The IST Programme
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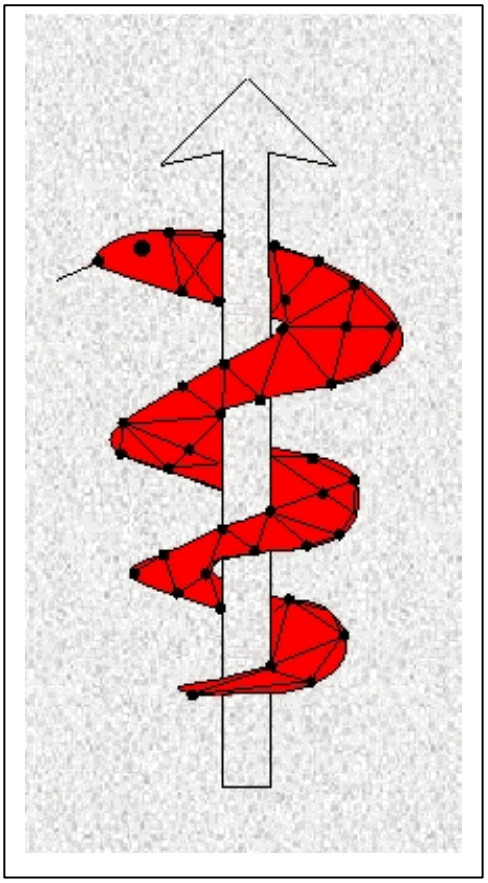
SimBio

SimBio - A Generic Environment for Bio-numerical Simulation

http://www.simbio.de



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Project Progress Report for Project Months 19-30

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1 Foreword

This report covers project months 19-30 (October 1st,2001 - September 30th, 2002) of the SimBio project and provides a summary of technical progress made. The report forms an update to the previous public progress report (Deliverable PP1 – available on the project web-page: http://www.simbio.de). Activities reported are in line with the project workplan as covered by Contract Amendment **No. 2,** following the successful SimBio-NAS proposal to provide an extended evaluation and validation subtask, Subtask 7.4 (c.f. Section 2.9). It should be noted that the two additional partners from Maribor, Slovenia (the University of Maribor and the Teaching Hospital of Maribor, referred to by acronyms UNI-MB and SBM, respectively) commenced activities in the project at the end of Project Month 27.

2 Progress Report

2.1 Workpackage 1: Geometric Model Generation

2.1.1 Subtask 1.1: Image Processing

Subtask 1.1 started late because of the withdrawal of one partner from SimBio and hence the first preliminary IP-Tool release was allowed to be delayed until 18 months from the start of the project, a delay of 6 months, although some components of the toolbox were available before then. The 18-month preliminary release date was achieved. The components of the toolbox from MPI have been well-tested during their development and should prove robust. The registration based segmentation tools have been developed for SimBio and enhanced progressively over the lifetime of the subtask, with both practical and theoretical developments.

It was hoped that extensive testing of the new components of the preliminary toolbox would come from use by other members of the consortium but in practice this has not happened to any great extent. The new components of the IP tool-box have been tested locally within the context of ST 1.2 and it has been shown, by using several data sets, that registration based segmentation is a reliable method of segmenting knee images and for mapping reference meshes onto patient images. The inclusion of Maribor (ST7.4) in the consortium from July 2002 will prove a useful additional external approach to validation of registration based segmentation. However, the delayed start of this subtask means that it has not been possible to validate the new components of the IP toolbox before the end of ST 1.1.

The final deliverable for ST1.1 has been delivered on time (at the end of PM30) and development work has finished officially. However, we will continue to support any changes required arising from work undertaken in ST 7.4 until SimBio is completed.

MPI has completed image processing tools for head segmentation of CT and MRI datasets. In order to setup biomechanical and electromagnetical forward models, a finite element mesh must be provided that describes the individual object under study precisely and covers all material compartments as relevant for the given problem. In addition to the intracranial compartments white matter, grey matter and cerebrospinal fluid (CSF), the meninges have to be taken into account for biomechanical simulations. The meninges consist of a thin layer of tough skin which encapsulates the brain and separates it into mechanically partially decoupled compartments, the hemispheres and the cerebellum. This sheath is at most 1 mm thick, but relevant for a precise modelling of mass shifts in the intracranial compartment. The skull has a rather low electric conductivity and a rather high stiffness in relation to other tissues of the head. The thickness of the skull varies between 2 and 8 mm depending on the region, which is expected to influence simulation results strongly. The skull is imaged best by cranial computer tomography (CCT). However, the relatively high radiation dose is prohibitive for research purposes, but may be acceptable for clinical questions. Thus for EM simulations in SimBio, we segment the skull from PD-weighted MR images. As we are primarily interested in intracranial processes, the extracranial tissues (e.g., skin, muscles, facial bones, fat, connective tissue, nerves) are collectively given a single label. The complete segmentation procedure as encapsulated in *vcompseg* needs approximately 3 minutes computation time on a typical Linux workstation.
CCT datasets of the head are much easier to segment, as we are interested in discriminating soft tissue from bone only for biomechanical simulations as specified in ST7.2, group A. However, the gantry and head holders should be removed for modelling, so some pre-processing is required. The module *vctseg* implements this functionality.

2.1.2 Subtask 1.2: Mesh Generation

Within the SimBio project two novel approaches for mesh generation based on medical scan data have been realised and one tool has been evaluated:

- the VGrid Approach and
- the Mesh Template Approach.
- the ZMD tool has been evaluated

The VGrid Mesher
VGrid offers the options to generate
- uniform hexahedral meshes (taking care of fine structures like e.g. the skull)
- non-uniform tetrahedral meshes (taking care of fine structures as above)
- smooth tetrahedral meshes (using a novel algorithm described below)

The originally pursued strategy of applying a delaunay tessalation to the boundary nodes of an octree cell (to arrive at a tetrahedral mesh) was skipped because of various reasons:

- It is difficult to assure that tesselations match across octree cells, at least f cells are to be processed in sequence, independently of each other
- Due to the highly regular nature of the input, and an inherent weakness of the delaunay triangulation in 3D, some kind of degenerate tetrahedra (so-called slivers) cannot easily be avoided.

Therefore, a different algorithm has been designed. It has the following useful properties:
- It runs completely local, that is, considers only the nodes of the current octree cell
- It guarantees consistency across octree boundaries
- It guarantees a minimum quality of the resulting tetrahedra
- It is insensitive to vertex coordinates, and therefore very stable
- It is very efficient (linear in the number of nodes)
- It provides meshes of high surface smoothness.

The main idea of the tesselation algorithm is recursive: If we have a (simplicial) subdivision of the boundary facets of an octree cell, we get a subdivision of the octree cell itself by connecting its midpoint with the boundary simplices.
For the boundary facets themselves, we can apply the same idea recursively. This tesselation is evidently consistent across facets, because the subdivision of a facet depends only on the data of the facet, namely, its boundary nodes.

Quality of the resulting meshes
The algorithm described before does guarantee a minimum quality of the resulting tetrahedra. This is evident from the following observation: First, the non-uniform meshing algorithm does generate only a finite number of different tetrahedra, the worst-case quality depending essentially on the balancing level of the octree. Second the marching tetrahedra algorithm does generate only a finite number of configurations. While an analytical investigation of the occuring case has not been performed, numerical studies show that the quality of resulting element is acceptable (using the mesh quality tool described in D12c).

The Mesh Template Tool
To ensure a successful project outcome (with respect to the smoothness of mesh surfaces), the mesh template mesh generation method was developed in parallel. The approach relies on utilising the registration tools developed under Subtask 1.1 and described in D1.1c to morph a pre-existing mesh. Although considerable effort is expended in creating the template mesh initially, much of the effort in ensuring smooth surfaces and good element quality is rewarded by the subsequent automatic generation of patient-specific meshes that have inherently smooth surfaces.

In addition to the mesh template approach for the generation of patient specific finite element meshes, several tools have been developed to aid in the generation of the template mesh. The tools centre on producing smooth surfaces that do not contain 'terracing artefacts', which result from pixelation of the data in the medical images.

The ZMD Tool
The ZMD tool is an intensity based image processing software. Its main application is the automatic segmentation of arteries. For the knee, though the whole process is not automatic, it was possible to extract in a few steps the outer surface of the main structures such as bone, ligament and cartilage (T1 sequence) with a good quality. Regarding other structures such as cruciate ligaments, separation between cartilages or menisci, the images provided do not contain enough information to allow as accurate a segmentation.

In the future, more precise scans of the knee will be performed. These scans may enable an easier segmentation of these small structures. The extension of the application of SIMBIO tools to other structures than the knee could also be performed by that tool.

Second, an automatic sequence of operations was designed for meshing segmented images of the knee into 3D tetrahedral elements. This sequence was used to generate meshes of 3 structures, while proved inefficient for 7 others. The level of manual work and try-fail attempts necessary with these remaining structures will decrease interest in this software, as the goal is an automatic generation. The few generated meshes anyway can in no way be used in the domain of explicite finite element calculations. This is due to the fact that the mesh generator tool being designed for flow applications doesn't strive on reducing the number of elements but on following the surface geometry. Making these surfaces smoother requires a lot of manual work.

2.2 Workpackage 2: Compilation of Material Database

Soft tissue investigation
In the beginning of the project we have developed a conventional experimental environment including set up and protocol procedures, which allow performing reliable experiments comparable to the approach developed and applied by other groups. Therefore a traction machine had been set up, which allows carrying out experiments on small samples of soft tissue in compression mode. Numerous inventions and modifications had to be realized to meet our goal to be able to perform experiments on the small fragile samples of brain tissue. Therefore we had e.g. to integrate in the traction machine a temperature and humidity controlled chamber. This enabled us to deal with the extremely sensitive brain tissue under reproducible conditions and increase the precision of measurements.
We had further to extend our experimental equipment recently since we are now on our way to complete the types of investigated brain tissues. Until now we took into account the brain matter only. Now we extend our investigations to membrane structures also. This means that we had to extend our experimental environment for traction experiments. In the recent project phase we performed experiments on Bovine cranial *pia mater* tested quasistatically in traction. The curves obtained could be divided into 1) an initial physiological part, 2) an elastic part, and 3) rupture, which was defined by the maximum force that could attain a sample. The important stiffness determined for the pia mater in these preliminary experiments shows that it is very important to include membranous structures into a realistic model as well. Therefore we are continuing this work.

One of the most intriguing problem one faces in small sample biomechanical experimentations is the reliable and reproducible sample harvesting and cutting. So this rests a permanent problem and we continue in ameliorating the already realized setup and in developing new approaches.

Our work concerning the MRSI-technique turned out to be extremely difficult since we faced enormous problems in detection and evaluation of force induced geometry changes in a reliable manner and with a sufficient resolution. The work on these problems continues. Actually we work on an amelioration of the MRI-sequences and the possibility to get higher effective contrast by fusing images of different protocols.

For the other soft tissue directly of interest for the consortium, the meniscus of the knee, we extended the so far performed compression experiments in applying increasing deformation rates in the three different directions. We found evidence for a complex strain depending but in any case thyxotropic like behaviour. This means that for the simulation of knee movements by the so far developed complex models the material properties which enter the simulation have to be controlled and adapted dynamically. Further experiments have to be carried out to determine reliable quantitative data.

Electrical Conductivity Measurements (DT-MRI)
In EEG/MEG source localization the human head is modeled as a volume conductor. The skull and the white matter are known to have anisotropic conductivity with a ratio of up to 1:10. Recently, formalisms have been described for relating the effective electrical conductivity tensor of white matter tissue to the effective water diffusion tensor as measured by diffusion tensor magnetic resonance imaging (DT-MRI). First studies show that skull and white matter conductivity anisotropy have an influence on the forward solutions for EEG and MEG.
The diffusion tenors of the hole head of a subject was measured in 8 DT-MRI sessions. Each session produced 4 axially oriented, 5 mm thick slices with in-plane resolution of 2×2 mm^2. Co-registered T1-MRimages allowed the registration of the DT-MR data on the 3D T1-MR data set. The highest fractional anisotropy value was found in the splenium of the corpus callosum (0.74)
The measured conductivity tensors were used to set up an anisotropic finite element model. The eigenvectors of the water diffusion tensors were used to compute the conductivity tensors for each white matter finite element of the brain with an anisotropy ratio of 1:10 (transversal : longitudinal to the white matter fibre direction).
Finite element simulations of the potential distribution in the brain showed the influence of the conductivity anisotropy on source localization.

Material-Database
We continued in collecting of data of living tissues mechanical and electrical properties. The database delivered as D2a is permanently extended based on periodically evaluations of literature. Thus a broad collection of most actual and interesting data of living tissues properties is now available in standard literal form.
Even so this will already meet the interest of a big number of users there rests the problem that most material properties depend highly on numerous parameters, which might change during a real world experiment as well as during a simulation. Here one value given in a table is not sufficient to perform a realistic simulation. This parameter dependency of material properties is investigated by numerous authors, which publish their results in form of graphs. These cannot be entered directly in tables and are there for not usable for the purpose of modelling and simulation.
To overcome these problems we extend our database in digitizing these graphs and creating tables, which provides the parameter depending numbers, and which can be entered directly in simulations. For to present this information together with the complete bibliography in an easy accessible manner, we developed and installed an according database structure using the standard database 'MS-ACCESS'. This database will be accessible via WWW also.

2.3 Workpackage 3: Numerical Solution System

The final version of the numerical solution system (NSS) comprises the following components:

I. Linear Solver Libraries and Partitioning Tool
- **DRAMAtool**, a software component for partitioning finite element meshes for efficient parallel execution.
- **An interface for PEBBLES**, a public domain library for parallel equation solving (AMG-preconditioned CG).
- **PILUTS**, a highly efficient NEC linear equations solver library (**P**arallel **I**ncomplete **LU** with **T**hreshold preconditioned **S**olvers).

II. Full Problem Solvers
- **NeuroFEM**, a full Finite Element (FE) code for parallel execution with coupling for parallel solvers (SimBio: static electromagnetics in the brain).
- An interface for **PAM-SAFE**, a fully non-linear explicit FE code for biomechanical applications (SimBio: knee-mechanics).
- **HeadFEM**, a non-linear fully parallel FE code for special biomechanical applications (SimBio: head-mechanics).

The following sections summarise the status of the final implementation per software package:

DRAMAtool: The DRAMAtool caculates suitable domain decompositions for improved parallel efficiency. It exploits the features of the DRAMA library, which give special support to the SimBio applications for the partitioning of sparse symmetric matrices. The repartitioner tool uses file interfaces based on the latest common VISTA format definition. It can be linked with VGrid, NeuroFEM, HeadFEM and the PILUTS solver (standalone) tool in a linear chain. The software is fully functional including a test-suite for verification. It has been released via the SimBio web page on time at the end of March 2002. The installation and its use are documented in the deliverable D3c.

NEC Solver Library PILUTS: Integration has been concluded**.** All PILUTS methods, CG, symQMR, and BiCGstab can be called with a common interface now. The specific iterative solver is selected by a parameter. For advanced preconditioning BiCGstab, simple diagonal scaling, simple row and column scaling, block **I**ncomplete ***LU*** factorisation with **T**hreshold (ILUT), block ILUT with preceding diagonal scaling, block ILUT with preceding row and column scaling, distributed Schur complement (DSC) preconditioning using ILUT for local diagonal matrix blocks, DSC preconditioning with preceding row and column scaling using ILUT for local diagonal matrix blocks,

and DSC using complete *LU* decompositions of the local diagonal matrix blocks are available. The PILUTS library was successfully integrated and tested in the simulation codes HeadFEM and NeuroFEM. The PILUTS software was released on time.

NeuroFEM: Realistic solution times for inverse source reconstructions in isotropic high resolution tetrahedra and cube head models were achieved by using parallel computers with a moderate number of processors. The Algebraic MultiGrid (AMG) methods are used as efficient preconditioner for the CG algorithm in the finite elment solution software NeuroFEM. On an SGI ORIGIN computer the speedup was 75 on 12 processors for the parAMG solver compared to the Jacobi-CG method (7.5 through AMG-CG compared to the Jacobi-CG and 10 through parallelisation). The computation time for one forward simulation was reduced to 1.5 sec using 12 processors of a PC-Cluster and the parallel algebraic multigrid preconditioned CG solver. We further showed that the AMG approach is stable towards realistic head tissue anisotropy in the brain. The NeuroFEM software was tested and released together with the inverse toolbox of St 4.1. It is available to the project partners for evaluation via the SimBio web pages.

PAM-SAFE: The PAM-SAFE code is a commercial product marketed by ESI. The PAM-SAFE™ package, the solver and its pre-processor, GENERIS™, have been enhanced to facilitate the modelling of biological materials, especially the menisci. Two types of tetrahedral elements have been developed for the project: 4-nodes and 10-nodes tetrahedral elements. It is important to take into account the microstructure of the biological material, in particular for the knee model, the microstructure of the menisci and of the ligaments. Recently the definition of the orientation of fibres has been largely improved.
In order to enable the remote computing evaluation within Subtask 7.4 (in the final project period), work has been invested into a port to the Linux-SCore environment of the recently installed NEC PC-cluster. This included adaptations for the Intel compiler and the SCore system in addition to incorporation of the FLEXLM licence system for Linux.

HeadFEM: HeadFEM is designed for the pre-operative planning of maxillo-facial surgery. It is a fully parallel code for the solution of non-linear, finite deformation, large strain finite element problems employing neo-Hookean hyperelastic compressible and incompressible (for soft tissue modelling) constitutive equations. The solution to the non-linear equations is achieved using the non-linear Newton-Raphson iterative method. The HeadFEM implementation uses the Finite Element Interface (FEI) definition from Sandia National Laboratories, which serves as an abstraction layer between finite element routines managing matrix-assembly and linear-solver modules. Via FEI, HeadFEM is linked to the NEC PILUTS linear solver library, which comprises a variety of state of the art parallel iterative solution (CG, BiCGstab, symQMR) and preconditioning procedures ranging from simple diagonal scaling to incomplete Cholesky, threshold and DSC methods. For improved parallel efficiency, the partitioning tool based on the DRAMA load-balancing library is used. The HeadFEM solutions have been verified against reference results obtained with the commercial FE code ADINA™ for several engineering problems with simple CAD geometry. In the present release a test-suite is provided for verification purposes. The tests are based on a comparison of reference output with output from a current run. The software has been released to the project via the SimBio web page on time at the end of March 2002.

2.4 Workpackage 4: Inverse Problem Component

2.4.1 Subtask 4.1: Inverse methodology

The release notes of the final release of the generic inverse toolbox are completed. The final release contains a class library with a collection of algorithms and a three shell user interface, which gives access to a huge variety of inverse procedures. The class library consists of two major parts: 1. A flexible and modular framework, which provides in the final release an almost complete set of state of the art inverse methods. Inverse procedures can be coupled to forward solvers for spherical, BEM (both EEG, MEG) and FEM head models. 2. A software framework to assess the sensitivity of inverse

results to inaccuracies, errors and simplifications of the forward model. First applications of the sensitivity analysis framework were presented at the BioMag conference in Jena.
A new version of the ASA source localization software of A.N.T. Software is close to being finished. First test versions are distributed to selected customers and collaboration partners. This software uses the generic inverse toolbox as the mathematical core for inverse and signal processing algorithms. The MEG group of the MPI of Cognitive Neuroscience in Leipzig integrated the inverse toolbox in their signal analysis environment and uses the toolbox for the analysis of experiments using MEG registrations.
The coupling of the inverse procedures with the time consuming FEM forward computations on a parallel computer system could be achieved on two levels. The first level uses a file coupling of results computed on a parallel system. The second level combines both the serial algorithms of the inverse toolbox, which have to be called recursively for a selection of the inverse methods, with the parallel forward computations using a close coupling between inverse procedure and forward computation. High speed-ups were achieved on parallel computers and on LINUX Clusters.
The sensitivity of the inverse source localization towards conductivity anisotropy in high resolution FEM head models was shown with the inverse dipole fit algorithm on a parallel computer. Our results demonstrate that skull and white matter anisotropy has a big influence on moving single dipole source localization results. The forward calculation and inverse localization errors indicate the necessity of the chosen complex realistic head model.

2.4.2 Subtask 4.2: Inverse field reconstruction

Two approaches to bio-mechanical inverse field reconstruction have been pursued within ST4.2, *consistent linear-elastic* and *fluid dynamic* image registration. Both approaches differ with respect to their applicability. The consistent linear elastic scheme (implemented as modules *vlet*) allows for smooth, diffeomorphic transformation fields, but is restricted to small deformations. The fluid dynamic approach (implemented as modules *vfluid*) explicitly considers large deformations. To derive realistic models, both elasticity operators are driven by realistic material parameters, as provided in database WP2.
Both registration approaches are computational expensive. Therefore, additional effort was spent on performance optimization (in terms of HPC and amendment of cost functions, as proposed by D4.2a and b). The gradient decent minimization used for optimisation in the linear-elastic approach is enhanced by a multi-resolution decomposition (Fourier series parameterisation) of the displacement fields. In case of the fluid dynamic approach, the intrinsic minimization routine is provided by a multi-resolution version of a Gauss-Southwell optimisation. Both registration schemes support multi-threading. Additionally, the current ST4.2 release comprises tools to postprocess the registration output. A program is provided to analyse vector fields for its critical points (*vcpdetect*). Another modules (*vdcdefo*) decomposes the registration results in order to achieve advanced visualization with the vm tool. The program *vassignshift* allows the application of deformation fields to images.

2.5 Workpackage 5: Visualisation

This final release of the visualisation module (VM) of the SimBio project was provided on the SimBio website on-time. The purpose of this module is, as its name suggests, to visualise the results from other SimBio modules, e.g. stress fields from bio-mechanical simulations or source localisation and influence from bio-electrical simulations. In comparison with the first release, it introduces additional and modified visualisation modes of different kinds of data (scalar, complex, vector and tensor valued data) defined on different topologies (images and geometrical objects), includes means for interacting with geometrical data, allows overlaying of geometrical objects on geometrical objects and image data on image data and offers the use of clip planes for geometrical objects. An accompanying document specifies the functionality implemented in this final release, including any deviations from the functionality described in the requirement specification of the VM. Both, software and report, are considered as the final deliverable from SimBio WP5.

2.6 Workpackage 6: Component Interaction

The Workpackage 6 activities were carried out by ESI and NEC in collaboration with the other SimBio partners.

ESI will deliver the final prototype of the Scenario Editor to NEC for evaluation at Mid October. It will then be released through the WEB page for all partners. Based upon the feedback, improvements and additional features may be added.

The following SimBio application are now completely integrated (or in the process of being integrated) in this editor:

- From ANT: Inverse Toolbox
- From ESI: PamGeneris, PamSafe and PamView.
- From NEC and ESI: Remote PamSafe.
- From MPI: NeuroFEM.
- From NEC and MPI: Remote NeuroFEM and Remote HeadFEM.
- From Sheffield: Vgrid and Vsegment3D.
- Simple way to add new applications without programming.

Intially, only the binary files for the Editor will be available to the partners via the Web page, however, source code will be provided to any partner upon request. Also, ESI agrees to add new applications during the rest of the project if necessary or to help partners to do so themselves.

The SimBio pilot and the CORBA compute server were repeatedly tested and debugged. The CORBA clients and servers were ported from ORBacus to MICO. Furthermore, the clients were restructured to be statically linked so that the users do not need to install a CORBA environment at their site. CORBA clients are now provided for the following applications: HeadFEM, NeuroFem, vlet3d and vfluid3d.

2.7 Workpackage 7: Validation & Evaluation

2.7.1 Subtask 7.1: Source Localisation

Diffusion Tensor Imaging (DTI) is a very promising technique to improve forward modeling in EEG and MEG by including information about spatial anisotropy. DTI is based on diffusion weighted imaging which utilizes the effect of signal loss due to strong so-called diffusion gradients. To validate the technique of DTI we performed several investigations using isotropic phantoms in a clinical scanner. One of the aims was to analyze the influence of the imaging gradients on the diffusion sensitivity factor b. The original equation for computation of the b-value was solved for a conventional spin-echo sequence. The results show that in some cases the influence of the imaging gradients on the b-value can not be neglected. By using a small FOV, high in-plane spatial resolution and/or a small slice thickness the strength of the imaging gradients can be comparable to the strength of the diffusion gradients. For example, using the typical PGSE (pulse gradient spin echo) sequence with a small FOV (70 mm) the contribution of the imaging gradients on the b-value may reach up to 10% in the readout direction. This non-negligible contribution leads to errors in the estimation of diffusion tensor elements and the calculated anisotropies.

2.7.2 Subtask 7.2: Bio-mechanical Head Model

The central objective of ST 7.2 is to evaluate and validate bio-mechanical head models using the SimBio environment. Two different simulation strategies were pursued:
Forward models: The real locations and strengths of forces (or corresponding hypotheses) are known a priorily. The consequences of these forces acting on the whole system are computed, visualised and

evaluated. Computed deformation fields may be compared with scan data in order to check the validity of simulation results.
Inverse models: No prior information about forces is available. In this case, time series examinations are employed and analysed by a non-linear transformation. The resulting deformation field is used to derive a force field, based on incorporated realistic material parameters. Force fields need to be analysed for their singularities ("force sources" and "sinks") in order to provide a comprehensible 3D visualisation. Since a validation based on physical models is not possible here, force fields will be compared in a group of similar clinical cases for their plausibility and checked against prior neuro-anatomical knowledge.
At PM 24, Deliverable 7.2b provided a status definition for the evaluation and validation study. The remaining 12 months of the subtask are devoted to refine the models and to provide further validation results using normal and patient data.
For simulations using forward models, a group of currently 22 patients with in-born deformations of the skull were selected. CT datasets before and after treatment were segmented, converted into volumetric meshes, direction and strength of known forces (halo screws, surgical wires) addressed, and simulations performed. Due to limited project runtime and personal resources, we cannot focus on the second modelling aspect (calculating wire forces) of the forward simulation. The problems associated with such task are diverse: a sound medico-physical model for the restoring forces is still outstanding; handling of contact faces, sliding elements, and adaptive re-meshing is currently not achievable with the HeadFEM tool. We intent to carry on with this task beyond SimBio.
For simulations using inverse models, patients with mild cognitive disturbances, and a control group of healthy volunteers were examined behaviourally, clinically and by MRI scanning (currently 126 subjects) at 3 time points. The study is planned to finish within the next 12 months. As a second group, patients with focal brain damage (after cerebral infarction, hemorrhage or severe head trauma) were scanned by MRI at the time of admission and discharge (approx. 3 resp. 12 months after onset). Examinations of TP1 and TP2 were evaluated by inverse bio-mechanical models in order to derive the deforming forces induced by restorative processes after focal brain damage. Currently, 70 suitable cases with well-defined lesions have been selected; in 30 cases the follow-up control examination (TP2) took already place. To monitor structural changes of the brain in MRI data, a six step approach is pursued in SimBio using two different approaches for non-linear registration. A careful cross-validation of both registration schemes is still under way.

2.7.3 Subtask 7.3: Knee Prosthesis

There are two aspects to the 7.3 evaluation and validation subtask. The first is generating patient-specific knee meshes from high-resolution MR scans and running knee simulations. The second is validating the behaviour of the resulting simulations by comparing with *in-vivo* acquired quasi-dynamic MR scans.

The template mesh generated from the 256 x 256 resolution MR images (with an in-plane resolution 0.7mm) suffered from problems with penetration (overlapping volumes) between meshed structures e.g. the cartilages and the menisci, resulting from inaccuracies in segmentation. Considerable effort has been expended to devise a new scanning protocol that has good in-plane image resolution (0.35mm) and tissue contrast, together with an acquisition time that is acceptable for patient use. The new protocol has been tested and has been used to acquire volume scans for a total of 11 patients. Each volume scan takes approximately 20 minutes to acquire. In addition, developmental work has been undertaken to improve the MR sequence used to acquire the quasi-dynamic slices. The registration algorithm developed under ST1.1 has been used to register the sparse slices to volume and the mapping function generated used to permit dynamic motion analysis of the femur with respect to the tibia. The clinician employed by USFD has been responsible for recruiting and organising the scanning of the patients, together with segmenting the patient MR images.

A new template mesh has been generated using the new protocol, which suffered reduced problems with initial mesh penetrations, although some further refinement to the meniscal meshes were necessary. Simulations for both simple rotation and a loaded knee flexion, constrained by the boundary conditions of the clutch pedal used to acquire the dynamic MR images) are being run. The

tools are in place to begin to generate patient-specific meshes, although some delay has occurred in exporting the template mesh from Pam Generis™ in vista format, which necessary for the mesh morphing tools to be used.

2.7.4 Subtask 7.4: Site-independent evaluation and validation

The objective of the subtask 7.4 is to perform site independent SimBio generic environment installation and evaluation/validation of results generated in order to solve the problem of Design of novel replacement parts for the menisci of the human knee joint and methods for their surgical implantation (prosthesis design). The evaluation and validation of the application related to the optimisation of prostheses design consists in comparison of the simulated performance of the operated knee with recommended target values and with the performance of a healthy knee (kinematics and mechanical results).

The central objective of this subtask is to thoroughly evaluate and validate SimBio environment from its overall applicability point of view and, especially, the results will be validated from possible end-users. The feedbacks from medical end-users will improve the SimBio correctness, applicability, and comprehensibility. All activities will also lead to a more user-friendly SimBio generic environment, e.g. improved graphical user interfaces.

Subtask 7.4.1: SimBio Environment Installation

The purchase and installation of all necessary hardware, and related software, has been completed and the installation of the SimBio environment in Maribor is ongoing – some software components have not been finalised (in line with the project workplan) until project month 30.

In the project months 28-30, partners UNI-MB and SBM made several tests with a MRI device. Many MRI knee sequences were recorded under different settings of the MRI device. These sequences were afterwards investigated and studied by the orthopaedic surgeons, finally, the potential settings of MRI device were chosen. The coordination and selection of the suitable MRI device settings were performed by collaboration with the partner USFD.

Partner UNI-MB also prepared interfaces from MRI device (Toshiba MRI device) to transform imaging material to the SimBio environment. The entire procedure for the imaging material acquisition was fixed. In framework of this activity, also a converter for image sequences stored in an internal Toshiba MRI format to DICOM format was developed.

By the construction of the wooden foot plate of rig, we tried to direct the pedal forces by loading the heel of the patient, because we believe, that with the activation of the gastrocnemius muscle- (dorsiflexion of the ankle) and the quadriceps-muscle-group (extension of the knee), we will get as similar soft-tissue deformations (cartilage, menisci …) within the knee-joint, as you get them by walking.

In order to improve the MR-image quality by reducing the MR-noise, we add an adjustable knee-support to the knee-platform, which minimise the knee movements during the dynamic tests, by fixing the different angle positions of the knee (8, 16, 24, 32, 40 deg.).

Partner UNI-MB is now developing an optical sensor for measuring the force value on the foot plate pedal and to determine the exact knee position angles during the dynamic tests.

To check the real position of the knee joint during testing, especially by obese patients, we will try to measure the knee-flexion-angles direct on the MR-image and so check the difference between the optical sensor measurements and the real angles on the MR-image.

Subtask 7.4.2: Validation of Image Segmentation

To validate segmentation results of the registration methods from the SimBio environment credible, an appropriate reference image must be selected and carefully segmented by hand. A set of patient images collected with the same MRI protocol would also be segmented by hand, although these need not be segmented in the same detail, for example only a sub-set of slices would be segmented. Manual annotation of the MRI knee image sequence is very tedious and, at the same time, very boring task for clinicians (orthopaedic surgeons). However, these annotations must be done very carefully and accurately. Therefore, an application IST (An Image Segmentation Tool) was developed by the partner UNI-MB. The IST tool is a part of the SimBio environment tools.

An Image Segmentation Tool (IST)

An IST application has been designed as a MRI image manipulation and analysis software. This tool is in the first place meant as a helping tool for manual segmentation/annotation of the MRI images (not necessarily knee images). It enables that clinicians manually annotate (segment) every 2D slice of the MRI sequence. Marked interesting regions for each 2D slice are afterwards stored as a XML document (output).

All features that are supported by the IST application are as follows:

easy reading and writing of MRI documents,
simple navigation through the MRI images,
tool for segmentation/annotation of the MRI images,
a conversion tool from internal Toshiba MRI image format into DICOM image format,
an advanced help.

A segmentation tool, a core of IST application, has been added as utility for a verification phase inside the SimBio project, but it can be used also for other intentions. It enables to create, manipulate, delete and save contours or regions. It has advanced GUI (e.g. popup menus). Each annotation (e.g. meniscus) is represented with own colour, some descriptive text etc. There are integrated some user friendly routines like copying annotations from previous slices, importing annotations, zoom, etc.

Partner SBM has tightly collaborated in a developing phase of the IST tool. Many bugs and awkwardness, especially logical, were thus suppressed. Partner SBM also performed two sample segmentations of the MRI knee image sequence with the IST tool.

An Image Processing Verification Tool (IPVT)

Because a final release of WP 1.1 tools, especially image processing tools, is dated for the end of project month 30, the partner UNI-MB could start verification of image segmentation results of the SimBio environment only with the working versions of registration routines. Partner USFD kindly provided current versions of his registration methods, all required template images, a sample patient image, and short guidelines for usage. Registration methods are currently written in the Matlab, however, partner UNI-MB has successfully installed and test them.

In the project month 30, partner UNI-MB started to write an auxiliary tool for validation of image segmentation results. The segmentation results of the registration methods from the SimBio environment will be compared according to two independent measures: 1) manual segmentation provided by Partner SBM, and 2) results of automated prediction-based segmentation algorithm provided by Partner UNI-MB. An Image Processing Verification Tool (IPVT), as this tool is named, is meant as tool for the statistical verification of the image processing results. Partner UNI-MB has already designed the IPVT tool for 2D verification, i.e. differences between image processing results of the SimBio environment and manual annotations of clinicians will be observed on every 2D slice. A GUI and some utility methods for the IPVT tool are already written.

Subtask 7.4.3: SimBio Evaluation and Validation

As discussed above (Subtask 7.4.1) the completion status of all SimBio components means that the evaluation of the environment as a whole will commence in the next project period. However, resaercheers at UNI-MB have been building knowledge & expertise (supported by ESI) in the performance of bio-numerical simulations on knee models with PAM-SAFE/BIO.

The first and very practical benefit of the SimBio project in SBM, is to improve the MR-image quality by testing and modifying the different MR-parameters on our Toshiba 1.5T MR device. Our tests determine the optimal imaging parameters for this specific Toshiba MR device.

As described in the activities for Subtask 7.4.1, UNI-MB developed a converter for image sequences stored in an internal Toshiba MRI format to DICOM format and so transform imaging material to the SimBio environment. DICOM format permit also the direct imaging transfer form Toshiba MR device to the PC workstation at SBM, with the possibility of the on-line control of the imaging procedure.

2.8 Workpackage 8: Assessment, Exploitation, Info Dissemination

Collaboration with caesar:

The software framework *Julius* was developed as a general platform for a complete medical pipeline, including data import, image processing, visualization and navigation. Owing to its platform independence, ease of extensibility and scalability it can also be used for rapid tool development by third party researchers. Within the collaboration with the SimBio project, specific plug-ins have been developed. The first plug-in implemented was the import of the Vista file format into Julius. The types of Vista datasets which are supported are volumes, surfaces, meshes and vector data. A plug-in for stereo-rendering provides a 3D mode using stereo glasses. This is a useful plug-in for getting a sense of location on disconnected structures in 3D datasets. It can also be used for manual inspection of mesh quality during pre-processing for finite element analysis. The flythrough plug-in is capable of generating animations from a scripted sequence of camera waypoints. The animation can be calculated and visualized on the fly. Overlays can be used to visualize two or more datasets at the same time in the slice view diagram. Currently several polymesh datasets can be shown simultaneously in the 3D view and combinations of any types in the slice view. Cut planes allow for the superposition of volume and slice view information. Further information is included in the (additional) deliverable D8Xb and these features will be demonstrated to the project review team and included in multi-media material.

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Presentations at International Conferences and Workshops:

P. Aimedieu, "Comparative study of the influence of the sacrificing procedure on the mechanical properties of the white matter of cow brains", 27th Annual Congress of the French Biomechanics Society, Valenciennes, 12-13 September, 2002

D. Barber, "A novel image registration application for the in-vivo quantification of joint kinematics", MIUA 2002, 22-23 July 2002,Portsmouth, UK

D. Barber, "Automatic ROI generation using image registration: application to MUGA scans", BNMS Autumn meeting, 12-13 September 2002, Durham UK:

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2.9 Workpackage 9: Management

A project meeting was held in Brussels on Oct. 4th, following the IST Simulation Concertation meeting, at which the status of all developments was reviewed. The 3rd external review meeting was held in Sheffield at the end of January, 2002. The review was most positive: the reviewers were satisfied by project status and developments and with the project management. A further project meeting was held in Jena (May 23rd-24th), where exploitation planning was a major focus, in addition to a review of project status.

NAS Extension
In October, 2001, the Project Management Board came to a decision on the proposed extension by 2 partners from Maribor, Slovenia (University & Hospital clinic) – a proposal for activities was sent & the proposal construction assigned to the University of Maribor. The SimBio-NAS extension proposal was completed, submitted and approval to negotiate a contract received in April, 2002. The contract amendment was received and signed in June, allowing the modified project workplan to come into force in July. The project period was extended by 3 months (to the end of June, 2003) to allow the new partners from Maribor to complete a full, 12-month evaluation task.