied multiple coupled views, including linked cursors and brushing on 3D renderings and scatterplots to dynamic contrast-enhanced MRI (DCE-MRI) mammography data [14].

2.5 Illustrative Visualization

Illustrative visualization is primarily motivated by the attempt to create renditions that consider *perceptual capabilities* of humans. As an example, humans infer information about shapes not only from realistic shading but also from appropriate hatching and from outlines that support the mental separation of nearby objects rendered in similar colours.

Illustrative visualization is related to the computer graphics term *Non-Photorealistic Rendering*, or NPR for short. The term NPR was used since around 1990 when the seminal paper of Saito *et al.* clearly illustrated that complex 3D shapes could be rendered more *comprehensible* by using certain *feature lines* [57]. Compared to NPR, illustrative visualization is the more focussed term that covers rendering techniques serving clear visualization goals, namely to convey shape information efficiently. In medical visualization, either surfaces or volume data are rendered in illustrative styles. For illustrative volume rendering, the term *volume illustration* was introduced by Ebert *et al.* in 2000 [18]. Boundary enhancement based on gradient approximation [15] and curvature-based transfer functions [36] are landmarks in illustrative medical visualization. Tietjen *et al.* applied silhouettes and other feature lines for various scenarios in liver surgery planning [64]. Besides silhouettes, stippling and probably even more hatching has great potential to reveal details of shapes [28].

Later, Bruckner *et al.* made a number of important contributions that support depth and shape perception with adapted transfer functions. In particular, they considered the peculiarities of interactive exploration of 3D datasets and elaborated on the idea of preserving essential context information [9–11]. These and later refinements are integrated in the VolumeShop-system that is publicly available and used by several research groups

2.6 Multi-subject data

Medical visualization has also started to work on the problem of dealing with multi-subject data. These are datasets that include measurements, including imaging, of more than one subject. The goal is to be able to extract patterns that affect sub-groups of the whole collection, for example to explore which aspects of the data correlate with a specific disease outcome. Examples of this type of work include LifeLines2, a information visualization approach to visualize and compare multiple patient histories or electronic medical records [69]. More recently, work has been done on the interactive visualization of the multi-subject and mixed modality datasets acquired by medical cohort studies [59]. In these studies, mixed modality data, including imaging, genetics, blood measurements and so on, is acquired from a group of subjects in order to understand, diagnose or predict the clinical outcome of that group. Steenwijk *et al.* demonstrated that it was possible to create a highly interactive coupled view visualization interface, integrating both information and

scientific visualization techniques, with which patterns, and also hypotheses, could be extracted from the whole data collection.

3 Challenges in Medical Visualization

3.1 *Advances in data acquisition*

Toshiba's 320-slice CT scanner, the Aquilion One, was introduced in 2007. It is able to acquire five 320 slice volumes *per second* [27] and can thus image a beating heart. Rapid and continuous advances in the dynamic nature and sheer magnitude of data in this and other mainstream medical imaging necessitates improvements to existing techniques in terms of computational and perceptual scalability.

High Angular Resolution Diffusion Imaging (HARDI) [66] and Diffusion Spectrum Imaging (DSI) [23] datasets contain hundreds of diffusion-weighted volumes describing the diffusion of water molecules and hence indirectly the orientation of directed structures such as neural fiber bundles or muscle fibers. This is a rather extreme example of multi-field medical data that is becoming more relevant in both medical research and clinical application. Completely new visual metaphors are required to cope with the highly multi-variate and three-dimensional data of diffusion weighted imaging in particular and many other new imaging modalities in general.

Molecular imaging enables the *in vivo* imaging of biochemical processes at macroscopic level, meaning that for example pathological processes can be studied and followed over time in the same subject long before large-scale anatomical changes occur. Examples are bioluminescence (BLI) and fluorescence (FLI) imaging, two molecular imaging modalities that enable the *in-vivo* imaging of gene expression. Molecular imaging yields datasets that vary greatly in scale, sensitivity, spatial-temporal embedding and in the phenomena that can be imaged. Each permutation brings with it new domain-specific questions and visualization challenges. Up to now, most of the visualization research has been focused on small animal imaging [37, 38], but due to its great diagnostic potential, molecular imaging will see increased application in humans.

The integration of microscopy imaging is an essential task for the future, where data handling, interaction facilities but also more classical rendering tasks such as transfer function design become essential. With more and more large scale and 3D microscopy data available, there are many opportunities for visualization researchers. Recent examples include techniques for interactively visualizing large-scale biomedical image stacks demonstrated on datasets of up to 160 gigapixels [30] and tools for the interactive segmentation and visualization of large-scale 3D neuroscience datasets, demonstrated on a 43 gigabyte electron microscopy volume dataset of the hippocampus [29].

With these examples, we hope to have illustrated that advances in image acquisition are continuous, and due to the increasing demands of modern society are

accelerating. Each new advance in imaging brings potentially greater magnitudes and exotic new types of data leading to new challenges for medical visualization.

3.2 Heterogeneous display and computing devices

Mobile devices, in particular the APPLE products IPAD and IPHONE are extremely popular among medical doctors and indeed solve some serious problems of desktop devices in routine clinical use. In particular, bedside use of patient data is an essential use case for medical doctors of various disciplines.

Meanwhile several mobile devices are equipped with powerful graphics cards and using the Open GL ES (Embedded Systems) standard, they are able to provide high-quality interactive rendering. Although the performance still tails that of modern desktop devices, slicing medical volume data and 3D rendering is feasible [48].

The rapid and widespread use of mobile devices also made gesture input popular. In particular, multi-touch interaction is considered an intuitive interaction since many potential users know a variety of gestures from their everyday activities with smart phones. Therefore multitouch interaction is also incorporated in large displays in medical use, e.g. the Digital Lightbox¹ by BrainLab and the multi-touch table of Lundström et al. [46].

3.3 Interactive image segmentation

Image segmentation is important in clinical practice, for example diagnosis and therapy planning, and also in image-based medical research. In these applications, segmentation is complicated by the great deal of variation in image acquisition, pathology and anatomy. Furthermore, in matters of diagnosis or therapy planning, the accuracy of the segmentation can be critical. It comes as no surprise that user interaction is often required to help ensure the quality of the results, by initializing an image processing method, checking the accuracy of the result or to correct a segmentation [51].

A well-known interactive segmentation technique is the live-wire or intelligent scissors [47]. These ideas were later extended and applied to medical images [19]. More recently, visualization has been applied to the challenge of explicitly dealing with the uncertainty inherent in interactive 3D segmentation [52, 56].

Medical visualization research often combines elements of image analysis, graphics and interaction, and is thus ideally equipped to address the challenge of developing and validating effective interactive segmentation approaches for widespread use in medical research and practice.

¹ <http://www.brainlab.com/art/2841/4/surgical-pacs-access/>

3.4 Topological methods

Topological data representation has played an important role in medical visualization, since it can allow us to segment specific features such as human organs and bones from the input medical datasets systematically and identify their spatial relationships consistently. Actually, such topological concepts have been already introduced in the earlier stage of medical visualization. For example, the 3D surface of a human cochlea were reconstructed from a series of 2D CT cross-sectional images by identifying correct correspondence between the cross-sectional contours [58].

Topological approaches have also been extended to analyze 3D medical volume data. Contour trees [2] have been employed for designing transfer functions in order to illuminate human organs and bones systematically since the associated anatomical structure can be effectively captured as topological skeletons of isosurfaces [71]. Spatial relationships between bones and the position of aneurysm were successfully extracted respectively from CT and angiographic datasets using a variant of contour tree [13]. Interesting features in medical volume data can be visually analyzed using an optimal camera path, which can be obtained by referring to topological structure of human organs [61] (See figure 3).

Topological methods are now being developed for visualizing multi-variate and high-dimensional datasets, and thus potential for analyzing tensor fields obtained through DT-MRI, multi-subject data in group fMRI studies, and time-varying data measured by high-speed CTs.

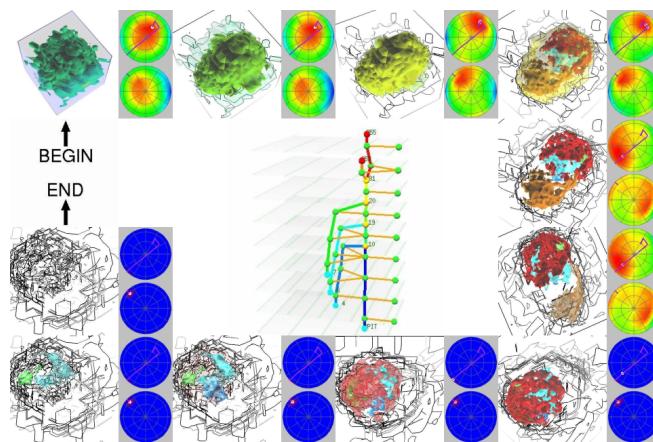


Fig. 3 Previewing a sheep heart volume along the optimal camera path. Image taken from [61].

3.5 Integration of simulation models

In their 1999 predictive medicine paper, Taylor *et al.* argued that surgical planning should not only address questions of surgical approach but also of the expected outcome, for example predicted future states such as the efficacy of a treatment option or the performance of an implant [62].

Medical visualization approaches become significantly more valuable when enhanced with simulation models that help to predict the outcome of a disease process or therapeutic procedure, or that enrich measured data with expected physiological phenomena. Examples besides the blood flow simulations of Taylor *et al.* include interactive skeletal range of motion [39] and biomechanical stress [16] simulation models for implant planning in orthopedics and nasal airflow simulation for reconstructive rhinosurgery [73].

The integration of these predictive models, although potentially valuable, brings with it new challenges. The addition of potentially complex and dynamic simulation output data to existing visualizations requires new visual representation techniques. Furthermore, for the simulation results to be maximally useful, the models should be tightly coupled to and steered by the user's interaction with the medical visualization. Finally, most simulations yield data with a certain degree of inherent uncertainty. The role of this uncertainty should be fully explored and it should be carefully but explicitly represented as an integral part of the visualization.

3.6 Mappings and reformations

In 2002, the American Heart Association proposed a standardised segmentation and accompanying 2D bull's eye plot (see figure 4) of the myocardium, or heart muscle, of the left heart ventricle [12]. This 2D plot is a simple but great example of reducing complex 3D data to a standardized 2D representation that greatly facilitates the interpretation of that data. Another well-known example is that of curved planar reformation, or CPR, where volume data is sampled along a curved plane following the trajectory of a blood vessel or other tubular structure, thus enabling the study of the vessel and its surroundings with the minimum of interaction [32]. Other good examples of reformation can also be found in brain flattening [20] and colon unfolding [68].

Recently, the idea of intelligently reformatting or mapping 3D data was further explored by Neugebauer *et al.* with aneurysm maps for the visualization of complex blood flow simulation data on the inside surfaces of aneurysms [49] and by Rieder *et al.* with their tumor maps for the post-operative assessment of radiofrequency ablation therapy [55].

These types of reformations and mappings entail that more effort has to be put into carefully designing simplified, usually 2D, representations of complex 3D data, as opposed to for example the relatively straight-forward projection of volume data.

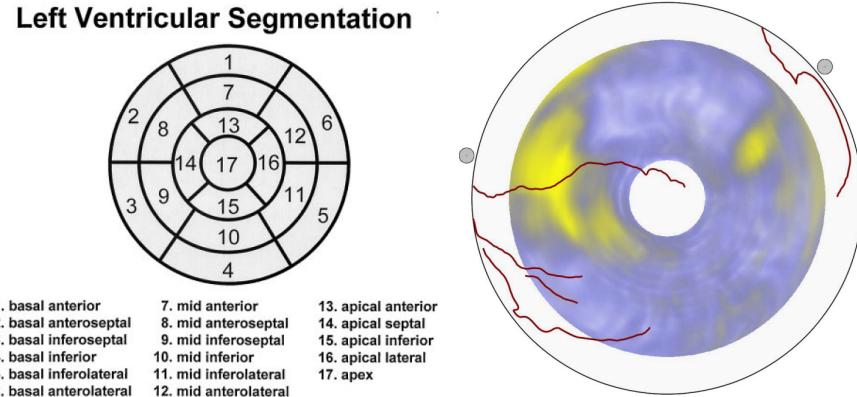


Fig. 4 On the left the American Heart Association standardized 2D bull's eye plot (BEP) of the left ventricle of the heart [12]. On the right the volumetric bull's eye plot, a modernized version by Termeer et al. [63].

The resultant visualization, if done right, requires less or no interaction and by definition avoids a number of problems inherent in 3D representations [70].

3.7 Illustrative Visualization in Medicine

For a long time, it was not possible to apply illustrative visualization techniques in practice due to performance constraints. With advances in graphics hardware and algorithms, such as GPU raycasting [41], it is now feasible from a computational standpoint.

Now that that computational problems have been largely solved, illustrative visualization approaches have to be finetuned and evaluated for diagnostic and treatment planning purposes. Recent examples of such work include the simulation of crepuscular rays for tumor accessibility planning [33], multi-modal illustrative volume rendering for neurosurgical tumor treatment [54].

Illustrative medical visualization becomes increasingly important when visualizations become more complex and multi-modal, integrating functional (measured and simulated), anatomical information and for example surgical instruments. Illustration techniques enable visual representations to be simplified intelligently by the visualization designer, whilst still communicating as much information as possible. An example of this is the work of Zachow *et al.* on the visualization of nasal air flow simulation where boundary enhancement was used as illustrative technique to convey the simulated flow and the anatomy simultaneously [73].

3.8 Hyper-realism

Analogous to the case of illustrative visualization, the rapid development in graphics hardware and algorithms has now enabled the *interactive* rendering of medical imaging datasets with physically-based lighting [40]. Figure 5 shows an example of such a visualization. These techniques make possible the simulation of an arbitrary number of arbitrarily shaped and textured lights, real shadows, a realistic camera model with lens and aperture, and so forth, all at interactive rates.



Fig. 5 Two examples of *interactive* visualizations made with the volume renderer of Kroes *et al.* [40]. Through the use of GPUs, physically-based lighting has become possible in an interactive volume rendering setting, enabling increased realism through soft shadows, depth of field and in this case mixed phase function and BRDF surface scattering.

These techniques enable not only photo-realism, but also a technical form of *hyper-realism* in art, where it is possible to enhance visualizations with *additional* realistic detail in order to better convey information. Whilst there are strong indications that for example global illumination and shadows can have a positive effect on task performance in normal volume rendering [44], the possibilities and value of hyper-realistic effects in medical visualization need to be explored.

3.9 Visual Analysis in Healthcare

Visual analysis is becoming an essential component of medical visualization due to the rapidly growing role and availability of complex multi-dimensional, time-

varying, mixed-modality, simulation and multi-subject datasets. In our view, the magnitude and especially the heterogeneity of the data necessitate the use of visual analysis techniques.

Existing examples involving time-varying data include the work of Coto *et al.* on DCE-MRI mammography [14] and Oeltze *et al.* on perfusion data in general and MR perfusion of the brain in particular [50]. Blaas *et al.* applied visual analysis techniques to multi-modal medical data, whilst Zachow *et al.* focused on nasal air-flow simulation data combined with anatomical information [73].

There is great potential for visual analysis in medical visualization, with clinical applications including advanced diagnosis and medical research and, even more importantly, treatment planning and evaluation, e.g. radio therapy planning and post-chemotherapy evaluation. The new Visual Analysis in Healthcare (VAHC) workshops that were held at IEEE VisWeek in 2010 and 2011 underline the emerging importance of this research direction.

3.10 Population imaging

In population imaging, medical image data and other measurements are acquired of a large group of subjects, typically more than one thousand, over a longer period, typically years, in order to study the onset and progression of disease, general aging effects, and so forth in larger groups of people. Examples include the Rotterdam Scan Study focusing on neuro-degeneration [42] and the Study of Health In Pomerania (SHIP) focusing on general health [31].

This application domain is an extreme example of multi-subject medical visualization discussed in section 2, integrating large quantities of heterogeneous, multi-modal and multi-timepoint data acquired of a large group of subjects. The scientists running these studies usually do not formulate strictly-defined hypotheses beforehand, instead opting for meticulous data acquisition, followed by an extended period of analysis in order to extract patterns and hypotheses from the data. Recently, Steenwijk *et al.* set the first steps for the visualization of population imaging by applying visual analysis techniques to cohort study imaging data [59].

The extreme heterogeneity and magnitude of the data, coupled with the explorative nature of the research, renders this a promising long-term application domain for visual analysis and medical visualization.

4 Conclusions

In this chapter, we gave a compact overview of the history of medical visualization research, spanning the past 30 years. Based on this history and on our own observations working in the field, we then identified and discussed the research challenges of the coming decade.

Our discussion of classic medical visualization problems related to efficient and high quality display of *one* static dataset was brief. We devoted more space to data that change over time, to the integration of anatomy with simulation and finally to cohort studies. We refer to problems where such time-dependent and high-dimensional data are employed as *MedVis 2.0* problems. While the classic problems are – from an application perspective – solved, there are many research opportunities in MedVis 2.0 problems. These data are significantly more difficult to analyze, to process and to visualize. Time-dependent MRI data, e.g., exhibit all artifacts of static MRI data but a number of additional artifacts, e.g. due to motion. Integrated analysis and visualization is a key feature of MedVis 2.0 solutions. In general, successful solutions to these problems require a considerably deeper understanding of the medical background and thus favor close collaborations with medical doctors over merely having access to medical data.

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