

More Mathematics into Medicine!

1.Mr. Gorekh Prasad Nayak 2.Soubhagini Mohapatra

Nalanda Institute of Technology, Bhubaneswar

Dept. of Basic Science & Humanities

E-mail ID: gorekhprasad@thenalanda.com

SoubhaginiMohapatra@thenalanda.onmicrosoft.com

Abstract

The three success stories in this article demonstrate how the fusion of mathematics and medicine has accelerated the development of patient-specific models built on top of cutting-edge medical imaging and "virtual labs," which will soon play an increasingly significant role. Because of this, it appears that the aims of mathematics and medicine are similar: both fields need accurate and timely outcomes. On the medical side, this means that the required computations must complete on a local Computer in the clinics in the lowest amount of time possible, and that their results must be reliable and accurate enough to be used as a foundation for medical choices. As for the mathematical side, this means that high-est level requirements for the efficiency of the applied algorithms and the numerical and visualization software have to be met. Yet there is still a long way to go, until anatomically correct and medically useful individual functional models for the essential body parts and for the most frequent diseases will be at hand. This will only be possible, if more mathematics enters into medicine.

Mathematics in Medical Imaging

History of a success

When Konrad Röntgen discovered the "X-rays" in 1895 in Würzburg, Germany, he opened a window to non-invasive insight into the human body. The attenuation of X-rays is strongly dependent on the tissue through which they travel, for example, bone attenuates more than fat. The thus produced shadow images deliver visual information about the interior of the body. The disadvantage is that dense tissue like bones masks the tissue along the same path of the X-rays, whence the application was restricted to those parts of the body with few bones. Examinations of the brain were, due to the surrounding skull, virtually impossible without the dangerous addition of contrast agents.

The conceptual and technical breakthrough was achieved in the sixties: Nobel laureates Allan Cormack and Godfrey Hounsfield suggested an imaging system, where shadow images of an imaginary cross section through the body and for many directions are registered simultaneously. Each of these shadow images contributes only little information. The exploitation of the fact that all of these images cover the same part of the body allowed for images of the interior of the body with previously unknown resolution. This was the starting point of a long success story.

Computed Tomography (CT). Computed tomography, also known as computer assisted tomography (CAT), is the name of an imaging system, where the role of mathematics is evident. With the large number of collected data the calculation of the desired image information can be achieved only by means of powerful computers. Fundamental for the use of computers is the development of efficient algorithms, based on a precise mathematical model of the complex connection between measured data and image information to be determined. The measured data, i.e. the attenuation of the X-ray intensity after travelling through the body, is related to the X-ray attenuation coefficient, interpreted mostly as the density of the tissue, along

the path of the rays. In mathematical terms, the observed attenuation is related to the line integral of the X-ray attenuation coefficient along the ray path. The arising integral equation is, in the 2D case, named as Radon transform, after the Austrian mathematician Johann Radon. In the first commercial scanners, Godfrey Hounsfield solved this integral equation by standard discretization methods. He projected the solution on a pixel basis, resulting in large, unstructured systems of linear equations that he solved iteratively. Only in the mid-seventies the integral equation was actually recognized as the Radon transform, for which Radon had derived an analytical inversion formula already in 1917.

However, it has been a long way to go from his mathematical formula to working algorithms, questions to be answered first concerned image resolution, non-uniqueness for finitely many data, and optimization of parameters and step sizes. In addition, a phenomenon typical for all imaging methods showed up: These problems are so-called *inverse problems*, where unavoidable input data errors, due to photon scattering, beam hardening, or miscounts in the detector, are extremely amplified in the solution. In order to avoid this unwanted effect, the problem has to be regularized, such that a balance between best possible resolution in the image and maximal damping of the noise is obtained. In th

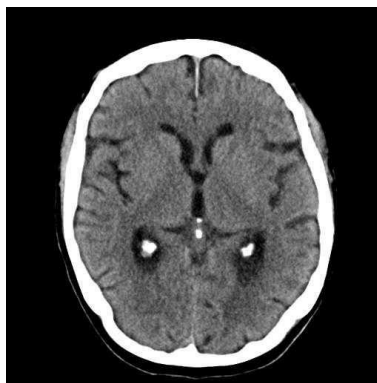


Figure 1: Reconstruction of a trans axial cut through the head. Source: Siemens Healthcare, SOMATOM Definition AS+.

case of CT this is achieved by elimination of the high frequency components in the data. Nowadays, the method developed by the mathematicians Shepp and Logan [17] is well established. The resulting algorithms consist of two steps, a filtering of the data, via discrete convolution in the two-dimensional application or via Fourier techniques in higher dimensions, and a backprojection of the filtered data onto the reconstruction region. Both steps can be performed in parallel during the measuring process, resulting in a dramatic gain in computer time. It is worth mentioning that the acceleration of computing time due to the progress of mathematical algorithms is much higher than the one due to the progress in computer hardware.

Of course, the advancement of engineering performance should be mentioned, which allowed for an essential speed-up in time and accuracy of the measurement process. This led to completely new scanning geometries and thus to new challenges in mathematics. The originally introduced parallel geometry, where one path was

measured at a time instance, was replaced by fan-beam geometries, where, at one time instance, the complete plane under consideration was covered by a set of divergent beams. The helical scan, where the patient is moved through the gantry, first realized with a few detector lines, was established in the early nineties. Today real 3D scanning with a detector array is the object of intensive research, already widely used in non-destructive material testing. The mathematical model remains to be line integrals over the paths of the rays. The thus computed reconstructions are often processed in order to enhance the diagnosis. Methods, wherein parts of the image process steps are integrated parallel to the reconstruction method are presently under development. Among the pioneers from the mathematical side are Gabor Herman, Kennan Smith, or Frank Natterer. An extensive presentation can be found in Natterer's most recent monograph [15].

Magnetic Resonance Imaging (MRI). Magnetic resonance spectroscopy, 1946 independently developed by Felix Bloch and Edward Purcell, gives information on the chemical surrounding in a molecule, by exciting it to resonance in a strong magnetic field. This was the starting point for magnetic resonance imag-

ing (MRI, formerly called nuclear magnetic resonance (NMR)). Paul Lauterbur, Nobel laureate for medicine in 2003, achieved a spatial resolution by modulating the primary homogeneous magnetic field by so-called gradient fields in such a way that the regions of constant resonance frequency became planes through the body. In that way, plane integrals over the proton distribution inside the body were measured. The corresponding mathematical model is the 3D Radon transform [14]. In the early eighties there were no desktop computers available, allowing for handling these huge data sets within tolerable time. Peter Mansfield, Nobel laureate as well in 2003, further developed gradient fields and excitations such that the Fourier transform could be used to invert the data. The regularization, already discussed above in the context of X-ray CT, was achieved by eliminating the high frequency components. In that way, with high technical complexity, the mathematical problem had been simplified to be solvable with the computers of that time.

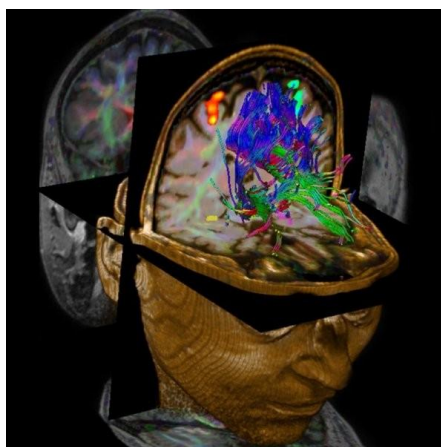


Figure 2: Reconstruction und visualization based on MRI-data. Source: Siemens Healthcare, Sektor Magnetresonanztomographie, MAGNETOM Verio 3T.

Ultrasound. This imaging technique has been used in medicine for quite a time. Well established are B-scan devices, acting as emitter and receiver at the same

time sending ultrasound waves into the body. Measured are travel times of the echoes, which are produced at interfaces of tissues with different acoustic impedance and scattering properties. Upon assuming that the speed of sound is independent of the tissue an image can be computed. Even though this is only approximately correct, nevertheless the images contain sufficient diagnostic information. If, in addition, the frequency shift is recorded, then using the Doppler effect, the speed of blood can be calculated.

Mathematics as innovation factor

For many years, medical industry worldwide has played an internationally leading economical role. The following numbers may document this statement for

Germany. In 2002, commodities in X-rays & CT for over 2 Billion Euro have been produced. The German trade surplus with respect to X-rays and CT figures around 1 Billion Euro, around 600 Mio. Euro for MRI systems.¹. Leading companies in Germany are Siemens Medical Solutions, but also Phillips Health Care and General Electric. A main location factor seems to be well-trained applied mathematicians and engineers with a sound understanding of mathematics.

Perspective: new imaging methods

The perspective in medical imaging is dominated by the development of newer measuring technologies.

3D tomography. In non-destructive material testing, *3D X-ray CT* is widely used in connection with a circular scanning geometry; i.e., the X-ray tube is moved on a circle in a plane around the examined object with the detector plane positioned at the opposite side. Helical geometry is favoured in medical applications, but the therein necessary variable shift of the patient has not been solved yet satisfactorily in existing algorithms. In principle, X-ray tube and detector can be moved along arbitrary trajectories around the patient. The determination of trajectories that are optimal with respect to resolution and stability remains a mathematical challenge. Higher hardware capacities will allow for new approaches different from the classical filtered backprojection type.

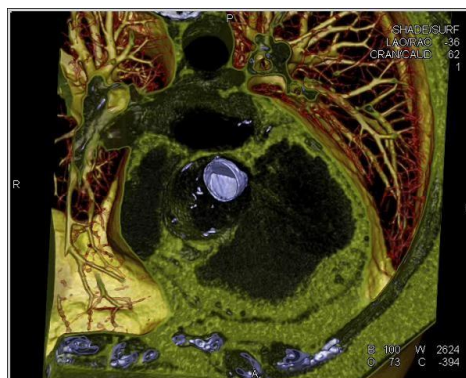


Figure 3: Three-dimensional visualization of two-dimensional CT scans through a human heart. Source: Siemens Healthcare, Sektor, Computertomographie, SOMATOM Definition AS+.

4D tomography. Since the early eighties, *3D spatial presentations* have been computed from a series of 2D images. If one combines these volumetric images for different instances, clearly *time* enters as a fourth dimension. The resulting movies, for example from a beating heart, are impressive: Figure 3 is a snapshot from such a movie. Certainly, it will take some time to develop this kind of technique for routine application. At present, each image frame is treated separately, a regularization with respect to time, as would be necessary, e.g., in current intensity reconstruction from MEG/EEG data, is not yet implemented.

Electron paramagnetic resonance imaging. In this technique a decoupling of the fourth dimension is not possible, since there, besides the three spatial dimensions, a *spectral* dimension shows up additionally. The corresponding mathematical model is the Radon transform in four dimensions. This technology is presently studied in the stages of pharmaceutical research and animal experiments. However, due to the limitations in field strength, the data in Radon space cannot be sampled completely with the consequence that a limited angle problem has to be solved. Theoretically, the desired distribution would be uniquely determined, if all data in the restricted range were available, but instabilities and strong artefacts complicate the reconstruction problem.

Ultrasound CT. In this approach sender and receiver are spatially separated, the corresponding mathematical model is an inverse scattering problem for the determination of the spatially varying sound impedance and the scattering properties. The difficulty here is that, in contrast to CT, the paths of the waves depend upon the variable to be computed, which makes the problem highly nonlinear. A linearization of the problem via Born or Rytov approximation neglects the effects of multiple scattering and is therefore not sufficiently accurate. That is why ultrasound tomography today is still a challenge to mathematics and algorithm development.

Transmission electron microscopy (TEM). For the visualization of biomolecules by TEM, various approaches are pursued. If one does not aim at averaging over many probes of the same kind, again a limited angle problem arises. In addition, wave phenomena enter for small sized objects, leading, as in ultrasound tomography, to nonlinear inverse scattering problems. Fortunately, linearization is feasible here, which facilitates the development of algorithms significantly.

Phase contrast tomography. In this technology, where complex-valued sizes have to be reconstructed, linearizations are applicable, too. The phase supplies information even when the density differences within the object are extremely small. Using data from a synchrotron, impressive results have been achieved, see Figure 4. Due to different scanning geometries, medical application still generates challenging problems for the development of algorithms.

Diffusion tensor MRI. This method provides a tensor at each reconstruction point, thus bearing information concerning the diffusivity of water molecules in tissue, see Figure 2. Here reconstruction and regularization are performed separately. Only after having computed the tensors, properties of the tensor like symmetry or

positive definiteness are produced point by point.

The above list of imaging techniques under present development is by no means complete. Methods like *impedance tomography* are studied as well as those applying *light* to detect objects close to the skin. In all of the mentioned measuring techniques, the technological development is so advanced that the

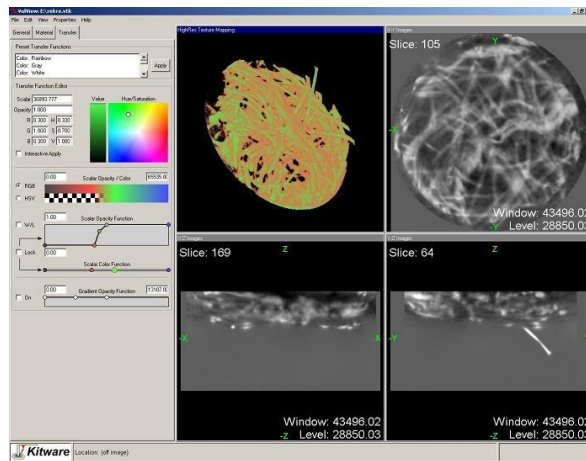


Figure 4: Phase contrast tomography: phase information, see [9].

solution of the associated mathematical problems – like modelling, determination of achievable resolution and development of efficient algorithms – will yield a considerable innovation thrust.

Image fusion. Different imaging systems supply different kinds of information, the fusion of which in a single image can give a lot more insight to the physician. Prerequisite of image fusion is an imaging of (almost) identical cross sections through the body or of volumetric presentations. Different physical formats have to be mapped to each other. This requires methods of image recognition, for example segmentation (see Section 3), to determine the geometric mappings. First methods exist, partially applied in connection with the rapidly developing *intensity modulated radio therapy* (IMRT).



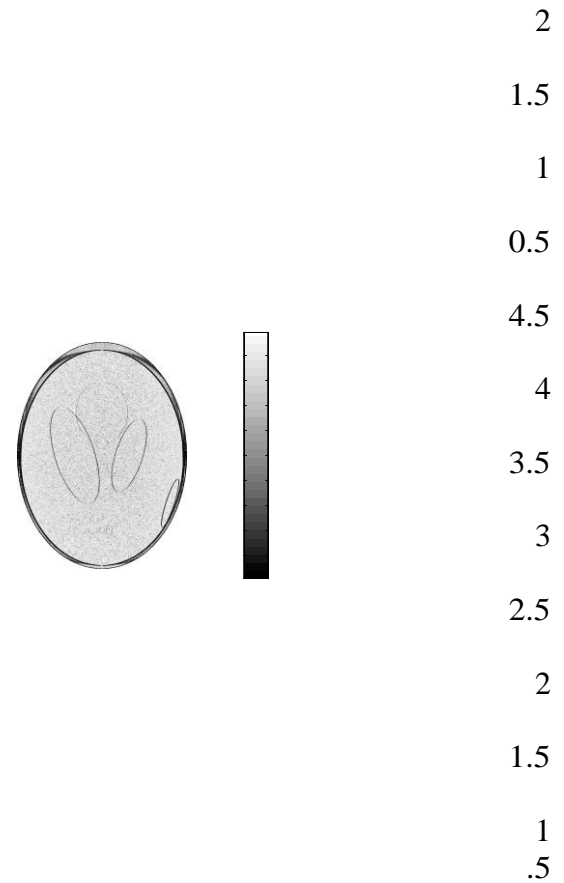


Figure 5: Comparison of image analysis methods, see [13]: *Left*: Integrated in the reconstruction algorithm. *Right*: Performed separately, as usual so far.

Feature reconstruction. Supporting medical doctors in the interpretation of the ever increasing amount of information is an extremely important task.

In non-destructive testing in materials science, where tomographic methods are applied as well, tools for an *automatic* recognition of precisely defined properties are in use, such as the detection of blow holes inside metal. In medical applications, this surely is not the aim at the moment. Nevertheless, a pre-processing of images is often useful. At present, the two steps, reconstruction and pre-processing, are performed separately. In [13], a novel technique has been presented, wherein the pre-processing step is optimally integrated into the reconstruction algorithm. In this way, significantly refined results can be realized, as shown in Figure 5. Nearly without any additional effort both the classical reconstruction and the enhanced images can be computed. This approach of combining image reconstruction and image analysis paves the way for *feature reconstruction*.

**1 Mathematics in Cardiology and Cardial Surgery
Success stories: ECG and biosignal processing**

Everyday some million Electrocardiograms (ECGs) are recorded, many of them Holter ECGs (long term ECGs). A single 24h ECG contains about 100 000 heart beats. It is practically impossible that a medical doctor can look through all these data to filter out events of diagnostic relevance. Not only that precious time would be lost, in addition there is the danger that alertness drops quitefast and important events are overlooked.

Telemedicine is an important future market – currently many companies position themselves in the market. Sportsmen and elderly people can buy a continuous monitoring of their state of health – 24 hours per day and 7 days per week. In addition to the ECG often also other vital health parameters are measured, like weight, body temperature, blood oxygen saturation etc. Also in this case it is neither practical nor would it be affordable that physicians monitor all these data.

A solution is offered by software packages that support the medical doctor in ECG data analysis. With their aid the essential characteristics of the ECG are revealed and the most important parts of the data stream are highlighted. During monitoring in the intensive care unit of the hospital or in Telemedicine, a life threatening state of the patient must be detected immediately and with high reliability and an alarm must be given. But which algorithm is able to perform this data analysis with the highest possible reliability? These algorithms must be applicable to all (!) ECGs, even if the ECG of an individual patient is extremely seldom and strange. And they must be very robust, since often artefacts are much larger than the biosignals of interest.

Today mathematical methods together with the implemented software are indispensable tools for good biosignal analysis. Companies of medical systems have recognized that the added value in the production chain for ECG and monitoring systems is only to one half due to hardware (e.g. in electronics). The other half comes from intelligent signal processing and analysis. Suppression of artefacts is carried out using filters in the frequency domain, but also wavelet transformation is applied, since it allows for best possible frequency separation simultaneously with good temporal resolution. Detection of data intervals of diagnostic relevance is realized by first extracting characteristic features using mathematical methods followed by a mathematical classification (nearest neighbor, Bayes-maximum-likelihood, neural networks etc.). This way, e.g., a QRS complex can be separated from an extrasystole [18]. Also model based techniques like Kalman filters or Markov models are employed. Figure 6 shows a typical ECG, as can be found in long term ECG acquisitions, together with the annotation of the most important time instants like the R-peak, the P-wave, or the T-wave.

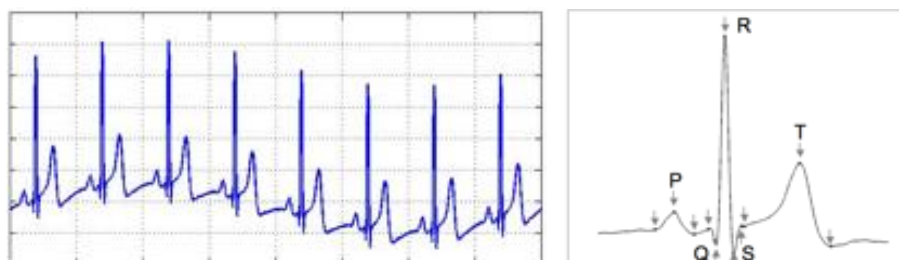


Figure 6: Measured ECG together with the result of a computer assisted annotation of the most important time instants [11].

For an early detection of trends in the ECG, new mathematical methods of time series analysis are employed. Using these methods, stochastic fluctuations can be separated from deterministic ones and significant changes can be uncovered long before the eye of the medical doctor can find it in the ECG. Currently, one is trying to find mathematical rules (linear and non-linear ones) that are able to predict the ECG of the next beat from the preceding ones. Once these rules will have been found, the detection of any deviation is an indication to an early stage of a disease. This research is right in the centre of the mathematical field of “complex dynamical systems” that will enable to detect many characteristics of diagnostic relevance in the ECG. For example, most often stable trajectories can be found in the state space of the heart, but sometimes they pass through bifurcations into chaos (like fibrillation [5]).

Mathematics as innovation factor

In medical engineering in general and in cardiology and heart surgery in particular it is of increasing importance to recognize the essentials out of a huge amount of information about a very complex system, and to draw the right conclusions. Algorithms and computers can help in this task. By no means it is planned to replace the medical doctor by a computer. But the computer with its implemented algorithms can already today give valuable advice to the physician and this trend will continue and gain relevance.

In the first stage, algorithms can highlight or zoom into information contained in the data that cannot be recognized with the naked eye: small changes of the ECG, unusual objects in the images, characteristic deviations of haematological data etc. In the second stage, values of diagnostic importance are determined quantitatively. Often the decision to choose one or another line of therapy depends on whether a specific value is above or below a given threshold. Using mathematical methods these values can be found as accurately as possible even in disturbed and noisy data. Finally, mathematical methods can be employed to optimize therapy by trying out various variants and evaluate the outcome using objective and traceable criteria.

In future, it will be decisive for manufacturers of medical devices to integrate the huge amount of patient data into a comprehensive view in an intelligent way and to support the medical doctor in his/her diagnosis and therapy decision. Only companies that can offer these options will play a major role in the future world market.

Perspective: the virtual heart

Integration of imaging, electrophysiology, and in-vitro diagnostics. The ECG described above is an important source of diagnostic information for the physician, but by far not the only one: Medical images and in-vitro diagnostics like, e.g., haematological data are indispensable additional sources of information. Mathematical methods will play a major role in integrating all these data into a comprehensive picture about the state of the patient. Purely geometrical information of the medical images like projection X-ray, CT, ultrasound or MRI is complemented by functional data. Some of these functional data can be gained from medical imaging devices: metabolism, e.g., from PET, flow, e.g., from Doppler ultrasound, or perfusion, e.g., from contrast enhanced X-ray. In the next step, other data have to be integrated like, e.g., ECG, blood pressure, blood oxygen saturation, haematological data, and enzyme activities and, on the long run, also genetic

profiles that show up a predisposition for a disease. The objective is to integrate all these data into a complete patient model so that finally important functional characteristics can be determined. (For readers with medical and physiological knowledge: such functional characteristics are, e.g., elasticity, contractility, propagation of electrophysiological depolarization, perfusion, enzyme activity, etc.)

Such an integrated heart model, a virtual heart, can depict how the real heart of the patient deviates from the physiological average. This opens many new options both in diagnosis and therapy planning.

Therapy Planning. Mathematical models of heart and circulation have many interesting applications in cardiology and heart surgery.

Upon using *electrophysiological models*, it will be possible to

- optimize RF ablation for atrial fibrillation,
- adapt stimulation sequences for heart pacemaker and cardiac resynchronization therapy,
- predict the effect of new pharmaceutical drugs for the treatment of arrhythmias.

Upon using *elastomechanical models*, it will be possible to

- optimize surgical cuts in open heart surgery for therapy of aneurysms and for surgical reconstruction of ventricles,
- evaluate the elastomechanical consequences of an infarction.

Using *fluid dynamical models* of vessels one can

- better understand the etiology of stenoses (plaque in a blood vessel),
- optimize stents to open stenoses and to treat aneurysms.

Using *circulation models* it will be possible to

- evaluate new drugs to treat hypertension (high blood pressure),
- control extracorporeal circulation during heart surgery.

For the purpose of further explaining these options, one of them is highlighted in the following.

Planning of RF ablation at atrial fibrillation. RF ablation means the precise destruction of cells (often tumour cells) by feeding a radio frequency current into the tissue. Using an image guided catheter the tissue is heated locally above 42° C so that the proteins are coagulated in an area near to the tip of the catheter. A well-defined scar is created. This therapy is also a preferred choice in case of atrial fibrillation.

Electrophysiological computer models of the heart start with the various ion channels in the membrane of cardiac cells. The dynamics of ion channels can be described by “stiff” ordinary differential equations. Their rate constants are a function of the transmembrane voltage [6]. Single cells lead to a nonlinear system of about 20 coupled differential equations. The spatial coupling of the cells is modelled by partial differential equations, e.g., in the so-called “bidomain model” [7]. As eventually electric potentials in the body are to be determined, basically the equations of electromagnetic field theory have to be applied. Electrophysiological processes in the human body are comparably slow, which is why only the Poisson equation of electrostatic problems - an elliptic partial differential equation - has to be solved. Numerical simulation of these equations requires the discretization of space and time. In biomedical engineering, an explicit Euler discretization is preferred up to now, [6], whereas the mathematical community applies stiff

integrators as a standard (see [1] and references therein). Here is space left for improvement via mutual exchange of methods and ideas. Spatial discretization is carried out, e.g., by finite element methods - with uniform or adaptive meshes - or by finite differences. In case of uniform discretization a problem with some million degrees of freedom has to be solved, preferably in the clock pulse of a second. Also the so-called “forward problem”, which is used to find the electric signals on the body surface (including the ECG) from the electric source distributions in the heart, leads to a Poisson equation. Figure 7 (top row) shows a simulation of the depolarization of a healthy human atrium: the electric depolarization starts in the sinus node, the natural “pace maker” of the heart, and then spreads out across the right and left atrium.

Next we present details of the modelling of pathologies, here especially of atrial fibrillation. For this application, new parameters have to be assigned to the atrial tissue that are able to describe the pathological case. In this case, the computer model switches into a chaotic state so that patterns of depolarization can be observed in the model which amazingly well resemble the patterns observed in real patients that actually suffer from atrial fibrillation. A more and more applied therapy now is to heat small spots on the atrial tissue in such a way that a scar is formed, which then will not conduct the excitation furtheron (this is the RF ablation, see bottom row of Figure 7). This procedure can easily be implemented in a computer model.

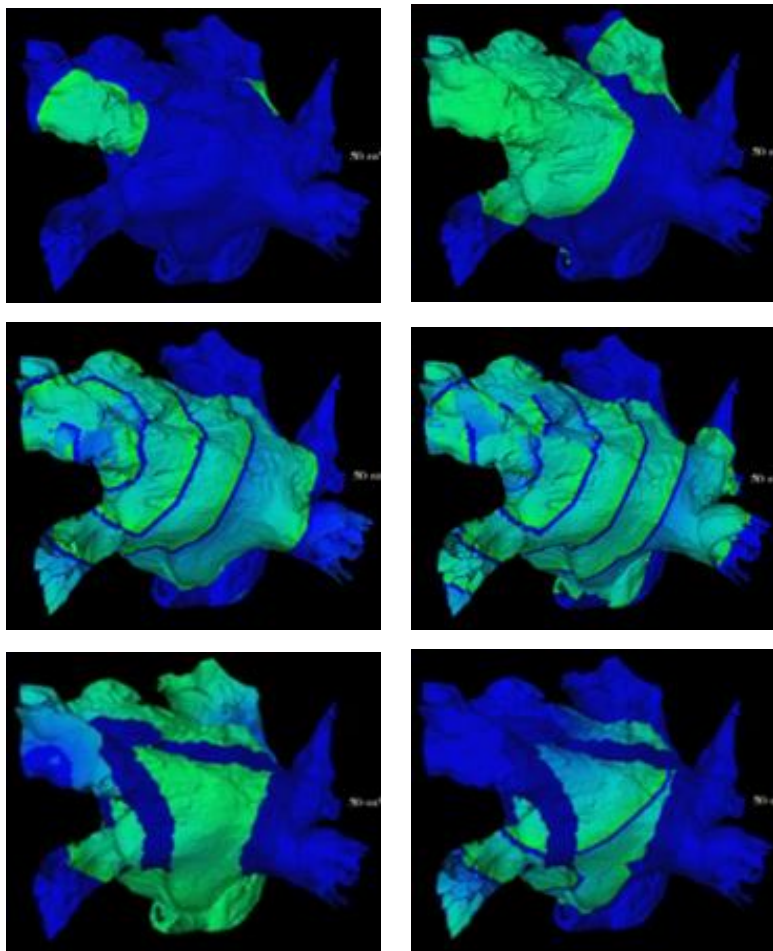


Figure 7: Simulation of the spread of depolarization in the human atrium. Transmembrane voltages at different time instants of depolarization, see [16]. *Top row*: healthy atrium. *Center row*: atrial flutter. *Bottom row*: test of an ablation therapy.

An important, but still open question is how to find the optimal strategy for RF ablation. What would be the best choice of ablation points and lines in the atrium so that fibrillation is terminated reliably using as little scar as possible and, in addition, protecting the patient from flaring up of the disease? Computer models can indeed answer this question by testing different strategies in the virtual atrium. With a “reset” the virtual atrium can be switched back to the original situation and a new test can be started. This is obviously not possible in real patients. A scar that has been burnt into the atrium cannot be removed again!

The above sketched method for optimization of RF-ablation has not been transferred to clinical practice yet. Validation requires still many more experiments. The biggest challenge will be to adapt the computer model to the individual patient using measurements (images and electrical data) to derive a patient-specific ablation strategy. A bottleneck on the way towards this goal are also algorithms for the computation of cell models and the field equations: Here new mathematical methods are needed to speed up the whole simulation process – so as to “catch up” with the heart dynamics.

2 Mathematics in Therapy and Operation Planning

In recent years, mathematics has gained an increasingly important role in medical planning. Palpable successes have been achieved in the cancer therapy hyperthermia as well as in cranio-maxillo-facial (CMF) surgery, liver surgery, and orthopaedic surgery.

Success story: CMF surgery

Problem formulation. A “beautiful” face has demonstrably social advantages. But the contrary occurs, when a face has been malformed from birth on or by an accident (cf. Figure 8). In CMF surgery, bony structures of the skull are operatively corrected with the aim of both functional and aesthetic reconstruction.



Figure 8: Patients with congenital malformations [4].

Success by mathematics. Already since the early 90’s, computer scientists have dealt with computer assisted 3D planning of cranio-maxillo-facial operations on the basis of CT data (see [21] and references therein). Meanwhile mathematics, too, plays a crucial role in the planning of highly complex operations. Its most important tools appeared to be *virtual labs* for therapy and operation planning [2]; this term describes extensive software environments (such



Figure 9: Comparisons of two patients: before operation, after operation, overlays with predictions [22].

as, e.g., AmiraTM[19]), within which patient specific geometric models are integrated with partial differential equations for elastomechanics, fluid dynamics, or diffusion as well as with fast algorithms for their numerical solution and visualization. Today, before the surgeon performs his first cut, reliable predictions about the postoperative appearance can be made. For the purpose of illustration, Figure 8 shows a series of patients whose operation planning has been done in cooperation of clinics and ZIB. In Figure 9, a comparison of the computed predictions and the actual outcome of two operations is given [21].

Mathematics as innovation factor

In the course of many years of collaboration between mathematics and medicine, a paradigm has crystalized that might be characterized as follows: (see Figure 10):

- Generation of a “virtual patient” from data of the real patient,
- mathematical therapy and operation planning in a “virtual lab”,
- transfer of the results back to the situation of the real patient.

The first step requires the construction of a sufficiently accurate 3D computer model of the patient from medical imaging data. The second step contains the fast numerical solution of partial differential equations over a realistic body geometry of the individual patient. The third step comprises techniques of registration and navigation for an exact implementation of the planning. All steps have the importance of an efficient 3D visualization in common. The corresponding mathematics and computer science is not treated here in depth; for interested readers, we refer to the papers [4, 21, 22].

On the way from the real to the virtual patient a sequence of sub-steps has to be taken, which contain a lot of mathematics themselves.

Geometric modelling [23]. Tomographic imaging (cf. Section 1) yields a stack of 2D planar cross sectional images. However, any therapy planning will absolutely require 3D models of the individual anatomy. For this reason, methods need to be provided, which generate a reliable geometric 3D patient model from this kind of 2D information.

As the first task therein, *segmentation* is incurred, whereby the organic substructure is to be derived from the pure density information of CT or MRT images by classification of image subdomains. This substructure is one of the crucial prerequisites of functional patient models. Methods available until a few

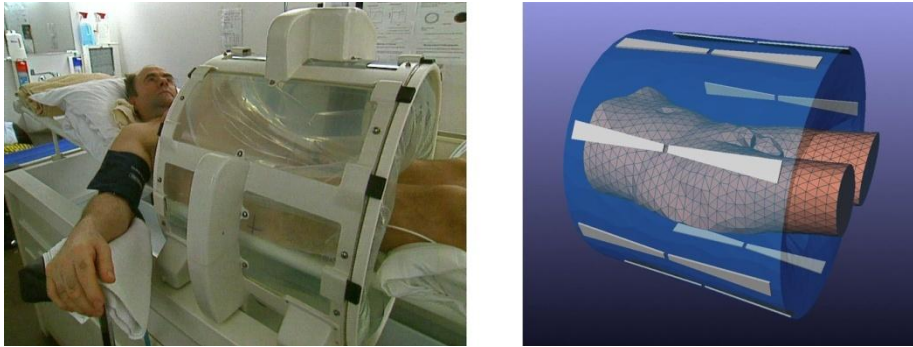


Figure 10: Hyperthermia: real versus virtual patient in applicator [3].

years ago (such as, e.g., region growing, watershed methods, intelligent scissors, active contours etc.), started from 2D stacks to generate the 3D model and were to their major part *interactive*, i.e. they required the intermittent action of experts. As a consequence, they were too time consuming for clinical practice. A new generation of *fully automatic* methods (see, e.g., [10]) uses methods of *statistical 3D shape analysis*: These methods start from some “averaged” 3D model combined with “essential coordinates” established via PCA (principal component analysis) applied to a “training set” of known patient data. With each new data set the training set can be enriched. The explicit use of shape knowledge thus mimicks the process in the mind of the radiologist, who, by education and experience, has a 3D imagination of the situation, into which he can cognitively insert the 2D image under consideration. Some insight into this methodology is given in Figure 11.

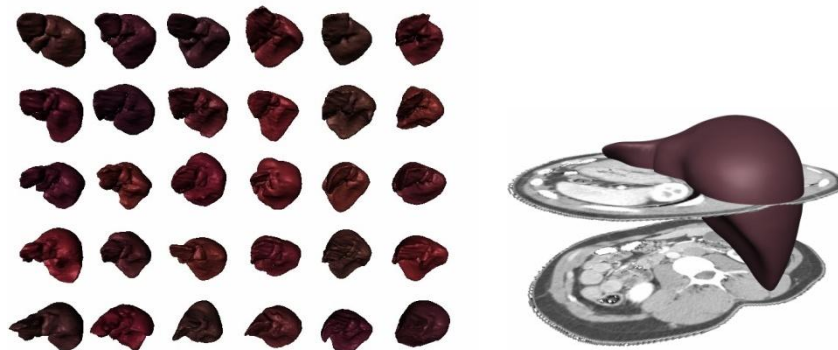


Figure 11: Statistical 3D shape analysis [10]. *Left*: Test set of known liver data of various patients. *Right*: Segmentation of new liver data (for the purpose of demonstration only two CT cross sectional images).

As a result of the segmentation procedure, one obtains *surface meshes* on all tissue interfaces (outer and inner boundaries). In order to achieve a decent balance of a low number of mesh nodes versus a high approximation quality, the surface meshes are coarsened depending on local curvature. These reduced surface meshes then build the basis for the establishment of *volumetric meshes* by tetrahedrons (see [23] and references). Such types of meshes are particularly well-suited for successive refinement – a feature that is crucial in connection with *adaptive multigrid methods* for the fast solution of partial differential equations.

Example: osteotomy planning [21]. Osteotomy means the surgical cutting of

bone. This part of the planning primarily aims at functional rehabilitation. Whenever several bone segments are involved, which need to be arranged in mutual relationship, or when different therapy variants come into play, then the expected aesthetic outcome will be an important criterion to be taken into account in the planning. A variety of different operation strategies can be planned in the computer with respect to cost efficiency and to surgical safety, in particular for complex bone dislocations. The simulation of the associated soft tissue appearance permits an assessment of relocations of the upper and lower jaws in view of aesthetics. Basic for a reliable prognosis of facial appearance after the intended arrangements of bone structures is, on one hand, an adequate geometric model of the tissue volume with all embedded structures and neighboring bone boundaries, and, on the other hand, a physical deformation model that describes the mechanical properties of biological tissue in acceptable approximation.

Already with the geometric model alone important tasks in medicine can be performed, such as

- the localization of a tumor for the purpose of an exact planning of surgical openings or radiological measures,
- the selection of a patient's hip, knee or tooth implant and its precise implantation into the body,
- a better planning of the relocation of some bone to be performed by computer assistance and navigation techniques.

On the way from a geometrical to a *functional* model some more mathematical steps are necessary, which will be presented in the sequel.

Mathematical modelling and simulation. A functional patient model comprises, beyond the geometrical model, additionally a sufficiently accurate mathematical-physical description, mostly via partial differential equations. For illustration purposes, let us mention a few: the Lamé-Navier equations for linear elastomechanics and its nonlinear generalizations (geometry and material properties) in biomechanics, Maxwell's equations and the bio-heat-transfer equation in the cancer therapy hyperthermia, the Navier-Stokes equations for the analysis of fluid motion in the context of plaque building in blood vessels and in aneurysms. Whenever the required answers to the questions from medicine allow, then simpler, so-called reduced models will do. Generally speaking, mathematical models are only useful, if their input parameters have been analyzed with respect to their sensitivity.

A typical feature of medical models is their *multiscale structure*: The mathematical equations express relations between microscopic spatial dimensions and our everyday life dimensions. By intruding sufficiently deep into the mathematical description, we obtain a whole hierarchy of scales to be taken into account, depending on the problems in question. An illustrative example is given by the international project PHYSIOME [8], which spans scales from *nm* (molecules) via *mm* (tissue) up to *m* (organs).

Virtual labs. The partial differential equations arising in the model must be solved numerically fast and reliably and, in view of clinical application, embedded in a 3D visualization environment, a "virtual lab". As for the simulation of the mathematical models, the aims of mathematics and medicine are in accordance: Both disciplines

want the solution in 3D, within short computing times and with reliable accuracy. Only, if these requirements are met, a mathematical therapy or operation planning can hope to be accepted in the clinics and serve as a basis for responsible medical decisions. Among efficient *algorithms* available are: (a) *domain decomposition methods* for fixed meshes in connection with parallelization or (b) *multigrid methods* in combination with *adaptivity* in space and time.

Example: hyperthermia [2]. Upt to now, research in regional hyperthermia has been restricted for ethical reasons to the treatment of deeply seated, non-operable tumors, i.e. to hitherto hopeless cases. The aim of this treatment is to heat cancer cells locally thus sensitizing them to radio or chemotherapy without damaging healthy tissue by too high temperatures. In Figure 10, the setting of the method is shown. The patient is positioned in an applicator with (here) eight antennas that emit radio waves into the body. The heat inside the body is generated non-invasively. By separate control of the individual antennas, the interference field can be adjusted to each individual patient, to locally apply high thermal energy to the tumor region only. The scientific question is: How should the antennas be tuned (in terms of amplitudes and phases) such that the tumor is heated within a temperature window between $42,5^{\circ}$ and 45° C, but no healthy tissue. The impact of the different tuning parameters on the therapeutically effective temperature distribution is so complex that optimal therapy plans can be determined only via numerical simulation. The associated functional patient model here comprises Maxwell's equations for the description of the electric fields and the bio-heat-transfer equation which governs the heat distribution inside the body.

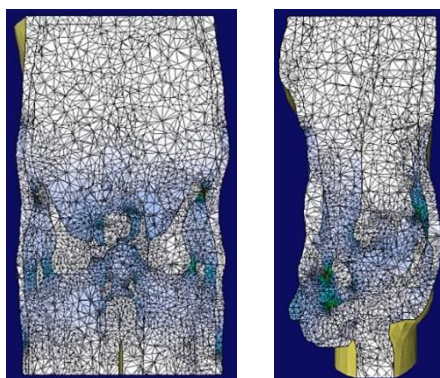
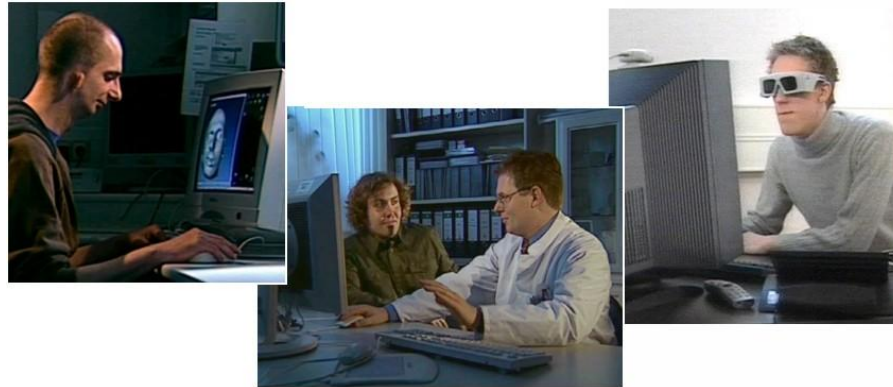


Figure 12: Hyperthermia: adaptive hierarchical spatial meshes (ZIB).

In order to illustrate the importance of spatial adaptivity, we show, in Figure 12, an actually generated mesh for the solution of Maxwell's equations: With space adaptivity we obtain about 120.000 nodes, whereas uniform meshes would have required an estimated number of 16.000.000 nodes. The applied multigrid methods require computing times proportional to the number of nodes, which implies that adaptive methods are about a factor of 130 faster – in this medically relevant example and at a comparable accuracy!

Example: soft tissue simulation [4]. In cranio-maxillo-facial surgery the mathematical model consists of the biomechanical differential equations. They are to be solved numerically (by efficient multigrid methods) to permit a reliable prediction



of the postoperative facial appearance – assuming the operation went well as planned. The present standard of prediction is represented in Figure 9 at two examples [21]; the presently achievable prediction quality is already excellent. Apart from the improved operation preparation, this kind of computer assisted operation planning including the soft tissue prognosis leads to an improved patient information and thus eventually to a higher patient motivation, see Figure 13.

Figure 13: Patient preparation by the virtual lab [22].

Perspective: the virtual patient

Beyond the described medical applications, mathematics (including computer science) already today provides extensive methods to accompany therapy and operation planning. On an intermediate time scale, it would be reasonable to open more space in public health to mathematics. The following lines of development can be foreseen:

Radiology will more and more move on from mere 2D image interpretation to 3D model reconstruction. This requires substantial “screening” of individual image data by means of automated segmentation techniques. The corresponding increase of patient specific data will lead to a twofold development: (a) the build-up of centralized medical data bases in large hospitals, and (b) a population-wide introduction of (only personally disposable) individual data carriers (the “electronic patient”). Google-med may be a possible format of storing such data; it will, however, need to be modified due to national differences in health organisations and mentality as well as with respect to its non-guaranteed security of individual data.

Central archives (such as PACS, S-PACS) will, apart from individual data, store general *geometrical anatomy models* on the basis of statistical shape models, i.e. via mean anatomical shapes (averaged over local populations) including essential coordinates that describe the variability of the underlying patient sets. In addition, *mathematical functional models* will be stored, i.e. mathematical descriptions of functions of organs or of moving parts of the skeleton via multi-scale models to be differentiated further. Provokingly, the function of an organ will not be fully understood, before it has been expressed by a realistic mathematical model covering both the healthy and the unhealthy case.

Both the legal and the order political frames will have to be clarified. Radiologists will certainly continue to bear the legal responsibility for the correctness of

the interpretation of medical image data and the therefrom derived anatomical models. However, in countries like Germany, insurance companies will need to include model assisted planning on the basis of geometrical 3D models and mathematical functional models into their catalogue of financially supported services. Apart from medical indication, the new kind of planning tools is useful in view of an improved patient information as well as of education, documentation, and quality assurance.

3 Vision and options

This article has shown, at selected examples, how the coaction of mathematics and medicine has pushed a dynamic development towards patient specific models (“virtual heart” in Section 2, “virtual patient” in Section 3) on the basis of modern medical imaging techniques (Section 1). This development will certainly expand in the near future. However, there is still a long way to go, until anatomically correct and medically useful functional models will be available even for the most essential body parts and the most frequent diseases. Within the German funding system, the corresponding research will, on a quite long run, remain dependent on public funding. In any case, political frames in health and research will need to be adjusted in close cooperation with selected medical doctors, engineers, and – mathematicians!

References

- [1] P. Colli Franzone, P. Deuffhard, B. Erdmann, J. Lang, L. F. Pavarino: *Adaptivity in Space and Time for Reaction-Diffusion Systems in Electrophysiology*. SIAM J. SISC., Vol. 28, No. 3, pp. 942-962, 2006.
- [2] P. Deuffhard: *Differential Equations in Technology and Medicine: Computational Concepts, Adaptive Algorithms, and Virtual Labs*. In: R. Burkhard, P. Deuffhard, A. Jameson, J.-L. Lions, G. Strang (eds.): *Computational Mathematics Driven by Industrial Problems*. Springer Lecture Notes in Mathematics, vol. 1739, pp. 70-125, 2000.
- [3] P. Deuffhard, R. Hochmuth: *Multiscale analysis of thermoregulation in the human microvascular system*. Math. Meth. Appl. Sci., vol. 27, pp. 971-989, 2004.
- [4] P. Deuffhard, M. Weiser, S. Zachow: *Mathematics in Facial Surgery*. Notices of the AMS, vol. 53, no. 9, pp. 1012-1016, 2006.
- [5] O. Dössel: *Kausalität bei der Entstehung, der Diagnose und der Therapie von Krankheiten – aus dem Blickwinkel des Ingenieurs*. Kausalität in der Technik, Berlin-Brandenburg. Akad. Wiss., pp. 69-80, 2006.
- [6] O. Dössel, D. Farina, M. Mohr, M. Reumann, G. Seemann: *Modelling and imaging electrophysiology and contraction of the heart*. In: T. M. Buzug, D. Holz, S. Weber, J. Bongartz, M. Kohl-Bareis and U. Hartmann (eds). *Advances in Medical Engineering*, Springer, pp. 3-16, 2007.
- [7] C. S. Henriquez, A. L. Muzikant, C. K. Smoak: *Anisotropy, Fiber curvature, and bath loading effects on activation in thin and thick cardiac tissue preparations: simulations in a three-dimensional bidomain model*. J. Cardiovascular Electrophysiology, pp. 424-444, 1996.
- [8] P. J. Hunter, T. K. Borg: *Integration from proteins to organs: the Physiome project*. Nature Rev., Mol. Cell Biology, vol. 4. pp. 237-243, 2003.
- [9] P. Jonas, A. K. Louis: *Phase contrast tomography using holographic measurements*. Inverse Problems, vol. 20, pp. 75-102, 2004.

- [10] D. Kainmüller, Th. Lange, H. Lamecker: *Shape constrained automatic segmentation of the liver based on a heuristic intensity model*. In: T. Heimann, M. Styner, B. van Ginneken (eds.). Proc. MICCAI Workshop 3D Segmentation in the Clinic: A Grand Challenge, pp. 109-116, 2007.
- [11] A. Khawaja, O. Dössel: *Predicting the QRS complex and detecting small changes using principal component analysis*. Biomed. Technik, pp. 11-17, 2007.
- [12] A. K. Louis: *Medical Imaging: State of the Art and Future Development*. Inverse Problems, vol. 8, pp. 709-738, 1992.
- [13] A. K. Louis: *Combining Image Reconstruction and Image Analysis with an Application to Two-dimensional Tomography*. SIAM J. Imaging Sciences, Vol. 1, No. 2. pp. 188-208, 2008.
- [14] R. B. Marr, C. Chen, P. C. Lauterbur: *On two approaches to 3D reconstruction in NMR zeugmatography*. In: G.T. Herman, F. Natterer (eds.): Mathematical aspects of computerized tomography, Springer LNMI pp. 225-240, 1981.
- [15] F. Natterer, F. Wübbeling: *Mathematical methods in image reconstruction*. SIAM, 2001.
- [16] M. Reumann, J. Bohnert, B. Osswald, S. Hagl, O. Dössel: *Multiple wavelets, rotors, and snakes in atrial fibrillation – a computer simulation study*. J. Electrocardiology, pp. 328-334, 2007.
- [17] L. A. Shepp, B. F. Logan: *The Fourier reconstruction of a head section*. IEEE Trans. Nucl. Sci. NS-21. pp. 21-43, 1974.
- [18] L. Sörnmo, P. Laguna: *Bioelectrical signal processing in cardiac and neurological applications*. Elsevier Inc., 2005.
- [19] D. Stalling, M. Westerhoff, H.-C. Hege et al.: *Amira: A Highly Interactive System for Visual Data Analysis*. In: C. D. Hansen, C. R. Johnson (eds.): The Visualization Handbook. Chapter 38, pp. 749 - 767, 2005. URL: amira.zib.de
- [20] K. H. ten Tusscher, A. V. Panfilov: *Alternans and spiral breakup in a human ventricular tissue model*. Am. J. Heart Circulation Physiology, pp. 1088-1100, 2006.
- [21] S. Zachow: *Computergestützte 3D-Osteotomieplanung in der Mund-Kiefer-Gesichtschirurgie unter Berücksichtigung der räumlichen Weichgewebeanordnung*. Medizininformatik, Verlag Dr. Hut, 2005.
- [22] S. Zachow, H.-C. Hege, P. Deußhard: *Computer Assisted Planning in Cranio-Maxillofacial Surgery*. J. Comput. Inform. Technology – Special Issue on Computer-Based Craniofacial Modelling and Reconstruction, pp. 53-64, 2006.
- [23] S. Zachow, M. Zilske, H.-C. Hege: *3D Reconstruction of Individual Anatomy from Medical Image Data*. In: Proc. ANSYS Conference & CAD-FEM Users' Meeting, Dresden. Siehe auch: Report 07-41, ZIB, 2007.