Publishable summary

This report covers the developmental work on the project IMPPACT during the first project year.

1.1. Project concept and objectives

The project's major objective is the creation of the Intervention Planning System (IPS) for RFA-treatment of malignant cancer in the liver. The IPS shall be based on a patient specific physiological model of the liver under local hyperthermia intervention. Further objectives comprise:

- The development of a **new bio-heat equation** modelling cell heating and cell death that fits a validated model.
- Application of the multi-scale approach when modelling **microscopic treatment** effects for **macroscopic prediction.**
- The use of **interactive simulation** for fast computation, **real-time visualization** and interactive manipulation of IPS.
- The development of **image processing tools** for 1) fast and accurate reconstruction of identifiable anatomical and pathological structures; and 2) for analysis of histological samples and fusion of results with the reconstructed structures in 3D.
- Model validation bridging the gap between theoretical modelling and clinical practice

By integrating modelling, imaging and visualization in a full simulator, IMPPACT will create the IPS as a clinically relevant application. Creating a tool for validation on the highest level by visualizing treatment results together with simulation results, the models will provide input to the clinical practice whereas feedback from the clinical practice will in turn support the modelling. This way **confidence in the model predictions will be established**.

1.2. Work performed since the project's start

During the period M1-M12 of the project, the consortium has set up a common framework for an experimental cycle to be conducted on pigs. The framework structure defines a closed-loop experiment with several complementary components. Each component generates a set of data in a compatible format to be consumed by one or several other components. Overview of the structure and dataflow between the components in one experimental cycle is illustrated in Fig. 1.

First objective within the common experimental framework was to coordinate input / output format for data flow between different experimental components. An essential part of this development was establishment of the new medical protocol and coordination of measurements and data exchange. For this, data acquisition in the required format has been carried out and this data was processed and exchanged between the partners. In particular, image data acquisition and physical measurements have been carried out in liver ablation experiments with healthy pigs; histology samples have been extracted, different straining procedures have been applied and their suitability has been tested via automatic segmentation to establish the most convenient staining.

After setting up the common framework and data formats, the consortium proceeded with the development of each component within the experimental cycle.

Pig experiments.

In a first set of experiments, healthy pigs were treated with RFA using RITA Medical Systems' RF generator. The animals were anesthetized according to the protocols of the Austrian animal care law and the position of the liver was localized using computer tomography (CT) according to the protocols. During the

RFA continuous temperature at each RITA electrode, used power, and the efficiency of heating related to the tissue conductivity were recorded.

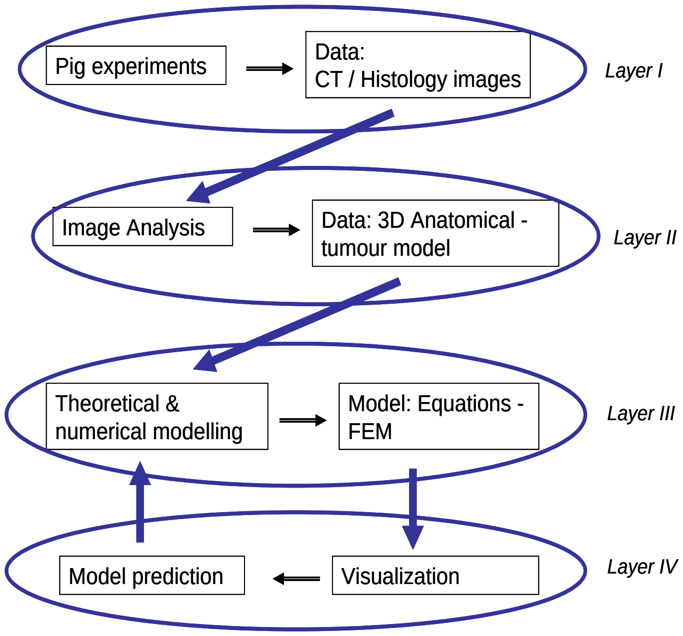

Figure 1. Structure of the experimental cycle conducted on pigs. The cycle comprises 4 layered components. The components in layers I through III are consecutive: each component generates data to be input to the subsequent component. Components in layers III and IV are engaged into an iterative adjustment of model parameters: Model prediction is compared against observed "ground truth" using the visualization component. Model parameters are updated t minimize inconsistencies.

After application of RFA the pigs were sacrificed after different surviving time spans. In a part of the treated animals, the livers were perfusion fixed and in the other half immersions fixed with formalin. Consequently, the livers were resected and trimmed for areas of interest and embedded in paraffin. Biopsies of the livers were also taken for storage in liquid nitrogen for further investigations. The perfusion fixed liver blocks were prepared for large scale sectioning and histological staining. To visualize the ablated area methylenblue-staining (MB) and chromotrope-aniline blue (CAB) staining were performed. Stained sections were scanned in high resolution (4800 dpi) for further processing by partner Fraunhofer.

In further experiments healthy liver tissue was resected and heated for 10, 20 and 30 minutes at different temperatures to investigate cell death in liver tissue. Also the influence of temperature on hepatocytes and fibroblasts in cell-culture system was investigated.

To incur cirrhosis in pigs, N-Nitrosodiethylamine (DENA) injection was performed once a week. Each second week blood samples were taken to monitor liver enzymes and the pigs' general condition. These samples were stored for further analysis. Each 2 to 3 months a CT scan was performed in order to check the state of the liver.

Image analysis

Image analysis was carried out on two levels: 1) macroscopic analysis of CT images to build a 3-D model of anatomical structures, and 2) microscopic analysis to segment and to register images of histological slices. A semiautomatic method for the segmentation of bright, connected tubular structures in CT images has been applied to build an accurate 3-D vessel model. The segmentation method employs several pre-processing steps including image enhancement using Hessian filters, linear normalization and isotropy correction. Vessel segmentation is based on an adaptive region-growing algorithm with manual initialization of seed points. The segmented binary image is converted into a graph-skeleton in line with distance transform methods. The skeleton graph is presented in the form of a directed piecewise linear tree. Using the developed refinement tools it is possible to prune the vessel trees. After pruning, the vessel skeleton is inflated back to its original size (Fig. 2).

The histology images are used for evaluation of the region of ablation. The corresponding image processing module needs to provide segmentation of (1) cells affected by ablation (dead region), (2) cells unaffected by ablation (living region), and (3) blood vessels to register the histology slice to the 3D model and 3D CT data of the liver.

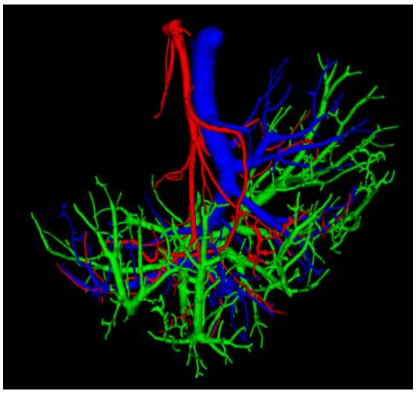

Figure 2. Example of a vascular tree after skeleton based pruning.

Probabilistic classification followed by the level-set segmentation has been employed for robust identification of those structures from CAB- and MB-stained histology slices. The probabilistic classifier outputs the probability of each pixel to belonging to a tissue class, which can be interpreted as a probabilistic measure of each class' membership. After registration, those probabilities are propagated onto neighbouring slices which allows for a robust detection of tissue structures. The tissue regions and vessel candidates are identified by a level-set segmentation over those combined membership measures producing a set of smooth contours of the vessel candidates and tissue regions, respectively. Those segmentations are combined into 3D histology segmentation. A dedicated tool for interactive segmentation and registration has been developed to allow manual refinement of the generated model.

Theoretical & numerical modelling

A theoretical model for determination of liver tissue temperature during RFA has been developed that is a novel approach to the standard bio-heat equation. The model comprises both a tissue and a blood sub-volume, with separate, but coupled, differential equations. Simulations have shown the importance of considering the two sub-volumes separately, even when the blood sub-volume is a small fraction of the total volume. Analytical solutions have been obtained for simple cases and related to existing models.

Based on preliminary image segmentation results, the cooling effect of large vessels has been separately considered and a criterion derived to distinguish between those vessels that have a cooling effect and those that do not, which will reduce the computational cost of the simulations. Based on experimental data provided by MUG, a new model of cell death in response to heating is also being developed, which will incorporate the different forms of cell death relevant to RFA. This will later be coupled with the bio-heat model to enable the prediction of the ablation zone.

Future work will also involve more detailed validation of the tissue response to heating, based on multi-scale models of cells linking to tissue properties. We will additionally examine how tumour vascularisation affects local heat transport, in order to obtain a more accurate bio-heat equation within the tumour region. Our work investigating the temperature and state dependence of material properties will be extended and added to the model, with a view to incorporating patient-specific information.

The modified bioheat equation was solved using the stabilised finite element method on an unstructured tetrahedral grid. The full RFA procedure requires a multi-physics approach to model the heat generation from the electric potential, the temperature diffusion in the tissue/blood system and the blood convective heat transfer due to the pressure boundary conditions (vessel inlets and outlets). The three solvers were coupled with the nonlinearities appearing in the heat equation due to the temperature dependent material properties. The threshold cell death model, i.e. cells die after a specified time at a specified temperature, was also included in the solver and will be refined as the theoretical model is developed. The tetrahedral volume mesh was created from a smoothed and reduced version of the segmented surface mesh boundary. The portal and hepatic vessel trees were truncated in order to simplify the volume meshing and to reduce the total degrees of freedom in the model. Several iterations are needed for each time step in order to solve for the nonlinearities in the bio-heat equation, therefore an optimum mesh size is vital to improve total analysis time. The latest release of the solver has been parallelised to run over multiple processors. An adaptive meshing capability is currently under development. The next step is to simplify the preparation of the surface mesh, perform a detailed analysis of the heat transfer characteristics of the pig RFA process including a mesh resolution study and to optimise the solver for improved performance.

Visualization

A completely new rendering pipeline was developed to meet the demands of the project data. A software-renderer was implemented on the graphics hardware which is able to combine multiple volumetric datasets with polyhedral surface meshes. The raw data which has to be considered for visualization is summarized in the following bullet list.

Medical Scans: The raw data are contrast enhanced volumetric CT scans stored in DICOM format. Furthermore histologies are stored as stack of images.

Segmentation Results: The liver surface, all vessel trees and RFA lesions or tumours are available as high-polygonal surface meshes. These datasets are rendered in the same scene with the volumetric representation of a patient.

Simulation Results: Simulation is done on volumetric unstructured grids, which allow a denser simulation around interesting regions like the tumour or vessels and computationally more economic calculations in homogenous regions. These datasets cannot be integrated directly into a rendering system and are post-processed – namely resampling in a volumetric dataset - or visualized separately.

All these data sources show different data formats, different resolutions and different scale. Furthermore, a virtual model of the RITA Starburst electrode in all extension states was created. The model is suitable for visualization as well as computation. The needle is represented as polygones.

1.3. Summary and outlook

Project work during the first year went on schedule with the concerted work of all partners. The consortium has conducted 3 regular meetings involving all partners at the beginning of the project, at M6 and M12. Many additional work meetings in smaller groups involving 2-3 partners have been carried out to facilitate project developments in short terms. Data exchange server has been set up by partner TUG. This contains all collected data as well as results of its processing including full digital models of pig's liver / tumour.

The up-to-date summary and results on the work performed so far is available on the project web-site www.imppact.eu.

Imminent project work will focus on finalization of the components in pig experiments and interpretation of results of these experiments as a whole. The physiological model validated in pig experiments will provide the basis for the next experimental cycle in clinical studies.

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