Chapter e22

Outlook

In the previous chapters, we gave an overview of the field of visual computing in medicine as it currently stands. In this chapter, we will attempt to predict the future of our field.

This is by nature more speculative and based on opinions and attitudes. In order to mitigate the risk of bias and to ensure a broader view, we discussed with a number of leading experts in the field, and integrated their visions with this chapter. These experts are Hans-Christian Hege (Zuse Institute Berlin), Timo Ropinski and Anders Ynnerman (both Linköping University), Anna Vilanova (Delft University of Technology), and Ivan Viola (Technical University of Vienna).

The majority see a number of important trends for the future that go beyond refinements and adaptations of existing techniques. At least one general aspect seems clear: The future of "visual computing in medicine" is closely linked to the future of medicine. Therefore, we briefly discuss emerging trends in medicine, such as personalized medicine and the design of large cohort studies to better understand diseases.

We start by discussing the main forces driving our field. Based on our analysis of these factors, we then try to predict the main directions in which our field will develop over the coming years. We conclude by presenting a number of specific current examples that illustrate these main directions. Our review is guided by the following three main questions:

1. What are the forces driving medical visualization research in the coming years?
2. What are the major general lines of development?
3. What are specific examples of these general ideas being applied to the problems in point one?

In previous work, we have discussed the challenges lying ahead for medical visualization [Botha *et al.*, 2012]. This chapter takes a slightly broader view and it is more up to date, but there is of course overlap with the previous paper.

22.1 DRIVING FACTORS OF ADVANCES IN MEDICAL VISUALIZATION

When looking at developments in medical visualization over the past decades, we notice that there are three main factors acting as the driving motivation for most of this work. The factors are:

1. advances in image data acquisition,
2. advances in computing, and,
3. the growing complexity of clinical tasks and the associated expectations in medicine.

Specific medical visualization *research challenges* are generally more fine-grained formulations of problems that should be addressed, because they are important, i.e., they would advance medicine, or because they are technically interesting, i.e., their solutions would improve our understanding of technology.

Each of these specific challenges is usually intertwined with one or more of the driving factors. Hence, we can increase our understanding of the specific challenges by studying the more general driving factors. In the following, we discuss each of the driving factors in turn, and analyze how they interact with and catalyze medical visualization research and development.

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22.1.1 Advances in Image Data Acquisition

In his TEDx talk *Visualizing the Medical Data Explosion*[1] at the end of 2010, Anders Ynnerman discussed the data explosion in the context of medical imaging by illustrating the increase in data produced by clinical CT scanners, from a hundred 512 × 512 images in the 70s, through 24000 slices today, to one hundred 1024^3 volumes per second in the near future. Indeed, Toshiba's 320 slice clinical CT scanner, the Aquilion One, which was introduced in 2007, is already able to acquire five 320 slice volumes *per second* [Hsiao *et al.*, 2010], and can thus easily image a beating heart in 3D. This large amount of data, however, is challenging to store and process efficiently even when the increasing computing power is exploited.

The continuing growth of dataset sizes is likely to have a significant impact on the current workflow of radiologists. Michael Forsting,[2] former president of the German Radiology society, recently used the term "the scrolling revolution" to emphasize the importance of the mouse scroll wheel in browsing through all the slices of current medical image data. 3D visualization, he said, will play a much more important role to guide radiologists who will no longer be able to look at all the details in all the slices. With respect to MRI, he explains, that the broader use of 7 Tesla devices has the potential to provide a resolution that may even replace some biopsies and would thus significantly reduce invasiveness. The increased resolution may even enable to display some cellular processes.

In addition to powerful 3D visualization and navigation techniques, progress in display technology will play an essential role in conveying the complex spatial relations.

New Imaging Techniques While the development described above could be summarized as "more of the same," there are also completely new imaging techniques and modalities on the way that require not only more efficient solutions but really innovative ones.

For diagnostic purposes, there are new imaging techniques that could not be discussed in the book, but that may become essential in the near future. Elasticity of tissue is a crucial property, e.g., for the diagnosis of unclear lesions or for assessing liver stiffness without removal of tissue in a biopsy. Elasticity may be measured with ultrasound [Selbekk *et al.*, 2012] but also with a special MR sequence [Glaser *et al.*, 2012]. Hybrid PET/CT imaging was established in the last decade. PET/MR imaging will follow and is likely to be useful not only for oncologic imaging, but also for cardiac imaging, where the metabolism of the heart muscle along with the anatomy is essential.

For intravascular imaging, Optical Coherence Tomography (OCT) achieves a very high spatial resolution (although only for a few millimeters of penetration into the vessel wall) [Bezerra *et al.*, 2009]. The analysis and visualization of these data may help to understand the composition of atherosclerotic plaque. So far, visual computing research toward supporting the analysis of OCT data has been quite limited.

Intraoperative imaging refers to a whole new class of imaging techniques that are developed from the ground up for intraoperative use, replacing complex adaptations of diagnostic imaging to OR settings. At the German medical image processing conference in March 2013, the director of the surgical planning lab of Brigham and Woman's hospital in Boston, Ron Kikinis, highlighted recent developments in this field. He mentioned freehand SPECT as an example. Intraoperative imaging is largely motivated by better resection control in cancer surgery, e.g., in neurosurgery of glioblastoma, where it is notoriously difficult to achieve resections with complete tumor free margins. While freehand SPECT is an expensive technique, (navigated) ultrasound has the potential for widespread use. Recent developments include contrast-enhanced ultrasound that potentially discriminates tumor tissue better from surrounding healthy

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[1] http://www.ted.com/talks/anders_ynnerman_visualizing_the_medical_data_explosion.html.

[2] Talk presented at the farewell symposium for Heinz-Otto Peitgen, September 4th, 2013 in Bremen.

tissue. There are great challenges in the intraoperative processing and visualization of such data [Lindner *et al.*, 2006; Unsgaard *et al.*, 2005].

Time-Varying Data Working with time-varying medical data, such as the dynamic CT mentioned earlier, does not come down to simply extending existing techniques by one extra dimension. Visualizing such data effectively and understanding the dynamic behavior that it represents pose significant challenges.

In Chapter 16, we discussed the visual exploration and analysis of perfusion data, a current example of the types of techniques that are required to extract insight from the dynamic distribution of contrast agents in the human body. One of the interesting observations here is that the dynamic nature of the data and the type of questions that need to be addressed benefit from the integration of visual analysis techniques (see § 22.2.2).

Multi-timepoint data is also time-varying, but instead of capturing dynamic low-level behavior, it can be used to study the long-term progression and development of respective pathology and anatomy. For example, Tory *et al.* [2001] used visualization techniques to study the progression of brain white matter lesions over time in multiple MRI datasets, taken one month apart, of a multiple sclerosis patient. In neuroimaging research, deformation-based morphometry (DBM) is a popular approach for studying global changes in the brain by calculating the 3D deformation between different multi-timepoint MRI datasets [Ashburner *et al.*, 1998]. In § 22.3.5 we discuss population imaging as a specific and major example of multi-timepoint data in medical research.

It is important to remember that human anatomy, physiology, and pathology are in fact all very much time-varying. Being able to study these time-varying phenomena is crucially important to medical research and practice, and hence will play an increasingly important role also in medical visualization.

Multi-Field Data In Chapter 15 we discussed High Angular Resolution Diffusion Imaging (HARDI) [Tuch *et al.*, 2002] in general and Diffusion Spectrum Imaging (DSI) [Hagmann *et al.*, 2002] as a specific example. These MRI-based neuroimaging acquisition approaches yield datasets that 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*, i.e., data that contains multiple value fields defined simultaneously over the same domain. However, datasets such as these are 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.

Multi-Scale and Heterogeneous Data 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 have to be extended. With more and more large-scale and 3D microscopy data available, there are many opportunities for medical visualization researchers. Recent examples include techniques for interactively visualizing large-scale biomedical image stacks demonstrated on datasets of up to 160 gigapixels [Jeong *et al.*, 2010b] 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 [Jeong *et al.*, 2010a].

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 [Kok *et al.*, 2007; 2010], but due to its great diagnostic potential, molecular imaging will see increased application in humans.

Besides relatively new imaging modalities that are becoming more mainstream in medicine and thus require the development of new techniques and approaches, another compelling development is the additional availability of non-imaging data such as genetic information. While the human genome project was a very large and expensive endeavor aiming at completely sequencing *one genome*, since then many genomes have been sequenced at much lower costs, leading to an increased availability of such data to prototype algorithms and systems and contribute to an understanding of risk factors and disease progression. As an example, the results of a project that analyzed 1.000 human genomes are now available.[3] Based on this project, it is estimated that many more low frequency genetic variants that are associated with diseases and represent risk factors of a moderate or large size still need to be detected [Abecasis *et al.*, 2012]. More and more genetic data is acquired to understand specific diseases, e.g., genetic disorders and cancer that is known to be correlated with genetic variants. A prominent example is the cancer genome project [Bamshad *et al.*, 2013].

In particular, comparative genomics studying relationships between genomes has become possible [Cristianini and Hahn, 2006; Bergman, 2007]. Genetics is essential not only for the diagnosis of certain genetic diseases, but also for the treatment of some widespread diseases that we discussed throughout the book. Mutations of certain genes largely determine how tumor cells respond to treatment, in particular with chemotherapy or drugs.

To add value to the research, diagnosis and treatment pipeline, imaging and non-imaging datasets have to be intelligently combined. *Personalized medicine*, which we discuss in § 22.3.4, is an especially compelling use case for this integration.

Multi-Subject Data Medical visualization traditionally focuses on single-subject data, e.g., applying visualization techniques to an MRI dataset of a single patient for diagnosis, or of a single study participant to explore their brain connectivity. However, work has started in earnest on the problem of dealing effectively with multi-subject datasets. These are datasets that include both imaging and non-imaging measurements of more than one subject. The goal is to be able to extract patterns that affect subgroups 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, an information visualization approach to visualize and compare multiple patient histories or electronic medical records [Wang *et al.*, 2008] More recently, work has been done on the interactive visualization of the multi-subject and mixed modality datasets acquired by medical cohort studies [Steenwijk *et al.*, 2010]. 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 hypotheses, could be extracted from the whole data collection. More examples of this type of data and medical visualization applications are discussed in § 22.3.5.

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[3] http://www.1000genomes.org/.

22.1.2 Advances in Computing Hardware and Software

Moore's law stipulates that the number of transistors on integrated circuits doubles every 2 years [Moore, 1965].[4] Similar observations hold for storage cost per unit of information, for network capacity, and for display resolution.

For traditional CPU architectures, this progression is starting to slow down due to the power scaling requirements associated with ever-shrinking transistor sizes. However, by employing highly parallel computing architectures, such as those found in GPUs, the exponential growth in processing power is still expected to continue for a while.

In any case, the computing infrastructure available to us is growing exponentially. In his inaugural lecture,[5] Professor Bram van Ginneken posits that, for a large part based on these rapid advances in computing, computers are already getting better than humans at certain tasks until recently considered to be by nature reserved for humans, such as playing Jeopardy[6] or driving a car in busy traffic. [7]

Furthermore, they are even getting better than humans at performing certain *radiological* tasks that were until recently thought to be by nature reserved for humans. Careful combinations of advanced CAD (Computer-Aided Detection) may outperform even specialized radiologists for tasks such as lung nodule detection, as recent publications indicate [Niemeijer *et al.*, 2011; Eadie *et al.*, 2012]. For example, as also highlighted by Van Ginneken, the BoneXpert method has replaced radiologists and technicians with bone age rating from radiographs [Thodberg *et al.*, 2009]. Other examples include computer-aided detection (§ 3.6.4) of breast cancer in X-ray mammography and tuberculosis in thorax X-rays. The integration of advanced machine learning in diagnosis and treatment monitoring is of crucial importance for the vendors of image scanners. A good survey is given by Wang and Summers [2012].

In the midterm, many evaluations and improvements are necessary to apply principles of automatic diagnosis to new diagnostic tasks. In medical visualization, techniques need to be fine-tuned that emphasize findings and present them in an overview. Like human experts, CAD systems not only produce binary decisions (malignancy yes or no), but probabilities reflecting various degrees of certainty. To develop, evaluate, and refine visualization techniques that convey this degree of certainty will be an important task.

For medical visualization, the enormous growth of performance and flexibility in GPUs and the introduction of new interaction and output devices enable the design of more effective solutions, such as real-time analysis, more realistic graphics, and more realistic simulation of treatment procedures. However, effectively harnessing these new technical developments will require a great deal of research effort.

Another essential trend is the growing availability of monitoring devices that enable to check health conditions of patients or elderly persons. Sensor-based systems enable to analyze, e.g., the blood pressure, pulse, and other properties that may enable remote monitoring by a physician. The visualization needs for both patients and physicians need to be better understood before appropriate systems can be developed.

Open Source and Open Repositories Not only hardware development, but also powerful software toolkits and libraries act as enabling technology for further progress. The progress achieved in the last decade, in particular in medical image analysis and computer-aided detection, is largely based on the increasing availability of public databases providing carefully annotated medical datasets. In addition, open source software, such as ITK and VTK, as well as much of the software that was built based on these libraries, is

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[4] Moore's original observation was that transistor count had doubled every year from 1958 to 1965, and predicted that this would continue for some years. The two year period is due to the results of the past decades.

[5] http://vimeo.com/50718382.

[6] IBM's Watson won this contest in January of 2011.

[7] http://www.ted.com/talks/sebastian_thrun_google_s_driverless_car.html.

publicly available as well, enabled more efficient research. For almost all kinds of medical image computing, including biomedical simulations, surgery simulation, DTI processing, and vascular modeling, there are powerful open source solutions available that may be used as a starting point for developing more advanced solutions or solutions that are adapted to specific applications or data.

22.1.3 Task Complexity and Requirements

The complexity of medical practice is further increasing. The amount of elderly patients suffering from a multitude of diseases requires gentle treatment strategies and requires to consider various interactions between drugs, other treatments, and the different diseases. At the same time, treatment options and the possibilities to combine them also increase and lead to a growing demand for *decision support*. As an example, let us briefly discuss radiation treatment planning (that was discussed in Chap. 3). With recent progress, it is possible to flexibly combine different sources of radiation and to adjust the radiation intensity along a path (*intensity-modulated radiation treatment*). Moreover, based on better imaging and a better understanding of tumor biology, physicians aim at identifying different regions in the tumor that are likely more or less resistant to radiation treatment to adapt the level of radiation correspondingly—using a high radiation level only at the most resistant parts of a tumor. This highly accurate treatment plan needs to be delivered accurately to a living patient with breathing and other movements. Thus, the requirements for pre- and intraoperative imaging, image analysis, and visualization have increased tremendously.[8]

Medical image data plays a key role by its ability to depict pathologies and surrounding anatomy as well as to overlay access paths, measurements, and other treatment-related information. However, only a subset of diseases is clearly visible in medical image data. Thus, combinations with other sources of information gain importance.

The further automation of frequent and simple tasks enables radiologists to focus on more difficult tasks, in particular on those where different types of image data and non-image data need to be integrated. Examples include the integration of findings from CT and MRI data with those from endoscopy and from laboratory tests.

22.2 MEDICAL VISUALIZATION: AN INTEGRATIVE APPROACH

Moving on from the factors driving advances in medical visualization to the major lines of future development, we see an important trend. In order to keep up with the afore-mentioned driving forces, medical visualization development needs to be better *integrated* with developments in a number of related fields.

This includes tight integration with simulation technology, where for example patient-specific biomedical simulations will be used increasingly in diagnosis and treatment. HCI-related research, e.g., with respect to interaction techniques, input devices, and mobile technology will be crucial for the development of visualization-rich software in medicine. There are a number of further integration aspects that are considered in the following.

22.2.1 Integration of Data Sources

In most medical informatics-related fields, integration of data sources has been a core activity of the past years. However, this development will gain much more momentum in the coming years as demands grow for more accurate information. In particular, the vision of *personalized medicine* (§ 22.3.4) requires the

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[8] A EU-funded project, called SUMMER, explores refinements of medical physics, image acquisition and software support for radiation treatment planning, http://summer-project.eu/.

generation of comprehensive digital patient models that are based on a collection of highly heterogeneous imaging and non-imaging datasets.

On the more well-developed imaging side, the integration task comprises various tomographic imaging data and related datasets, such as endoscopy. Here, the overall goal is to fuse the different data modalities and to make them available in one coherent coordinate system. However, since a great deal of valuable information is locked up in non-imaging data, such as genetics and textual data (patient histories, other literature), the integration of non-imaging information in the diagnosis and treatment pipeline has become increasingly important (see [Zhang *et al.*, 2013] for a recent example dealing with electronic medical records).

Atlases and Other Model-Based Information In the context of medical imaging, an *atlas* refers to a standard template describing some part of the anatomy. Such an atlas can be constructed by selecting a specific dataset that is representative of a whole collection, or by somehow combining a number of datasets into a single representative dataset, for example by averaging. When an atlas is further enriched by performing a manual segmentation (labeling the anatomical structures in the data), it can be used to segment new image datasets in a process called *atlas-based segmentation*. This is done by performing image registration between the atlas and the new image dataset. This registration yields a transformation that can then be applied to the manual segmentation as well, thus "morphing" it onto the new image data. In this way, information that has been added to the atlas once can be transferred to any number of new datasets.

This powerful concept can also be applied in medical visualization. By making use of a suitable atlas, medical data can be automatically enriched with the model-based information that is encapsulated in that atlas. Using this technique, anatomical structures can for instance be automatically identified. This information can again be used to apply the most applicable visualization technique to each of the structures, depending on the application.

The VOXEL-MAN project used the Visible Human dataset, enriched with segmentations and symbolic descriptions, to create one of the most well-known 3D digital atlases [Höhne *et al.*, 1995]. Efforts like *The Unified Anatomical Human* are attempting to build atlases based on the integration of more heterogeneous collections, including tomographic data, segmentations, scientific literature, anatomical expertise, and histology [Smit *et al.*, 2012]. With such detailed atlases and purpose-designed registration techniques (which themselves make use of specific anatomical knowledge in the atlas), it will be possible to augment patient-specific datasets with a whole range of new information, leading to new visualization approaches. This kind of atlas-based processing will naturally play a role in patient-specific predictive simulation (§ 22.2.3).

22.2.2 Integration with Analytics

We have already discussed the recent progress and potential for further advances in computer-aided detection. Besides this development, also the conventional diagnostic processes would likely benefit from further automatic processing of medical image data. This automatic processing aims at the streamlining and acceleration of diagnostic processes. Machine learning techniques are used, for example, to automatically detect lesions in a follow-up exam that correspond to lesions in an earlier examination. Thus, features are extracted and candidate regions are classified in order to determine corresponding pairs of lesions and to support their comparison. Visualization techniques need to be considered that convey the results of such automatic processing. This automatic processing cannot be 100% correct. Thus, users must also be enabled to verify the results or influence the parameters that guide the automatic process. Moreover, datasets are analyzed to identify probably relevant regions, such as certain organs, to focus the visual exploration to relevant subsets. Again, it may be essential to enable the user to steer this process with appropriate parameters, including appropriate previews.

Visual Analytics 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 analytics techniques, such as combinations of clustering and 3D visualizations that convey certain subgroups.

Existing examples involving time-varying data include the work of Coto *et al.* on DCE-MRI mammography [Coto *et al.*, 2005] and Oeltze *et al.* on perfusion data in general and MR perfusion of the brain in particular [Oeltze *et al.*, 2007]. [Blaas *et al.*, 2007b] applied visual analysis techniques to multi-modal medical data, while Zachow *et al.* focused on nasal airflow simulation data combined with anatomical information [Zachow *et al.*, 2009b].

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 from 2010 to 2012, and in conjunction with the American Medical Informatics Association (AMIA) Annual Symposium in 2013, underline the emerging importance of this research direction.

22.2.3 Integration with Predictive Modeling

Therapy planning was one of the first real applications of medical visualization and remains important. In 1993, Altobelli *et al.* published their work on using CT data to visualize the possible outcome of complicated craniofacial surgery [Altobelli *et al.*, 1993]. 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, the expected outcome of a craniofacial procedure could be visualized. Although still rudimentary, this could be considered one of the earliest cases of *predictive or outcome simulation* integrated with visualization for surgical planning. Another inspiring and early work on predictive modeling was performed at the Zuse Institute Berlin where regional hyperthermy was simulated based on patient-specific geometric models Stalling *et al.*, 1995]. Quarteroni and Veneziani [1997] performed blood flow simulations and suggested to fine-tune such simulations to predict the natural course of atherosclerosis and to support treatment decisions.

The idea of predictive simulation, or predictive medicine, was further explored by [Taylor *et al.*, 1999] for cardiovascular surgery. Taylor and colleagues 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 [Taylor *et al.*, 1999]. 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 (Krekel *et al.*, 2006), biomechanical stress simulation models for implant planning in orthopedics (Dick *et al.*, 2009) and nasal airflow simulation for reconstructive rhinosurgery (Zachow *et al.*, 2009).

Visual computing researchers will find many opportunities in collaborating with biomedical researchers trying to simulate various functions of the human body. While the simulations discussed in this book were restricted to *one aspect* and *one level of detail*, more accurate predictions require the coupling of different simulations and running simulations at various scales. As an example, blood flow simulations may be coupled with the simulation of the elastic behavior of the vessel wall—an aspect that is particularly important for larger vessels, such as the major coronary vessels. Moreover, to accurately predict treatment success, the behavior of the individual blood components as part of a thrombosis model needs to be incorporated. The vision of the physiome [Fenner *et al.*, 2008] is to model the human biology at the levels of molecules, genes, cells, and organs and requires, of course, to consider the interaction between processes at these different levels.

The integration of these predictive models 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, simulations yield data with a certain degree of inherent uncertainty, since many assumptions and simplifications are involved [Ristovski *et al.*, 2013]. The role of this uncertainty should be fully explored and it should be carefully and explicitly represented as an integral part of the visualization.

Advanced visual computing solutions will not only help to explore and understand these simulation data, but can also be tightly coupled with the simulations themselves in order to support the model verification process, where expressive visualizations may reveal problems to an expert.

22.2.4 Heterogeneous Display and Computing Devices

Radiology is a medical discipline that embraces telemedicine. Remote access to medical image data with laptops or other devices that have a reduced spatial and gray level resolution compared to specialized monitors is already a reality in particular in rural areas and during weekends and the night. Visual computing solutions may be developed that "recognize" the capabilities of the display and eventually adapt techniques and parameters.

Mobile devices, in particular the Apple products iPad and iPhone, are extremely popular among medical doctors and already solve some serious problems of desktop devices in routine clinical use. In particular, the 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 that support the OpenGL ES (Embedded Systems) standard. Thus, 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 [Moser and Weiskopf, 2008].

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 smartphones. Therefore, multi-touch interaction is also incorporated in large displays in medical use, e.g., the Digital Lightbox[9] by BrainLab and the multi-touch table of Lundström *et al.* [Lundström *et al.*, 2011].

We expect growth in the number and heterogeneity of mobile devices, and we also expect these devices to play an increasingly important role in the workflows of medical visualization users. This will mean that new medical visualization techniques have to be developed that make effective use of the special displays and interaction capabilities available in future mobile devices.

22.2.5 Advanced Rendering

Due to the continuing advances in computing discussed in § 22.1.2, and due to related continuing advances in algorithmics, GPU raycasting [Krüger and Westermann, 2003] being an early example, new rendering approaches, that were previously thought to be impractical because of computational constraints, can now be used in interactive settings.

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[9] http://www.brainlab.com/art/2841/4/surgical-pacs-access/.

FIGURE e22.1 *Two examples of interactive visualizations made with the volume renderer of Kroes et al. [2012]. 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.*

A good example of this phenomenon is illustrative medical visualization, which is becoming increasingly important when datasets become more complex and multi-modal, integrating for example functional (measured and simulated), anatomical information, and surgical instruments. Illustration techniques enable visual representations to be intelligently simplified by the visualization designer, while still communicating as much information as possible.

On the other side of the realism spectrum, the *interactive* rendering of medical imaging datasets with physically-based lighting has now also become possible [Kroes et al., 2012]. Figure e22.1 shows an example of such a visualization. These techniques enable the simulation of an arbitrary number of arbitrarily-shaped and textured lights, real shadows, and a realistic camera model with lens and aperture, and so forth, all at interactive rates. 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.

Now that computational problems have been largely solved, these and other advanced rendering approaches have to be fine-tuned and evaluated for diagnostic and treatment planning purposes. Application-oriented examples of such work include the simulation of crepuscular rays for tumor accessibility planning [Khlebnikov et al., 2011] and multi-modal illustrative volume rendering for neurosurgical tumor treatment [Rieder et al., 2008], whereas a recent example of evaluation-oriented work showed that global illumination and shadows can have a positive effect on task performance in normal volume rendering [Lindemann and Ropinski, 2011].

22.2.6 Integration with Workflows

Radiology, the major speciality involving medical image data, is characterized by an ever higher degree of specialization to support referring physicians raising highly specialized questions. As an example, the treatment of complex cardiovascular diseases, such as congenital heart defects, mitral valve defects, or coronary heart diseases, requires that radiologists are able to interpret all relevant imaging data, integrate the findings and focus a written report and potentially the oral demonstration to specific treatment options. This is a task that is too complex for a radiologist with a general education only. Similarly, neuroradiology and pediatric radiology are becoming increasingly specialized and musculoskeletal and abdominal imaging benefits from specialized radiologists. For the scientific community, it remains a challenge to identify and refine *general principles and workflows* for software and algorithmic support instead of creating a large zoo of applications that are very hard to compare.

While this workflow-centered thinking is close to mainstream in radiology, it will also become essential in pathology where more and more digitized microscopy data are processed. Due to the large sizes of digitized microscopy data, storage and processing without significant delays and simple efficient display are essential. However, the "integration with analytics" is, of course, even more important. While looking at all details in all slices of radiologic image data is cumbersome, but at least feasible, the size of microscopy data is prohibitive for a detailed inspection of all details. Thus, it is of paramount importance to automatically detect cell nuclei and to decide whether they are atypical (and require attention) or not. On the other hand, due to the different staining techniques, staining artifacts and blurring, machine learning in this area is at least as challenging as it is for radiological image data [Fuchs and Buhmann, 2011].

22.3 SPECIFIC EXAMPLES

Here we discuss some specific areas that will see rapid development and prominence in the coming years.

22.3.1 Microscopy/from Nano to Macro

Within this outlook chapter we have discussed several examples where the *macroscopic level* of understanding pathologies is not sufficient to make progress in the development of new treatments but also in the selection of an existing treatment for a particular patient. The macroscopic level, represented in image data from radiology and nuclear medicine, as an example, would depict plaques or tumors as spots with some brightness contrast to surrounding tissue. At this level, neither the particular characteristics of inflammatory processes in a plaque nor the specific biology of a cancer disease can be understood. As a consequence, at this level it cannot be reliably determined, whether the patient is in severe danger due to a plaque or a tumor cannot be determined reliably. More and more, microscopy data is employed to understand normal and pathological processes at the cellular, subcellular, and molecular level. In clinical settings, this understanding often aims at identifying *biomarkers* that are essential for the prognosis of the patient (*prognostic biomarkers*) or for the success of treatment (*predictive biomarker*). As an example, the rate of cell proliferation is a prognostic biomarker in a tumor disease since it directly correlates with the biological aggressiveness of the tumor.

We briefly discussed predictive modeling (recall § 22.2.3), which is heavily based on experiments and data from microscopy as a basis for a model-building process. Due to the high variety of microscopes, staining techniques and the difficult preparation, the processing of these data is difficult. Fuchs and Buhmann [2011] therefore consider interactive and online learning of classifiers as a promising approach to cope with this variability, and to enable human experts to integrate their knowledge. Comparing the current state of processing radiological imaging data with that of microscopy data reveals a number of essential tasks for the future. More publicly available segmented and annotated microscopy data is required to train classifiers, and to prototype and validate analysis techniques. In addition to "real" microscopy data, phantom data may be generated that resemble real microscopy data and can be parameterized, e.g., with respect to noise or other characteristics.

22.3.2 Uncertainty Visualization

For more than a decade now, *uncertainty visualization* is considered to be an important topic for the future of visualization [Johnson and Sanderson, 2003]. Visualization pipelines involve various steps that have a limited accuracy. In medical imaging, these are the artifacts from imaging, e.g., bias fields in MRI, the limited spatial resolution of imaging data, inaccuracies in preprocessing and segmentation, and finally the sampling strategies and parameters in volume rendering. Uncertainty is probably even more important when high-dimensional data, such as blood flow measurements or DTI is involved, and relates to the orientation of fiber tracts and streamlines. The analysis and subsequent visualization of uncertainty are of major importance in simulations (recall our discussion on predictive modeling) where the results may be very sensitive to details of the simulation model and the specific choice of parameters. Despite the undisputed importance of this topic, progress during the last decade has been limited, primarily due to two reasons:

- The specific amount and characteristics of uncertainty, e.g., a probability distribution, is very hard to determine, in particular for the more interesting sources of uncertainty.
- The visualization of complex data, such as simulation results along with 3D anatomy, together with the locally variable uncertainty is an interesting academic endeavor, but almost inevitably leads to visual clutter.

Recently, there has been noticeable progress that has laid the foundations for further (fruitful) research. Overviews and taxonomies of uncertainty visualization provide guidance and explain a design space of possible techniques structured according to the dimensions of the data domain and the attribute space. In particular, the recent review of Ristovski *et al.* [2013] is tailored toward the typical problems in medical visualization. Showcase examples include uncertain isosurfaces representing temperature visualizations in RFA and uncertain fiber tract visualizations. Still, a great deal of research is still required, and it should be more *user-centered*, e.g., focused on the kind of uncertainty that users are actually interested in, instead of a merely physics-based approach that quantifies whatever is possible. Uncertainty visualization has to consider perception and consequences of uncertainty, e.g., the influence on diagnostic and treatment decisions in clinical medicine or the interpretation of simulation results in medical research. The uncertainty analysis is particularly challenging in complex biomedical simulations with many parameters involved. A comprehensive analysis of the high-dimensional parameter space to study the sensitivity of parameters is computationally less feasible and thus requires smarter solutions.

22.3.3 Virtual Physiological Human

The virtual physiological human (VPH) initiative is a large and long-term effort that aims at modeling the human body at all levels. It was initiated in 2000 [Bassingthwaighte, 2000] and so far has yielded many results that are relevant to both medical doctors and visual computing specialists. The VPH project also pioneered new and intensive forms of cooperation, exchange of data and software, and infrastructures for this compute-intensive endeavor. Modeling the human body requires many separate models for different functions of the human body, models at different scales and data to support the creation of models and their validation in later stages.

While the overall goals of this initiative are broad and comprehensive, researchers naturally have to focus to make concrete progress. The most essential focus, so far, was achieved in cardiac modeling [Kohl and Noble, 2009]. It includes models of electrophysiology of the heart, cardiac mechanics, and metabolism, which closely interact with each other. Visual computing may play a crucial role in the exploration or guided analysis of the high-dimensional data resulting from running such models in order to validate or refine them. Moreover, the findings, that the VPH initiative tries to achieve, are highly relevant for tasks discussed in this book at various points, such as surgery and intervention planning. The insertion of stents, prostheses, or other implants should consider not only the patient anatomy and the implant geometry but also functional aspects, as we have discussed, e.g., with respect to ear implants and hip prostheses, where biophysical or biomechanical simulations may help to better predict treatment success (recall Chap. 19). The VPH-related research goes an important step further and considers also *interactions* between implants and tissue at a cellular and subcellular level answering questions such as "How likely is an inflammation in the surroundings of a stent with a special geometry, material parameters, such as elasticity, exerting a certain force on the vessel wall?" As an example, Perez *et al.* [2010] describe a comprehensive model of the human trachea, consisting of trachea rings with a very characteristic composition. The model is focused on consequences of endoprosthesis implantation and thus on providing decision support for this special treatment.

To give another example of research directions within the VPH initiative, we briefly mention attempts to comprehensively model pressure and velocity fields in vascular systems. In Chapter 19, we discussed blood flow simulations based on Navier-Stokes equations. This is a rather simplified model where blood is considered as a coherent fluid with some global properties (the viscous behavior is often completely neglected). As part of a selection of papers from the VPH initiative, Obrist *et al.* [2010] consider the local distribution of individual blood components, in particular of red blood cells which represent the most common type. The distribution of these deformable components has a strong influence on the overall blood flow, in particular in the small capillary networks, since the red blood cells have almost the same size as these vessels. This whole branch of research not only aims at mathematical descriptions backed up with measured or experimental data but also at efficient algorithms to simulate these models.

22.3.4 Personalized Medicine

Diagnosis, treatment planning, and treatment monitoring will be based on an increasing number of (image) datasets. Both the sheer amount of the data as well as their heterogeneity will increase. A special aspect of this trend is *personalized medicine*. In our interviews with experts from the field, personalized medicine was the only topic that was considered by most of them as highly important for both medicine as well as visual computing research in medicine.

Personalized medicine entails that medical treatment is tailored to an individual patient based on comprehensive information of this patient.[10] One might argue that medical treatment has already in some sense been personalized, e.g., it is adapted to symptoms and anamnesis as well as to the preferences of the patient. Also the patient age and sex are considered. As an example, the potential harm of ionizing radiation is different for a young woman compared to an elderly patient. The new trend is to increase significantly the level of personalization by means of new technology. It includes data derived from medical imaging, various laboratory tests as well as metabolic and genomic features. This data is promising, since it allows to avoid treatments that would not be effective due to a particular mutation of a gene, or to select a treatment that is only effective in case of particular mutation. In particular in cancer treatment, it is essential to avoid an expensive trial-and-error strategy that delays a potentially successful treatment.

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[10] http://en.wikipedia.org/wiki/Personalized_medicine.

For practical reasons, e.g., the cost of sequencing the whole genome instead of a truly personalized medicine, it will be *stratified*. That means an individual patient is assigned to a certain (rather narrowly defined) category based on a number of biomarkers. The selected treatment, e.g., the choice of a specific chemotherapy or drug, is tailored to this category in order to ensure a high probability of treatment success. There will be

- *research tools* to identify and verify relevant characteristics and
- *clinical tools* for using these categorizations and applying them to new patient data need to be distinguished.

Research tools will incorporate various clustering techniques and will enable the parameterization of these techniques as an example for a family of techniques for the exploration of data. Clinical tools, on the other hand, will contain more basic information visualization techniques and provide more guidance, probably at the expense of flexibility. With clinical tools, users may quickly understand which treatment options should be considered for a particular patient.[11]

Personalized medicine is based on but significantly extends the use of patient-specific geometric models that we discussed at various points in the book. The use of simulation models that integrate patient-specific information, primarily the patient-specific anatomy with general assumptions about biophysical processes, is a natural next step, illustrated primarily in Chapter 19. The simulation of biomechanical load (for implant placement), blood flow (for interventional treatment of vascular diseases) and temperature distribution (for integrating the cooling effect of vascular structures in RFA treatment) are examples of this combination of patient-specific information and information that is derived from the literature and thus represents average values from large studies.

As an example of a research initiative that contributes to the VPH vision and simultaneously to personalized medicine, we briefly describe the VIGOR++ project.[12] The major goal of this project is to develop a virtual model of the human colon with a level of detail that is useful to support the diagnosis (in particular the grading) and treatment of Crohn's disease—a chronic inflammatory disease of the colon that is suspected to be due to a combination of genetic variants and environmental factors. CT and MRI data as well as endoscopic images are essential, in particular in severe cases, when surgery of the affected tissue is required. The analysis of MRI plays a crucial role, but laboratory test data, microscopy data, and histological analysis need to be considered as well [Schüffler *et al.*, 2013].

Based on our own observations and input from key researchers in our field, we believe that the trend toward personalized medicine is the most important trend for the future of our field. More difficult to predict is what should be done to support this trend. Certainly, image data from radiology and genetic information as well as microscopy data need to be integrated. Visual abstraction is probably needed to avoid visual clutter and to enable an effective exploration of this wealth of information. In particular, clinical tools benefit from guidance and clear workflows integrating predefined visualizations.

22.3.5 Population Imaging

Epidemiology deals with relations between genetic predisposition, measurements, such as blood pressure and life style-related factors on the outbreak, severity, and prognosis of diseases. In population imaging, medical image data and other measurements are acquired from a large group of subjects, typically more

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[11] Based on a discussion with Hans Christian Hege, Zuse Institute Berlin.

[12] http://www.vigorpp.eu/.

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. This application domain is an extreme example of multi-subject medical visualization discussed in § 22.1.1, 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 [Steenwijk *et al.*, 2010]. 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.

Classic epidemiological studies were based on interviews, rather simple measurements and registers for crucial diseases, such as cancer. Based on large studies, carefully designed to reduce the effect of bias factors, e.g., the strongly increased risk for smokers to get cancer could be shown. The strongly improved feasibility of acquiring and analyzing genetic and proteomics data leads to the incorporation of these data in epidemiological studies (see the recently started UK Biobank as a prominent example, [Petersen *et al.*, 2013]). Thus, the joint influence of genetics and environmental factors may be employed.

Challenges Population imaging studies incorporate also medical image data, primarily those that do not require ionizing radiation (MRI and ultrasound) to study more subtle effects. The Rotterdam study [Hofman *et al.*, 2011] and the SHIP study [Völzke *et al.*, 2011] are two examples, both involving the multi-timepoint datasets of several thousand persons acquired in a highly standardized and thus comparable manner. Within the scope of this book, these developments are fascinating for two reasons. On the one hand, a whole set of new analysis, visualization, and interaction techniques is necessary to support the knowledge generation from this wealth of information. On the other hand, large sets of standardized medical image data with annotations, verified segmentations, and further information are an excellent basis for training medical image analysis techniques and testing related visualizations.

More specifically, epidemiologists are interested in relations between descriptors of organ shape, organ texture, life style, and diseases. As an example, they may analyze the spine, the vertebrae, the curvature of the spine (based on reliable segmentation) and explore changes of the spine related to (normal) aging or disease. A better understanding of the differences between normal (healthy) aging and beginning diseases that require immediate treatment is among the general goals of recent epidemiological studies. Visual analytics strategies, such as dimension reduction, cluster analysis, analysis of correlations combined with information visualization techniques, such as scatterplots and parallel coordinates, are a good starting point [Steenwijk *et al.*, 2010]. However, epidemiology-related research has specific features that require not only the extension of existing techniques but the development of completely new techniques. In particular, epidemiology is largely based on testing hypotheses with advanced statistics. Therefore, a tight integration of statistic tools and visual analytics is required.

The ambitious promise of visual analytics is to go beyond the confirmation of known hypothesis and to generate new findings or, in other words, to support *hypothesis generation*. An inspiring example of early work in this direction was recently published by Turkay *et al.* [2013]. They give an overview of all dimensions of the data, indicating whether the attributes follow a symmetric or highly skewed distribution. Comparative visualizations of data from different persons or different groups of persons are essential and require careful normalization and registration.

22.4 CONCLUSION

In this chapter we attempted to gaze into the future of medical visualization. We did this by first analyzing the three main forces driving medical visualization development:

1. Advances in image data acquisition.
2. Advances in computing hardware and software.
3. The growing complexity of tasks in medical practice and research.

Rapid and continuing increases in dataset sizes are certainly pushing medical visualization forward. However, particularly the increasing heterogeneity of data types, the introduction of completely new imaging and non-imaging modalities, and the increasing use of multi-timepoint and multi-subject datasets, are driving our field to come up with new techniques and approaches that are able to cope with these datasets. Computing power is growing exponentially, which is enabling techniques that were hitherto not practical to implement. Finally, the growing complexity of the tasks in our application domain, medicine, is necessitating the search for new and improved visualization techniques.

The general future directions of development that we see all share a theme, that of integration. We note that medical visualization has much to gain by integrating its evolution with (visual) analytics, with modeling and simulation, and with workflows that augment clinical and medical research processes. Besides these integrations, we expect that the ability to integrate multiple heterogeneous data sources, and embracing advanced rendering techniques on the growing multitude of new display and interaction devices at our disposal, will play a key role in future developments.

Finally, we identified five key examples of medical visualization and imaging research that we expect to generate a great deal of new medical visualization research work in the coming years: Microscopy, Uncertainty Visualization, The Virtual Physiological Human, Personalized Medicine and Population Imaging.