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SPECIAL ISSUE PAPER

Challenges of medical image processing

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Abstract In todays health care, imaging plays an important role throughout the entire clinical process from diagnostics and treatment planning to surgical procedures and follow up studies. Since most imaging modalities have gone directly digital, with continually increasing resolution, medical image processing has to face the challenges arising from large data volumes. In this paper, we discuss Kilo- to Terabyte challenges regarding (i) medical image management and image data mining, (ii) bioimaging, (iii) virtual reality in medical visualizations and (iv) neuroimaging. Due to the increasing amount of data, image processing and visualization algorithms have to be adjusted. Scalable algorithms and advanced parallelization techniques using graphical processing units have been developed. They are summarized in this paper. While such techniques are coping with the Kilo- to Terabyte challenge, the Petabyte level is already looming on the horizon. For this reason, medical image processing remains a vital field of research.

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Keywords Medical imaging · Bioimaging · Neuroimaging · Visualization · Giga-Voxel · Tera-Voxel · Picture archiving and communication systems (PACS) · Content-based image retrieval (CBIR) · Virtual reality (VR) · Graphics processing unit (GPU) programming · Parallel algorithm · Grid computing

1 Introduction

Recent advances in biomedical signal processing and image processing have frequently been reviewed [21, 35, 36]. Usually, such review articles are driven by classifying the methods that are used for processing pixel and voxel data, e.g., image segmentation, or their applications in diagnostics, treatment planning and follow up studies. In contrast, this paper focuses on processing large data volumes of medical images and its related challenges.

During the last years, the amount of medical image data grew from Kilo- to Terabyte. This is mainly due to improvements in medical image acquisition systems with increasing pixel resolution and faster reconstruction processing. For example, the new Sky Scan 2011 x-ray nano-tomograph has a resolution of 200 nm per pixel and the high resolution micro computed tomography (CT) reconstructs images with $8\,000 \times 8\,000$ pixel per slice with 0.7 µm isotropic detail detectability. This results in 64 Megabyte (MB) per slice. New CT and magnetic resonance imaging (MRI) systems can scale the image resolution and the reconstruction time. Whole human body scans with this resolution reach several Gigabytes (GB) of data load.

Large medical image data occurs in two different ways: first, a huge amount of image data from thousands of images such as in picture archiving and communication systems (PACS) and second, a large amount of image data from a single data set. In practice, both ways multiply.

This paper discusses both aspects and is structured in the following manner: Sect. 2 outlines specific current research projects dealing with the problem of large image data. Section 2.1 considers the management of thousands of medical images, the difficulty of image content-based queries and the acceptance by the physicians. Section 2.2 focuses on a large data set from fluorescence microscope images depicting molecular and cellular bioimaging probes. These images can be tracked over time and need several GB to save the raw data. Section 2.3 introduces another problem handling GB data. In virtual reality (VR) stereoscopic real-time interaction and visualization use multiple views rendered from a single huge data set. The efficiency of these methods depends on the number of views, the pixel size of rendered images and the size of medical data sets. The rendered views can be blended with additional information from analyzed data like the flow field inside a human nasal cavity. Another example of large medical image data is described in Sect. 2.4. It considers the problems associated with Giga- to Terabyte data sets created by collection microscopic images from human brain cuts in nerve fiber resolution. These cuts are registered to a single volume data set. Three-dimensional (3D) visualization and interaction with Giga- to Tera-voxel data require specific modern software techniques. Section 3 gives an overview of advanced programming techniques on this topic. In Sect. 4, we summarize and conclude this paper with an outlook on future challenges.

2 Examples of large medical imaging

2.1 Medical image management and image data mining

PACS is a field, where an "explosion" of data has been observed. In clinical routine, most modalities such as plain x-ray, CT, MRI, ultrasound (US) as well as optical imaging techniques such as endoscopy and microscopy have turned direct digital, feeding the PACS with large amounts of image data. Several TB per year must be handled by the systems [41], which is regarded as a logistic problem. In medical informatics, we refer to "information logistics" when we aim at providing the right information at the right time to the right place [48, 49]. Several milestones of information logistics have been reached already [23, 24]. Regarding medical images, however, retrieval from PACS archives still is based on alpha-numerical annotations, such as the natural language text of diagnosis, or simply the name of the patient, the date of acquisition, or some study meta-information.

Almost 15 years ago, Tagare et al. already reported on the impact expected from accessing image archives and mining image data by content rather than textual description [56], and content-based image retrieval (CBIR) in medicine has become a subject of intense research [13, 38]. Appropriate image features (signature) and similarity measures have been analyzed, ranging from

- *global* (i.e., the entire image is described by a single signature) to
- *local* (i.e., each image object or region of interest (ROI) is indexed with its own signature) to
- *structural* (i.e., a signature is assessing the local or temporal constellation of relevant objects) approaches.

CBIR-PACS integration has also been addressed in recent research [15, 46, 61]. However, CBIR-based methods are still unavailable in today's radiological routine. Possible obstacles to the use of CBIR in medicine include the lack of (i) translational cooperation between biomedical and engineering experts, (ii) effective representation of medical content by low-level mathematical features, (iii) comprehensive system evaluation and appropriate integration tools [38].

The image retrieval in medical applications (IRMA, http://irma-project.org) approach aims at providing a framework for medical CBIR applications including interfaces to PACS and hospital in formation systems (HIS) [19, 34]. In other words, IRMA exactly addresses the Kilo- to Terabyte challenge in medical image management and data mining. Figure 1 depicts a web-based graphical user interface (GUI) build from standardized IRMA in put/output (I/O) templates [12]. In cooperation with the National Library of Medicine (NLM) at the National Institutes of Health (NIH), United States, a distributed retrieval system has been developed allowing shape-based access to a large database of spine x-ray images. In total, this database holds about 50 000 vertebrae. In terms of data volume, the IRMA-based application supporting screening mammography [43] is even more comprehensive. Currently, it holds 10 517 digital mammographies with annotated ground truth, each in high resolution and with replicates in different sample sizes. Depending on the vendor of the imaging device, a single mammography provides up to 54 MB of uncompressed data [58]. Here, the Kilo- to Terabyte step already applies. Hence, all issues related to performance are unresolved, still crucial and currently remain. Due to the steadily increasing amount of medical image data, fast feature extracting and indexing techniques are needed that simultaneously narrow the gap between the numerical nature of features and the semantic meaning of images. Combining image content with natural language-based access to medical case records will provide advanced case-based reasoning methodology for medical diagnostics as well as treatment [42]. Therefore, interfacing image processing with automatic text analysis forms the subsequent challenge in medical informatics.

2.2 Bioimaging

A relatively young field generating rapidly increasing quantities of image data is the investigation of biomolecular sys-

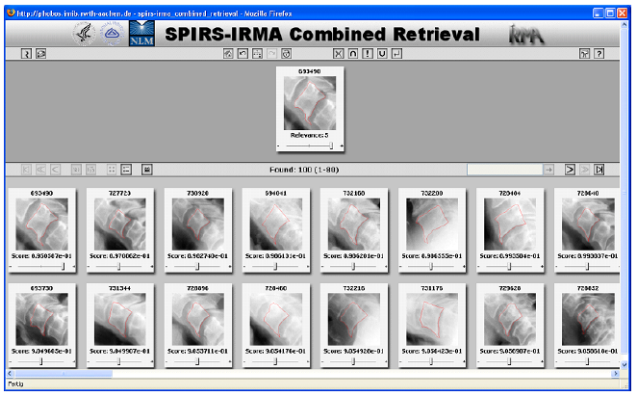

Fig. 1 Content-based medical image retrieval using the IRMA framework

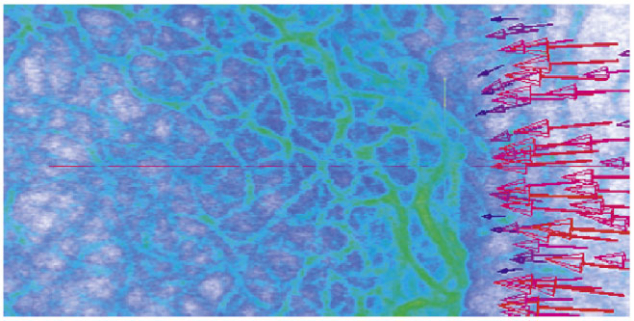

Fig. 2 Cytoskeletal filaments of a living cell superimposed with motion vectors

tems by molecular and cellular bioimaging [17]. A single $(3D + t)$-dataset acquired by fluorescence microscopy, for instance, can easily reach a volume of several GB of raw data. Recording only two such datasets per day leads to an estimated mean data volume of about 1 000 to 1 500 GB per year, making the visual inspection of this data impossible. Apart from the logistics of handling this data, their sheer volume also drives the need for automated analysis [14, 40] to replace visual examinations. Biomolecular systems are intrinsically dynamic, thus making the quantitative and reproducible analysis of motion the major challenge. Accordingly, various approaches for tracking molecular or cellular structures have been developed, with early work in the 1970s e.g., [1]. In [11], methods are described to evaluate polymer transport and turnover in fluorescent speckle microscopy (FSM), based on cross correlation and particle flow. Approaches for tracking micro-tubules can be found in [50], where active contours and a hidden Markov model (HMM) are used [39], or in [14] for a speckle-based technique. A global minimization method by simulated annealing for the tracking of fluorescent structures was developed in [47].

Many cell functions crucially depend on the dynamics of the cytoskeleton, which, in mammalian cells, consists of actin filaments, microtubules and intermediate filaments. An approach to assess the influence of proteins such as GAR22 on the polymerization of microtubules is described in [27]. In [31], a registration-based method for tracking the continuous translocation of intermediate filaments towards the nucleus is developed (Fig. 2). The motility of cells is influenced by so-called focal adhesions (FAs). The analysis of their dynamics requires the segmentation and tracking of FAs [63].

Motion estimation is often formulated as an ill-posed problem [5]. In addition to measurements on the image data the solution requires regularization via a priori knowledge of the typically expected properties of the motion field. These regularizers should reflect the properties of the moving structures, for instance by models from mathematical physics [45, 57] or fluid flow models [8, 10], and lead to mathematically tractable optimization criteria [16, 32, 33, 60]. In this context, an interesting question is how precise these regularizers agree with models of cellular mechanics, organization and formation.

2.3 Virtual reality in medical visualization

VR technology has long been a promising candidate for a more efficient analysis of large data [59], the key hypothesis being that the use of real-time, stereoscopic displays and direct user interaction enables better understanding in less time. General overviews on VR-based visualization are given in Part VII of the Visualization Handbook by Hansen and Johnson [22]. VR-based data analysis largely relies on the key concept of interactive data handling in order to facilitate an intuitive trial-and-error exploration. One of the major advantages of this approach is the rich user interface provided by VR technology, which enables us to combine interactive exploration and immersive sensation.

Although VR has become accepted as a valuable tool in the analysis of simulated technical and physical processes, in the medical world the situation is somewhat ambivalent. In the clinical practice of medical imaging, VR has not yet become widely accepted. Interviews with radiologists revealed that they are well trained on the extraction of 3D information from CT, MRI, and positron emission tomography (PET) data which is presented as two-dimensional (2D) slices. Also, presentation of medical images in VR requires the preparation of raw data in a pre-processing step, thus becoming a cost factor in the radiologists daily workflow. However, the situation is quite different in research-related activities. Here, scientists not only appreciate the potential of VR for gaining insight into complex and large medical data, but VR-based visualization has also proven its impact for the discussion of results across disciplines between medical experts and researchers from other fields.

Diffusion tensor imaging (DTI) is a good example for active research going on in the medical field, which can profit from VR-based visualization and interaction methods. DTI currently provides the most advanced method for the assessment of white matter fiber pathways in the living human brain. Hereby, the course of the fibers is estimated by measuring water diffusivity in the brain. From this DTI data, an effective diffusion tensor can be estimated within each voxel. The quantities as mean diffusivity, principal diffusion direction, or anisotropy of the diffusion ellipsoid, can be computed from the elements of the diffusion tensor [4]. In contrast to deterministic tractography, the probabilistic approach accounts for the uncertainty within the estimated white matter fiber pathways and allows for drawing a clearer picture of the overall fiber architecture within the human brain.

Traditional visualization software most widely used in DTI tractography research only reconstructs fiber tracts as solid paths in 3D without any information about the uncertainty. Therefore, in a project of Jülich Aachen Research Alliance (JARA, http://www.jara.org), a VR-based visualization tool for the analysis of probabilistic tractography data is being developed [30]. The interactive visualization of probabilistic fiber tracts allows the domain scientists to directly interpret their results in 3D space (Fig. 3). The mental workload previously required from judging 2D slices or missing uncertainty information in non-interactive plots can be significantly reduced. Different probability values are coded with different colors and transparencies, permitting a 3D impression of the fiber tract while still revealing its main direction and the uncertainty around it. Using specific 3D visualization and interaction methods, interesting parts of the probabilistic fiber tracts can be revealed intuitively and referenced with anatomical landmarks. This allows a more accurate inspection of the anatomic structures in the direct vicinity of fiber pathways. Domain experts have stated that by combining anatomical information from a reference brain with overlaying fiber tracking results in 3D, the visualization gives considerably more valuable insight than standard visualization methods.

The analysis of flow phenomena is another case where VR-based, immersive visualization technology has gained in importance in recent years. With the ever growing performance of modern high performance computers, simulations that are run on those machines are becoming more and more complex. Today's common visualization techniques are inadequate for analyzing current simulations, which are usually based on unsteady 3D processes. Here, utilizing VR technology promises to facilitate the analysis procedure, because it allows for a visualization and interactive, explorative analysis of complex, time-variant computational fluid dynamic (CFD) data directly in 3D space. In the domain of computational engineering science, VR technology has been successfully employed for nearly two decades. One of the first examples was the Virtual Windtunnel by Bryson et al. [7].

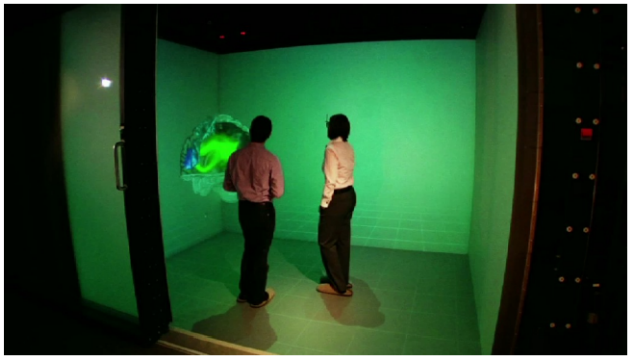

Fig. 3 Interactive exploration of probabilistic tractography data in a CAVE virtual environment

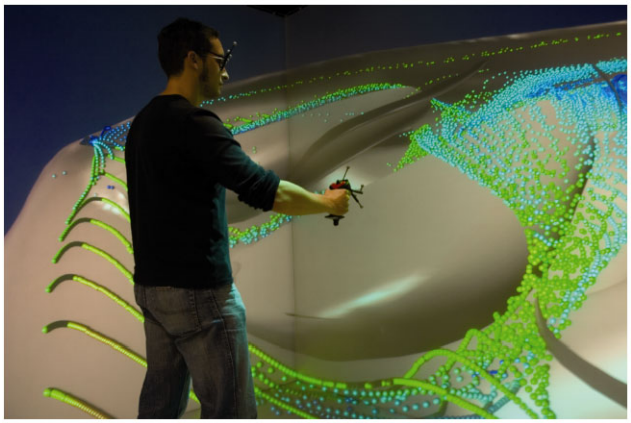

Fig. 4 The Virtual Windtunnel: Interactive exploration of the flow field inside a human nasal cavity by real-time particle tracing in 3D space

Recently, a growing number of research projects have been initiated in the medical field, where flow phenomena play a crucial role. Fluid mechanics researchers, computer scientists, and medical experts are collaborating within interdisciplinary teams one concentrating on the investigation of the aerodynamics of nasal respiration [25] and the other on the computational analysis of artificial blood pumps [26]. Using the Virtual Windtunnel paradigm implemented in a cave automatic virtual environment (CAVE)-like environment (Fig. 4) and direct interaction with the data in 3D space (Fig. 5), researchers significantly profit from VR for identifying and extracting relevant flow features in their datasets.

2.4 Neuroimaging

A new data set of the human brain with a volume ranging to GB is generated by 1 320 histological cuts [2, 44]. Each cut has a thickness of 100 µm and is scanned by polarized

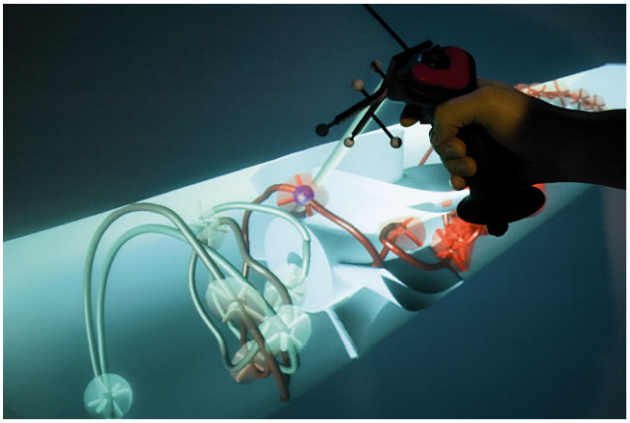

Fig. 5 (*Color online*) Direct interaction with "virtual *red* blood cells" flowing through a simulated artificial blood pump allows an intuitive navigation in space and time. Here, the domain expert picks a particle in order to navigate to a specific point in time

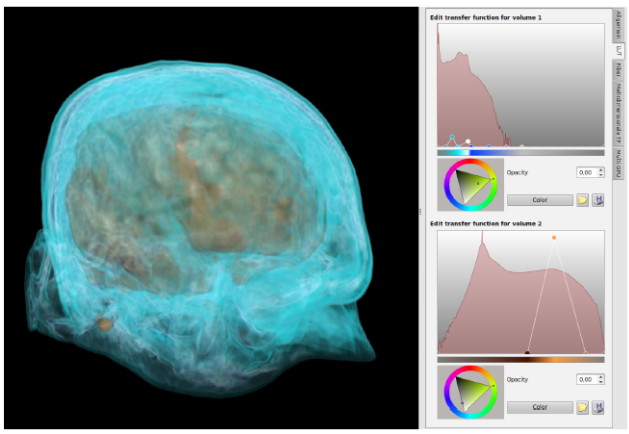

Fig. 6 (*Color online*) Multi-modal ray casting visualization of MRI (*blue*) and PET (*ocher*) data sets with two different 1D transfer functions

light imaging (PLI) with 3 569 × 2 700 pixel [3]. The total amount of memory for all scanned images reaches 47.4 GB or 11.9 GB using 32 or 8 bits per pixel, respectively. Nerve fiber paths are reconstructed from PLI scans and saved in a second huge data set. PLI-based reconstruction of nerve fibers is comparable to DTI. However, PLI provides an extra ordinary high resolution, which currently cannot be reached using in-vivo techniques. Further, the polarized histological cuts are scanned using a microscope and attain several TB of volume per data set. Micron resolution meets nerve fiber resolution and enables analysis of the architecture of nerve fibers in human brain.

Interactive visualization and navigation is a challenging task with these huge amounts of data. A particular 3D navigator has been developed to visualize specific areas of the brain with the corresponding nerve fiber data in real-time. Interactive visualization of nerve fibers combined with PLI scans can be achieved using a multi-modal technique. Here, multiple volume data sets are combined [51]. For this purpose, multiple data sets are loaded into the memory of the central processing unit (CPU) or the graphics processing unit (GPU), which requires memory space for all sets at once.

Figure 6 shows a multi-modal ray casting from two volume data sets (MTI and PET from a head) combined in a single 3D view using two different transfer functions. The images from the brain are combined in a 3D view with previously reconstructed nerve fibers. Figure 7 represents a 3D visualization of reconstructed nerve fibers from 36 PLI scans from a small area of the brain $27.39 \times 22.72 \times 3.20\ \text{mm}^3$.

3 Software techniques coping with large data

Due to the increasing load of data (Table 1) image processing and visualization algorithms have to be adjusted. For example, the artificial blood pump dataset consists of a 3.6 million cell tetrahedral grid for each of 200 time steps, leading to a total of 30 GB of data. Such data sizes are quite easy to handle in standard visualizations. However, interactive, real-time post-processing and rendering of the data on high-resolution, immersive displays is a challenging task, requiring the development of advanced parallelization, data management, and computer graphics methods. Future datasets in this field are predicted to reach the TB level.

Scalable algorithms must be developed using parallel techniques to reduce processing time and increase memory efficiency [28]. If the data amount exceeds the memory of the CPU or GPU, several techniques can be employed, including compressed or packed representations of the data [29], decomposition techniques, multi-resolution schemes [20, 53, 54], or out-of-core techniques [18]. Recent research combined bricking and decomposition with a hierarchical data structure.

Here, we consider the interactive rendering of large volume data containing billions of samples [37, 52]. Different programming steps are used for the data management: (i) decomposition techniques to reach a multi-resolution subdivision of the data, (ii) streaming techniques to asynchronously reach the right viewing data, and (iii) algorithms to render the volume visualization or to visualize the zoomed data.

Decomposition techniques of volume data subdivide into smaller bricks, which are processed further. Each brick decomposes the data into a hierarchical multi-resolution using data structures like binary space partitioning (BSP) tree, octree or kd-tree, can be used for the decomposition. The tree structure is hierarchical where the leaves represent the original data and the inner nodes hold a filtered, coarse-to-fine representation of the original volume data and are saved out-of-core. A streaming technique fetches the current viewing

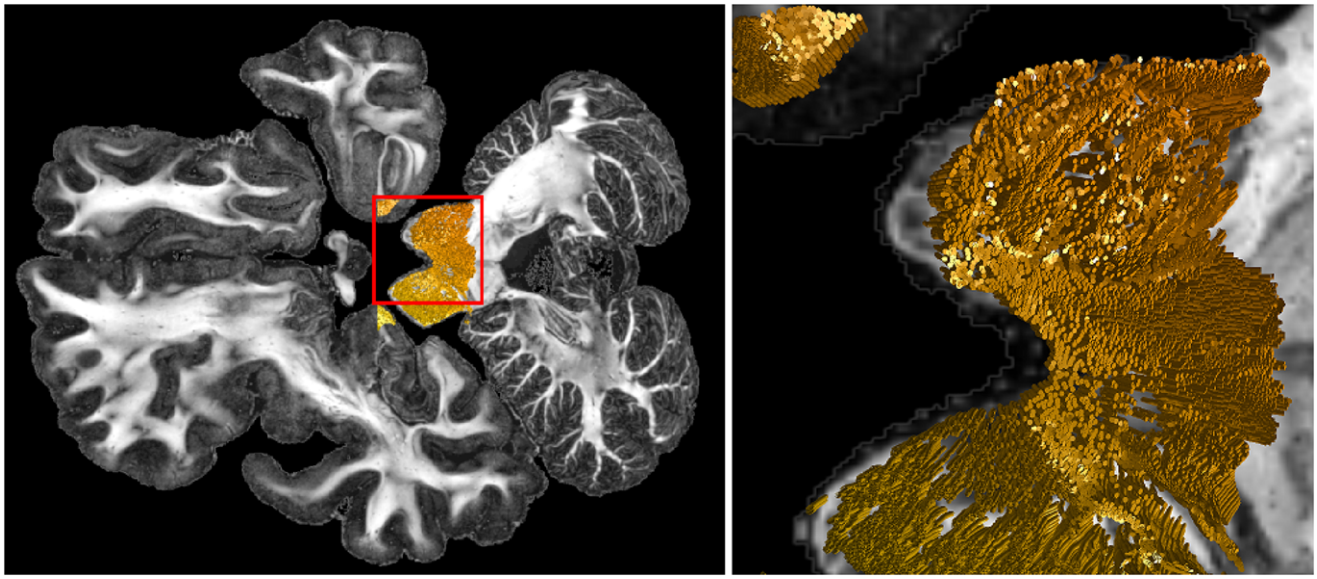

Fig. 7 (*Color online*) 3D visualization of 20 816 reconstructed nerve fibers (15 MB) from 36 PLI slides of a human brain. The region with size of 27.39 mm × 22.72 mm × 3.20 mm that is marked in *red* on the *left hand side* is zoomed on the *right*. The color of the nerve fibers represents their direction. In the *small area* shown, all fibers have nearly the same direction

Table 1 Examples of large medical image data (fps = frames per second; fpd = frames per day)

Data	Resolution	No of images	No of slices	No of pixel	No of bits	Total memory
Whole body MRI scan	8 mm	1	250	256 × 256	8	16 MB
Screening mammography	50 µm	4	1	5 000 × 6 000	16	230 MB
Whole body CT scan	1 mm	1	2 000	512 × 512	12	750 MB
4D sequence of a beating heart		20 fps	240	512 × 512	12	per sec: 1.75 GB
PLI human brain scan	20 µm	1	3 200	8 000 × 8 000	16	200 GB
IRMA mammography database	50 µm	10 517	1	5 000 × 6 000	16	590 GB
Fluorescence microscopy		2 fpd				per year: 1 TB
Microscopic human brain scan	1.5 µm	1	7 200	106 667 × 106 667	16	66 TB
LIFE full body MRI cohort	8 mm	200 000	250	256 × 256	8	3 PB

data asynchronously at runtime. Only this visible data is sent to the visualization pipeline which renders the specific 3D view by using a GPU-based ray casting algorithm.

The main disadvantage of working with Giga- to Terabyte volume data, aside from the logistic problem, is the runtime performance. The user can't accept waiting for answers from the program. Therefore, current research is focused on advanced parallelization techniques in order to reach an acceptable real-time response. These techniques require different hardware architectures, with one or more computers and one or more CPUs and GPUs. Several programming languages have been developed to support such architectures:

1. Parallel CPU-based programming on a single node (one computer with multiple CPUs) with shared memory using threaded programming techniques like OpenMP or QtThreaded.
2. Parallel GPU-based programming on a single node with one GPU or multiple GPUs using programming languages for the massive parallel cores on the graphic card [53–55, 62]. With advances in GPU architecture, several algorithms have reached higher efficiency by transferring the program from CPU to GPU. This means instead of four to eight parallel CPUs, 240 to 480 massively parallel processing cores on the graphic card are used. Several languages have been developed by the graphic cards industry to code algorithms for execution on the GPU, for example:
   - Compute Unified Device Architecture (CUDA) is the computing engine in NVIDIA graphics processing units. C for CUDA is a C-like programming language developed especially for NVIDIA graphic cards.
   - Open Computing Language (OpenCL) is a framework that executes across heterogeneous platforms consist-

ing of CPUs, GPUs, and other processors. OpenCL provides parallel computing using task-based and data-based parallelism. OpenCL is the common language for general purpose programming on any graphics card.

3. Parallel programming on multiple nodes in a cluster of linked computers connected through a fast local area network (LAN), which is also referred to as Grid computing [9]. Special software interfaces manage the communication between the processes, like the message passing interface (MPI).

4 Summary and conclusion

Current research in medical image management and data mining, bioimaging, virtual reality in visualization and neuroimaging has been discussed and advanced programming techniques have been summarized. Handling Giga- to Terabyte of image data, scalable programs have to be developed to support different parallel hardware architectures. Modern programming languages like C for CUDA, OpenCL and Qt-Threaded have been introduced supporting process threading on several CPUs and GPUs.

The next level, from Tera- to Petabyte, is already looming on the horizon. High-throughput nextgeneration sequencing produces up to 100 TB of data for a single investigation (30 repetitions). In translational medical research, whole body MRI is gaining popularity. The recently launched Leipzig Interdisciplinary Research Cluster of Genetic Factors, Clinical Phenotypes and Environment (LIFE) project in Germany already aims at full-body MRI scanning of a population cohort with 200 000 subjects. Assuming a gray scale resolution of eight bit, 256×256 pixel slices, and 8 mm slice thickness [6], one scan yields about 16 MB, and the entire cohort will be approximately 3 PB.

In the future, PACS, CBIR and HIS have to overcome the logistic problem handling Tera- to Petabyte of biomedical image data. Data compression, decomposition and parallelization techniques will be the keys in developing real-time applications, which also attain the acceptance from the physicians.

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